**CENTERS FOR DISEASE CONTROL AND PREVENTION**

**NATIONAL IMMUNIZATION PROGRAM**

# RECORD OF THE MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

**February 24-25, 2004**

**Atlanta Marriott Century Center Hotel**
**Atlanta, Georgia**

## Table of Contents


*FEBRUARY 24, 2004* ..... *2*

OPENING COMMENTS ..... 2

Report: Joint ACIP/NVAC OPV Stockpile Workgroup ..... 2
- Vote ..... 4

INFLUENZA SESSION ..... 4
- Overview ..... 4
- Introduction ..... 4
- Influenza Epidemiology; Vaccine Strain Selection ..... 5
- Vaccine Strain Selection Process ..... 6
- Influenza Vaccine Impact in Children ..... 9
- New Vaccine Surveillance Network (NVSN) Data ..... 11
- CDC Vaccine Effectiveness Studies ..... 13
- Rapid VE Assessment During Influenza ..... 14
- Rapid Assessment of Influenza Response Capacity ..... 16
- Summary of Vaccine Supply Issues ..... 17
- Summary of Antiviral Purchases ..... 19
- LAIV-Related Issues ..... 20
- Vanderbilt University Adult Shedding Data ..... 21
- Manufacturer Perspective; MedImmune Presentation ..... 23
- Sensitivity and Specificity of Self-Reported Vaccination Status ..... 29
- Universal Influenza Vaccination ..... 30
- FDA Perspective on 2003-04 Influenza Vaccine Production ..... 36

*FEBRUARY 25, 2004* ..... *37*
- NVAC Discussion of Influenza ..... 37
- Presentation by the National Foundation of Infectious Diseases ..... 38
- 2004 LAIV Influenza Vaccine ACIP Recommendations Final Text ..... 40

Review of the Childhood Immunization Schedule ..... 44
- Vote ..... 45

SMALLPOX SESSION ..... 45
- Smallpox Vaccine Safety Workgroup (SVS WG) Report ..... 45
- Considerations in Timing Smallpox Revaccination for Response Teams ..... 48
- Vote ..... 51

MENINGOCOCCAL DISEASE SESSION ..... 52
- Introduction ..... 52
- U.S. Epidemiology of Meningococcal Disease ..... 52
- Meningococcal ACIP Subcommittee Report ..... 53
- National Meningitis Association Statement ..... 56

ACIP Recommendations on Influenza ..... 56
- Vote ..... 58

Vaccine Safety Update ..... 58

VSD Thimerosal Screening Study ..... 58

Agency/Committee Reports ..... 61

Public comment ..... 65

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

**MINUTES OF THE MEETING**
**February 24-25, 2004**

**FEBRUARY 24, 2004**
A meeting of the Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention's (CDC) National Immunization Program (NIP) at the Atlanta Marriott Century Center Hotel in Atlanta, Georgia, on February 24-25, 2004. The meeting agenda (posted on CDC's Website, http://www.cdc.gov/nip/) had a major focus on influenza, but also addressed vaccine supply and safety, the childhood immunization schedule, smallpox revaccination, and meningococcal disease. The meeting was convened by ACIP Chairmen Dr. Myron Levin at 8:30 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 members: Drs. Ban Mishu Allos, Ed Marcuse, John Traenor and Robin Womeodu.
- New liaison: Dr. Clement Lewin of the Biotechnology Industry Organization.
- The June meeting will be the last for retiring members Drs. Levin, Abramson, Deseda and Zimmerman. Dr. Celine Hanson had resigned to pursue other endeavors.
- ACIP Workgroups to confer at this meeting were those to address influenza, MMR/VZV, HPV, and evidence-based recommendations.
- The ACIP homepage 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) qualified to vote. 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 recognized by the Chair. ACIP members with potential conflicts of interest were asked to disclose all vaccine-related financial interests and work and to refrain from discussion or vote related to such matters. Waivers of such conflicts of interest enable the provision of a members' expertise while serving on the Committee. They are issued, for example, to members conducting clinical vaccine trials or serving on Data Monitoring Boards (DSMB). The conflicts reported are noted on Attachment #1.

**PRESENTATIONS**

**Report: Joint ACIP/NVAC OPV Stockpile Workgroup**
Presenter: Dr. Charles Helms

Since the 1999 ACIP recommendation to use inactivated polio virus (IPV) vaccine for

routine immunization, and oral polio vaccine (OPV) for mass vaccination campaigns to control outbreaks of paralytic polio, no U.S. OPV manufacturer remains. The ACIP/NVAC joint workgroup reported on its examination of this situation and the related implications. Its members were drawn from ACIP, NVAC, FDA, CDC and the NVPO.

Four subgroups were formed, to address: 1) the rationale for the polio virus vaccine stockpile; 2) the characteristics of the polio virus vaccine stockpile; 3) manufacturing issues; and 4) the related complexities to providing OPV under an IND. Eight teleconferences between the workgroups and two with the World Health Organization were held, as well as the groups' communications with OPV manufacturers and decision analysis modelers. NVAC heard and accepted the final report at its February meeting. The workgroup's recommendations were focused on three topic areas, IPV stockpile, OPV stockpile, and definition of the challenges in creating an OPV stockpile.

The *IPV stockpile* target of eight million doses (two vaccinations for an entire U.S. birth cohort) should be met in 2005. In an outbreak and the absence of an OPV stockpile, it would be used among those for whom OPV is contraindicated or declined. Outside an outbreak, it will rapidly improve routine immunization levels. *Recommendation: Assure a continued availability of non-combined (i.e., with no other pediatric antigens) IPV vaccines.*

In an outbreak, an *OPV stockpile* can replicate the vaccine strain and interrupt wild-type polio transmission, boost immunity, and serve as primary immunization of naive individuals. Current data indicate that, absent OPV, IPV could control a domestic outbreak, due to our overall high immunity. But those circumstances might change, and an OPV stockpile may be required. Eight million doses could handle six large city outbreaks or a two-dose support for the newborn cohort. But there are challenges to creation of an OPV stockpile: no domestic manufacturer, the need to use an unlicensed vaccine manufactured abroad , and the related regulatory issues. Procedures for emergency U.S. licensure of OPV would be necessary. *Recommendation: Explore procedures for such emergency vaccine licensure/use. Concurrently, DHHS (CDC) and FDA should promote the development of an investigational new-drug (IND) protocol to create an OPV stockpile and ensure its effective utilization in an outbreak.*

*Challenges to creating an OPV stockpile* include the informed consent process needed for IND use. It should include information on the Vaccine Injury Compensation Program (VICP) and the availability of IPV. CDC, FDA, and the HHS collaboration at the international level is needed to help finance, create, and maintain a global polio virus vaccine stockpile. Local collaborations would support the development of state/local health department response plans, which should include aggressive education about the public and individual benefits and risks of OPV and IPV.

*Discussion* included:

- The international collaborative approach was appreciated. *Integration of U.S./Canada work was inquired of the workgroup, as was its definition of an "outbreak."* The workgroup has not yet addressed mechanics and definitions, but those definitions could emerge during planning with the states.
- Dr. Plotkin thought OPV use to be unnecessary unless the imported disease spread. He wished for more emphasis on stockpiles of monovalent Type I virus, and avoidance of a multivalent OPV with Types II and III, which have been associated with vaccine-derived

polio spread. Dr. Helms related the workgroup's focus on monovalent live vaccine in their discussions with the manufacturers. A protocol to license it here is possible, with manufacturer and WHO input.

- Dr. Decker questioned the low threshold for use of OPV in an outbreak, for example, in a naive population of immunization decliners (e.g., a religious community). He called for more explicit threshold indications to avoid potential negative publicity from adverse outcomes from OPV. Using IPV first may be better advised.
- Dr. Katz noted that there may be hundreds or thousands of cases of asymptomatic infection for every overt case of polio virus infection. So, the risk of one in 750,000 or a million of vaccine-associated paralytic paralysis (VAPP) has to be balanced with the disease risk for unvaccinated individuals, and with the longer term of IPV-activated immunity (several months for 2 IPV doses), versus the initial immunity from a single OPV dose. Dr. Cochi reported the workgroup's intent to provide maximum flexibility through both IPV and OPV stockpiles. The WHO and UNICEF oversee the rotation of a trivalent OPV stockpile (~50 million doses) worldwide. They are trying to have monovalent OPV licensed in the manufacturers' countries as well. The U.S. government will undoubtedly be involved with that development.
- Dr. Salisbury reported that the U.K.'s revolving OPV stockpile is likely to remain trivalent. The regular storing, discarding, and restocking involve cost, but they are assured of it upon need. Alternatively, the manufacturer could set aside inventory for the government's priority use, but this would not necessarily be appropriately packaged for use or batch-released, both issues that involve liability. Dr. Baylor stated that FDA is considering the potential of different criteria for batch release use of a product under IND. But, given a choice of IPV or OPV, he expected most to choose the former, compounding the difficulty of using OPV under an IND.
- Dr. Marcuse advised, rather than the report's reference to the "vaccine virus", use of the term "vaccine-derived virus".
- Dr. Paradiso asked if the VICP would cover IND use of unlicensed OPV vaccine or if a special coverage would be required. Dr. Evans said that any vaccines listed on the vaccine injury table are covered.
- Dr. Cochi reported that CDC had been working on an IND for OPV, but FDA will need greater flexibility and authority to approve foreign-licensed products for emergency domestic use. Dr. Baylor reported that FDA already will accept such an application from foreign manufacturers, but authorization for emergency use would require legislation.
- Dr. Plotkin recommended that CDC deal directly with an outside manufacturer to bring in material for FDA examination on a regular batch basis, as other polio vaccine lots have been submitted and reviewed. The retention of 2-3 years' stock is doable, with FDA's continuous examination of lots.
- *Why was the number of eight million doses of OPV chosen, with 85% of U.S. children already covered with IPV?* Dr. LaBaron reported that was chosen as a flexible and somewhat arbitrary figure. If or when coverage levels drop, a response at about that level would be needed (e.g., as seen with the measles-type resurgence in the 1990s). Dr. Seward reported this as a worst-case scenario target (e.g., mass panic although only a few cases) to allow for two doses to every child under five (basically, a birth cohort).

On Dr. Levin's suggestion, **Dr. Birkhead moved to adopt the Workgroup's report and recommendations**. Dr. Zimmerman seconded the motion. In further discussion:

- Dr. Poland raised the unknown cost of such a program and thought the 8 million doses to be unrealistically large. Dr. Cochi reported a present stockpile of ~4 million doses of

IPV, to be supplemented by another four million doses by 2005. Working globally with WHO/UNICEF and the manufacturers, a global stockpile would be more flexible and efficient to meet the needs of all.

- Dr. Orenstein stated the goal of eventually stopping OPV use except for an emergency, was something best addressed through regularly rotated licensed vaccine. IPV as a first use in an outbreak would be experimental due to little data on that; OPV is the standard. If there are five cases that translate quickly to ~1,000 infections, 8 million doses may already be grossly inadequate, but if they are part of a larger stockpile, more doses would become available if needed. A definition of sustained transmission needs to be developed to distinguish an outbreak from, for example, a person visiting and shedding virus, which is detected in a sewage sample.
- Dr. Abramson commented that, beyond simply OPV, maximum flexibility to move vaccine within and between countries will be needed.

**Vote**

**Conflicts,** since the report discusses IPV as well, involved GSK and Aventis Pasteur. Dr. Levin and Dr. Treanor had a conflict due to GSK and abstained.

In favor: Zimmerman, Salamone, Poland, Marcuse, Gilsdorf, Finger, Campbell, Birkhead, Allos, Abramson.
Opposed: None
Abstained: Levin, Treanor

**The motion passed and the OPV Stockpile Workgroup's report was accepted.**

**INFLUENZA SESSION**

Presenter: Dr. Zimmerman, Workgroup Chair

**Overview :** Influenza epidemiology to date, vaccine effectiveness and supply, issues related to live attenuated influenza vaccine (LAIV), update on the ACIP influenza recommendations published each spring, and future steps.

**Introduction**

Presenter: Dr. Keiji Fukuda, NCID

In addition to the above, the committee was asked to discuss universal recommended vaccination for influenza vaccine and issues related to the production of a vaccine against H5N1 influenza, now in discussion by the government.

This year saw the earliest flu season since 1976, and severe pediatric cases. Demand for vaccine continued into December, again risking an inadequate influenza vaccine supply. The match between the vaccine's H3N2 strain and that circulating was suboptimal, since the former was selected before the variance was confirmed. The year was also unusual with high media attention and the launch of the anticipated live attenuated influenza vaccine. The early onslaught and flu severity prompted activation of CDC's Emergency Operating Center (EOC), with staff CDC-wide reassigned to monitor it in a 24/7 fashion. Meetings with those concerned (e.g., DHHS, the Council of State and Territorial Epidemiologists [CSTE]) etc. were ongoing.

CDC accelerated implementation of the ACIP's recommendation to vaccinate children aged 6-23 months, which was originally planned to begin in October. A large number of activities and

studies were initiated and more are planned. Government discussion of vaccine and antiviral purchasing issues increased and influenza-related communications rose exponentially.

The world-wide attention to SARS from February of 2002 included a factor of concern about the expected influenza pandemic. In January 2004, reports from Asia of a large influenza epizootic of influenza A H5N1 heightened that concern. To date, this had involved hundreds of millions of poultry, 32 human cases of H5N1, and 22 deaths in Vietnam and Thailand. The epizootic is ongoing. Asian control efforts continue, but their success remains unsure. There is an unknown relation between that epizootic and recent reports of domestic avian influenza outbreaks in the U.S., involving multiple avian virus subtypes.

Discussions were already under way about how this season's severity should be gauged and whether the current approaches both to vaccine supply and vaccination strategies should be re-evaluated and changed. Response to an international H5N1 epizootic also requires discussion of what "control" of such an event means, as the normal concept of eliminating this infection may not be feasible.

The foremost question is whether the world is substantially closer to the start of another pandemic, particularly one related to H5N1, and whether the U.S. should produce and store supplies of H5N1 vaccine.

**Influenza Epidemiology; Vaccine Strain Selection**
Presenter: Ms. Lynette Brammer, NCID

The State and Territorial Epidemiologist System's weekly reports of influenza activity was mapped. In October, Texas was already reporting local but limited laboratory-confirmed outbreaks. This grew to widespread activity within two weeks, there and in other states. By mid-December, 45 states reported widespread activity in a single week, after which activity declined fairly quickly. Laboratory data from the WHO and National Respiratory and Enteric Virus Surveillance System identified 99% of the viruses as influenza Type A and subtyped as H3N2 viruses.

A charted comparison to recent influenza seasons showed the unusually early season and higher peak percentage. Influenza-like illness (ILI) data were similar. Mortality data rose above the epidemic threshold in mid-December, peaked at 10.3% in January, still above the epidemic threshold (by then for nine consecutive weeks). Antigenically, most of the H3N2 viruses were similar to Fujian 411, but 17% were similar to the vaccine strain (New Caledonia), as were the few influenza H1 viruses reported.
The two antigenically distinct lineages of influenza B viruses are co-circulating. This and last season's vaccine included the B/Victoria lineage; before that it had the Yamagata lineage viruses. Most of the few influenza B viruses this year are of the latter. European and Asian influenza activity was very similar to that in the U.S., with a very early start in the west that moved east, and with H3N2 Fujian-like viruses predominating.

In January, both the WHO and FDA's Vaccine and Related Biological Products Advisory Committees (VRBPAC) decided to retain the A/New Caledonia H1N1 component for next year's vaccine strains, and to change the influenza A/H3N2 component to an A/Fujian-like component. The influenza B component will be changed to a B/Shanghai

361 2002-like virus, the Yamagata lineage. FDA will review this decision in March if more data becomes available.

*Discussion* included:

- It is theoretically possible to have a quadravalent vaccine with two H3N2 strains to address both A/Fujian and A/Panama. But since that would require another component for the vaccine manufacturers to produce, it may reduce the total number of doses available.
- The ratio of Panama to Fujian viruses changed over the epidemic, beginning with the former and ending with almost all Fujian-like viruses.
- *The A/Sydney strain was severe in 1997-98 in Canada and continued for 3 years; was this year's severity comparable?* In the U.S., the third year of A/Sydney had the highest mortality; this year was comparable. The National Center for Health Statistics (NCHS) will not have the data for this season's mortality for two years, but the average season mortality (generally ~36,000) could well be exceeded.
- *How can FDA define the influenza vaccine, reformulated every year, as not a new vaccine, and therefore not subject to the testing required of other new vaccines?* Dr. Baylor responded that the influenza manufacturing itself does not change, only the strain used, and it is done by manufacturers who already have a license. A new producer would begin the FDA process anew for a new flu vaccine.

**Vaccine Strain Selection Process**

Presenter: Dr. Nancy Cox, NCID

Overview: How viruses are chosen for inclusion in influenza vaccines; why Fujian was not in that for 2003-04 vaccine; types of data collected to support the recommendations for vaccine strains.

Three groups of influenza viruses currently circulate in the human population: two subtypes of influenza A, H1 and H3, and influenza B viruses. They are monitored annually to select a representative vaccine virus for each. Occasionally, avian influenza viruses have jumped from a host species to humans. Work is ongoing to develop pandemic vaccine candidates to address those viruses if they manage to spread from human to human.

The structure of the influenza virus was outlined: surface glycoproteins, hemaglutinin (HA) and neuraminidase (NA) proteins. The surface glycoproteins change in response to immune selection. Two types of antigenic change are monitored. The first is *antigenic drift,* which occurs in both the HA and the NA glycoproteins. This type of change is associated with seasonal epidemics, and the continual development of new strains is produced by secondary mutations in these two proteins. Because new antigenic drift variants differ from their predecessors there is a need to update influenza vaccines on an annual basis.

The second type of antigenic change that is monitored is *antigenic shift* which is much more dramatic and consequential for human populations. Antigenic shift occurs when a totally new influenza virus subtype emerges, with such different antigenic properties that most of the

population is immunologically naïve. If the new virus can be transmitted from person to person, an influenza pandemic will occur.

The WHO's Global Influenza Network (GIN) has conducted annual surveillance for newly emerging influenza variants of influenza since ~1948. Currently, the GIN involves ~110 national influenza centers in about 80 countries. They isolate influenza viruses and identify them as influenza A, B, H1 and H3 or an "unsubtypeable" strain, and send a subset of the viruses to one of four international collaborating centers (CDC in Atlanta, London, Melbourne, and Tokyo.) The latter collect and transmit epidemiologic information to the WHO. The international collaborating centers analyze the viruses relative to what circulated previously to find any variants; they provide reagents worldwide for identifying influenza viruses and data for the WHO and VRBPAC vaccine recommendations.

The southern hemisphere's influenza activity peaks in July, when northern hemisphere influenza activity is low. The WHO recommends for the northern hemisphere in February for the following influenza season and in late September/early October for the southern hemisphere's next season. The national authorities then recommend for their respective countries.

To match circulated strains to the previous season's vaccine strains, any new antigenic variants and their spread to cause disease is examined. If the current vaccines can still induce antibodies to recent isolates, no update is required. Determining a new variant that could be useful for vaccine production is a balancing act between the latest virologic and disease surveillance data and the time required for vaccine production (8-9 months). The data are often limited before influenza season and there is often a lag-time between isolating the viruses, sending them to the collaborating centers, and then doing a complete work up of those viruses. The selection also occurs about a year before the influenza season in order to allow large quantities of vaccine to be produced.

Other challenges include potentially different epidemics between countries in the same hemisphere. The Fujian strain variant was identified by CDC on January 31, 2003, barely two weeks before the vaccine strain decision was to be made. However, both European and U.S. regulatory authorities require that influenza viruses used to produce vaccine must be isolated and passaged only in eggs or primary chick kidney cells. Passage Fujian strain variants were only available in April, and it required further characterization and then preparation of pools with which to standardize the vaccine. Those steps would have delayed vaccine availability, and there was real uncertainty about the antigenic differences among the circulating strains. The Sydney virus experience also differed this season, involving considerable cross-reactivity between Fujian viruses and Panama-like viruses, and very clear-cut antigenic difference between the previously circulating strains and the Sydney strains. This season involving a much grayer zone between the antigenic properties of the Panama-like viruses and the Fujian-like viruses. The above led to the decision to retain the Panama virus in the vaccine.
*Discussion* included:

- *It has been stated that there was concern that the Fujian virus would not grow very well in eggs, another reason to retain the Panama virus. What are they doing about that this season?* No, the problem last year was not that the virus could not be grown in eggs once isolated in MDCK cells, but that the virus could not be extracted from an original, clinical sample inoculated into eggs. Another system was used to inoculate primary chick kidney cells, gather an isolate, and then propagate that in eggs. With that appropriate passage history, which appears to grow reasonably well in eggs, no problem

in vaccine production is anticipated this year.

- *Laboratory data suggested substantial crossing activity between the two strains. How predictive is the laboratory data to clinical vaccine efficacy?* It is a reasonably good predictor. The HA gene sequence show that these viruses belong to the Fujian genetic group, but with a lot of heterogeneity; some are high reactors and some low reactors. Serological tests of people who received last year's vaccine showed that some of the viruses looked they were very well covered even though they were in that Fujian group, but other very low reactors would not have been well covered. This differed from the 1997 Sydney experience where the isolated viruses were both genetically and antigenically similar to Sydney .
- *Please apply this process to the H5 situation, relative to producing a new vaccine. That is, how would it apply to a potential pandemic strain of another H type?* The highly pathogenic Asian H5N1 viruses involve several safety as well as growth concerns relative to a vaccine. They are highly pathogenic for chickens and mammals and must not be introduced into the environment. The virus has to be genetically reverse-engineered to tame it. That is done by removing the hemaglutinin that makes them pathogenic, which then is rescued back into a background of PR8 genes that is used for the current vaccine. After safety testing, the vaccine reference strain can be used to safely manufacture vaccine. At what biosafety level H5 work would be done requires discussion (USDA will be involved in those discussions), as does how they would fit H5 production in with their normal trivalent production.
- *Is there a sense that a drift in the relative sensitivity of Fujian makes it less sensitive over time?* There is some movement through a flu season. At the beginning of this one, there were more viruses well inhibited by antiserum to the Panama strain than at the end.
- *Will CDC actually prepare the strain and give it to vaccine manufacturers, assuming it goes forward?* Three GIN laboratories are preparing candidate H5 reference viruses, one in the U.K., St. Jude Children's Research Hospital, and CDC. Each is using reverse genetics to modify the wild-type H5 strain and to prepare a candidate vaccine strain that would be appropriate for use by vaccine manufacturers should that become necessary. Providing all the vaccine strains free to the manufacturers levels the playing field for industry and between countries.
- *Do the other laboratories, like St. Jude's, receive government support?* (Yes) *If a strain given to a vaccine manufacturer is not sufficiently attenuated and wipes out the countries' chicken flocks, who is liable?* There is a very stringent safety testing protocol. The vaccine reference virus is tested for pathogenicity in chickens, mice, and ferrets before being provided to companies. NIH would work with the companies potentially to do clinical trials so that clinical pilot lots would be made first, and then tested in human trials.
- *Once you have a candidate vaccine strain, how long will it take to actually get it into people, licensed and released?* The current timetable is to have the reference seed virus available, and hopefully safety tested, by the end of March or early April. Then that virus, or those viruses, could be provided to manufacturers interested in making pilot lots, which takes ~3 months. Clinical testing could begin in July-August. Licensure is another issue.
- *Is it true that manipulation with reverse genetics was done last year with Fujian and virus in eggs was actually ready for production earlier than April?* This is a complicated matter. There are intellectual property issues associated with the use of reverse genetics that would have to be worked out, and although it is hard to say, the vaccine may not have been able to be produced on time.

**Influenza Vaccine Impact in Children**

Presenter: Dr. Jennifer Gordon Wright, NCID

Overview: Impact of influenza in U.S. children for the 2003-2004 influenza season; preliminary data on both influenza-associated encephalopathy and influenza-associated deaths in children aged <18 years.

Death is an uncommon outcome of influenza in children, but a few years ago, Japanese authorities reported influenza-associated encephalopathy. Background U.S. rates of encephalopathy and death due to laboratory-confirmed influenza are unknown since they are not nationally reportable. But with statistical modeling, Thompson (*JAMA*, 2003) estimated that <100 influenza-associated deaths occur annually among children aged <5 years, and it is believed to be rare for children aged CORRECT??≥5 years.

As described earlier, the U.S.' 2003-2004 influenza season began unusually early and that, along with the number of pediatric deaths, produced increased media attention.

*indication for influenza vaccine, which it is currently is not. Is there information on the type of underlying neurologic disorders in the encephalopathy or death cases?* Of 14 deaths, some children had multiple disorders (e.g., seizure disorder and developmental delay). The data can be delineated by the children who died as well as those who would not have been covered for vaccination by another underlying medical condition (e.g., asthma and a seizure disorder).

- There are no data to indicate the children's caretaking situation or the immunization status of the caretakers. Medical records are still absent for ~70% of the children. Twenty-two children were treated with antivirals (still unknown for 32 children). The treatment must have started late; the average treatment time was only 2-3 days.
- *Could the non-high risk group have had unrecognized underlying conditions before hospitalization?* That is very possible and may emerge when the missing medical records are received.
- *Is it possible that the difficulty in interpreting the mental status puts children with underlying developmental or other neural disorders at a higher risk of encephalopathy?* That is still being examined. It is hard to determine if the individual's underlying condition worsened. More records are being sought for some cases before making a final decision, and these are very preliminary data. The data also may be examined without those with underlying neurological conditions, if CDC can obtain more complete case numbers.

**New Vaccine Surveillance Network (NVSN) Data , 2003-04 Influenza Season**

Presenter: Dr. Marie Griffin, Vanderbilt University

Overview: Population-based surveillance to measure the acute respiratory illness burden in children aged <5 years in Rochester; NY; Nashville, TN; and Cincinnati, OH, to determine if : 1) 2003 was an unusual influenza year for children, with more hospitalizations, ED visits, outpatient visits, more severe disease or just more public recognition of influenza, and 2) if influenza vaccine protected children.

*Inpatient characteristics, 2003-04 influenza season.* The NVSN conducts outpatient surveillance (this was the second year) and inpatient surveillance (fourth year) of children aged <5 years who are county residents (n=141,000) and who are admitted with acute respiratory illness (ARI) or fever of unknown origin. They were enrolled for 4 days/week and nasal throat swabs were obtained for culture and PCR.

The resulting incidence data showed great variability in the influenza hospitalization rates between sites for children aged <5 years and <6 months, and 6-23 months. Incidence in the previous three influenza seasons was much lower than in 2003, except for a 2001 spike in Tennessee (which still was lower). The mean hospitalization rate over four years for children aged <6 months was 41/10,000; for those aged 6-23 months, 9/10,000 and for those 24-to-59 months, 3/10,000. Of hospitalized children, ~19% had high-risk conditions; 21% (mostly the youngest children) were given oxygen and 3.3% were in the ICU. No deaths occurred in the surveillance population, although there were deaths at the sites. Median hospitalization was 2 days. There was no evidence that influenza was more severe, but there was some evidence of increased recognition of influenza in 2003-04 (a 15% rise on influenza discharge diagnosis versus the previous three years). The latter may be due to rapid diagnostic testing.

*Outpatient surveillance* (for two years now) is done only during respiratory viral season, for children aged <5 years, with the same enrollment criteria. The early onset of the influenza season, before RSV began, caused the NVSN to miss the first two weeks of influenza surveillance. PCR analysis is done for influenza and RSV. The data showed increased patterns for emergency department (ED) visits due to influenza for children <5 months (from 38-45% versus 6-13% previously), and outpatient visits rising from 7-20% to 28-35%. Whereas in 2002-03, only 3-7% of total visits were due to influenza, 17-26% were so in 2003-04. Outpatient visits rose from 2-9% in 2002-03 to 10-13% in 2003-04. Based on national data for ambulatory medical care of children aged <5 months, the NVSN estimated that ~25% of all visits occurred during this respiratory season. The estimated rates of influenza-related ED visits per 1000 children aged <5 years rose from 5-11 in 2002-03 to 17-78 in 2003-04, and those for outpatient visits, from 17-78 to 87-113. For children hospitalized under age 6 months, 48% was due to influenza; 32% for those aged 6-23 months; and 20% for those aged 24-59 months.

*Vaccine effectiveness*. Parents reported that seven of 43 (16%) of children aged >6 months who were hospitalized with flu had been vaccinated; only one was fully vaccinated. Three were vaccinated >14 days (one dose) and three <14 days before admission. The NVSN is developed a control group to assess vaccine effectiveness.

*Implications to the influenza burden.* In these four years of surveillance, ~1/1000 children aged <5 years and those aged six-to-23 months were hospitalized for influenza in these counties. Hospitalizations are much higher in children aged <6 months. ED visits occurred in 1-4% of children, and outpatient visits in 2-11%.

With the NVSN data, the burden of disease can be compared from year-to-year and between sites. Population-based vaccine effectiveness assessment will be done in 2004 and, hopefully, annually thereafter, to further inform policymakers and vaccine evaluation.

*Discussion* included:

- *How do you weight the data for differing hospitalization criteria between communities, or how do you know that these data reflect a national trend of admission patterns?* The rates correlate fairly well with estimates based on other types of data, but they do differ between communities. That may relate to ER protocols, the testing done of the children, and maybe different admission criteria. For example, the New York hospitalization rates in general are lower.
- *But the rates of ED visits and outpatient visits are roughly the same.* Dr. Treanor, who practices in Rochester, reported his impression that 2003-04 was not an unusually severe year, although there was a lot of activity. But Rochester has a critically inadequate census of hospital beds, so only the very seriously ill are admitted. The patient may stay in the ER for a prolonged time (e.g., 23 hours), but that is not counted as an admission and may not be counted at all.
- Dr. Plotkin cited his own study of neurotrophic influenza strains. Some of these were adapted by intracerebral injection and were associated with interferon secretion, which supports the idea that of cytokine production as a cause of the encephalopathy. He asked about the NVSN's seizure data among the children diagnosed with influenza. Dr. Griffin reported that only one discharge diagnosis was used, but that could be examined more closely. A substantial portion of the children (perhaps 10-20%) had febrile seizures, but whether that differed from an other disease with high fever she did not know. Whether these were febrile or

non-febrile seizures due to brain swelling would not be diagnosed unless it was specifically investigated.

**CDC Vaccine Effectiveness Studies**

Presenter: Dr. Nidhi Jain, NCID

Overview: Retrospective cohort study to analyze the effectiveness of the 2003-2004 inactivated influenza vaccine used to prevent influenza or ILI among adults working at the Children's Hospital in Denver, Colorado (with 80% influenza vaccination coverage).

In the early part of the season, effectiveness of the current vaccine against the drifted strain was not known. The Children's Hospital laboratory virologic respiratory surveillance data were charted. They showed influenza A cases reported per week to be an order of magnitude above those of RSV and influenza B during November and early December. Other circulating cases (e.g., parainfluenza, adenovirus, rhinovirus, and B pertussis) were minimal compared to influenza A. ILI was the primary outcome since it could be rapidly identified, while laboratory-confirmed influenza cannot. Influenza was the predominant circulating respiratory virus, but ILI could also provide adequate estimates for vaccine effectiveness (VE). ILI was defined as a self-reported fever plus cough or sore throat beginning on or after November 1 (outbreak onset) to the survey's completion.

*Methods:* An questionnaire was distributed (e-mail and paper) for anonymous response by ~3100 employees to explore influenza vaccination, ILI occurrence and influenza testing. Frequent reminders produced a 60.8% response rate. Data was collected in December 11-17, 2003. By November 1, 54% of the staff were vaccinated and 78% were by the end of data collection on December 17.

Staff ILI cases paralleled the laboratory-confirmed influenza cases among patients. Of the 78% vaccinated, 75% were aged 18-49, 19% were male, 13% had high-risk conditions, and 69% had patient contact. Vaccinated employees tended to be older, have patient contact and certain occupations. Of the 16% of respondents reporting ILI, only 28 were tested for influenza, and 46% of those were positive.

Analyses were:

1. Categorical analysis to calculate ILI-type rates between employees vaccinated before November 1 versus unvaccinated employees. To allow for an incubation period of two weeks, employees were excluded who had an ILI within two weeks of vaccination. *Results:* An ILI-type rate of 14.9% among the vaccinated group and an attack rate of 15% among the unvaccinated group was found. The adjusted VE was 3% after calculating the relative risk and adjusting for age group, high-risk conditions, and patient contact, with confidence limits overlapping zero. When the nine employees who had an ILI <2 weeks after vaccination were considered as unvaccinated, their VE was 14% with a CI that overlapped zero.
2. A vaccinated and unvaccinated employee person-time analysis, from November 1 to ILI occurrence or survey completion (excluding days 1-13 post vaccination), produced an adjusted VE of -15%. This was considered as zero since VE cannot be lower than zero.

*Study limitations* included that the nonspecific case definition likely underestimated the VE; a possible response bias by those vaccinated (which would lower VE); self-reported vaccination and ILI status information unverified by medical records; self-selection for vaccination and more likely vaccination of older employees and those with patient contact. The respondents' high vaccination rate decreased study power to detect lower VE. The early influenza onset meant that some people were still being vaccinated during peak influenza activity.

*Conclusions*. The study could not demonstrate VE against ILI when H3N2 virus predominated, but the VE was likely higher against laboratory-confirmed influenza and influenza-related complications such as hospitalizations and deaths. Other studies to determine this are underway.

*Recommendations* were to: 1) continue influenza vaccinations for all high-risk persons, their contacts, and for healthcare workers. This is particularly important since H1N1 and Influenza B viruses may circulate later this season, and the vaccine is expected to protect against influenza-related complications; and 2) conduct prospective annual studies using laboratory-confirmed influenza as an outcome for more accurate evaluation of influenza vaccine effectiveness.

**Rapid VE Assessment During Influenza**

Presenter: Dr. Carolyn Bridges, NCID

Overview: Case-cohort and case-control studies, concurrent study to that reported above, examined VE among persons aged 50-64 years with laboratory-confirmed influenza (PIs were Marika Iwane and Guillermo Herrera); future studies to be reported.

Of >10,000 cases reported by December 31, 500 were among persons aged 50-to-64, but more serious cases were more likely to be reported.

*Methods.* In the *case-cohort study*, cases were interviewed by phone. Exclusion criteria were non-recall of being tested for influenza or non-report of a compatible illness. Data were collected on demographics, illness onset, vaccination, healthcare provider visits and hospitalization. Colorado Behavior Risk Factor Surveillance Survey (BRFSS) data provided the estimated 2003-04 vaccine coverage. The data analysis screened for a VE similar to 1.0 minus the relative risk, and a sensitivity analysis calculated the VE for possible different cohort coverage rates. In the *case-control study*, after random digit dialing, controls were frequency-matched by age group at a 3:1 ratio. The controls are hoped to increase certainty of the cohort's vaccination rate during the outbreak period.

Those who became ill <2 weeks after vaccination were counted as unvaccinated. Overall, ~42% were vaccinated and of those, ~50% were high risk. The vaccination rate for high risk people was ~52% and 32.5% for non-high risk. About 32.5% of cases overall were hospitalized, which included 17% of non-risk and 40% of high-risk persons. The proportion who were high risk or who were hospitalized was similar for persons who became ill <14 days after vaccination.

CDC believed that Colorado's coverage rate of ~45% was under-estimated, in a range

from 40%- 52% for those at high risk and 32% for non-high risk. Of the controls recruited to date, 21% were high risk, with vaccination rates of 66% versus 55% for non-high risk. With an estimated VE between 16-63%, and vaccination rates in the 50% range (from the case control study data), the VE was ~44% against laboratory-confirmed influenza. VE for the high risk population was hard to determine due to confounding factors, but often was a negative result.

*Study limitations* included the population of more ill and hospitalized patients, and the early season onset's effect on the vaccination rate, which frustrated the use of historical vaccine coverage data. The case-control study could help to clarify this issue.

*Other studies* underway were outlined: an HMO cohort study of 6-23 month-olds; a VSD analysis of 6-23 month-olds hospitalized for ILI; a case cohort pediatric study of laboratory-confirmed children aged 6-48 months in Georgia; the NVSN sites' study of inpatient and outpatient influenza laboratory-confirmed influenza in the same age group in a case-cohort design; and a cohort study in Iowa of college students with outpatient influenza.

*Discussion* included:

- Mr. Fred Ruben, of Aventis Pasteur, reported attending the VRBPAC meeting where other VE data were presented, and which differed from the CDC studies just presented. The French "NIH" surveillance system's studies, using consistent methodology over time, found a VE of ≥•″ℓℓ°•ℑ ℑ×∫ℏ 60% for both the past six years and this current season. Ongoing DOD studies also showed a VE in the current season of 60-100%. The purpose of influenza immunization is to prevent hospitalizations and deaths, not ILI; that is the relevant statistic that should be explored. Dr. Bridges responded that the French data and at least two of the military studies had ILI as an endpoint; one Air Force study looked at household contacts of a person with laboratory-confirmed influenza.
- In the first study among healthcare workers, the point estimate was almost zero for the 28 people who were tested for influenza and the 13 found to be positive.
- It may be possible to assemble a high-risk control group for comparison to determine VE for those at high-risk, but not by using the random digit dial method in this protocol.
- *The NVSN has a clear strength, of an ability to annually prospectively assess VE in a population-based, uniform manner. That would eliminate many of the biases of retrospective studies. Will the NVSN prospective surveillance be expanded to other geographic sites or age groups?* Dr. Bridges hoped for the NVSN's continued funding for surveillance, and its expansion to raise study power.
- Dr. Poland agreed, noting the frequency with which such retrospective recall studies are done, even though they functionally offer little or no information, and may even work against healthcare worker health/safety and the public's impression of the vaccine's value and efficacy. The will must be found to develop a system to gather better, consistent data for annual VE analyses. But, he asked why CDC rapidly published a less-than-optimal study that was poorly interpreted by the media. Dr. Bridges responded that, to remain credible as an agency, CDC does not hesitate to publish a negative outcomes as well as one positive. Dr. Poland understood, but remained uncertain of its value when the field is struggling to increase immunization rates.

- Dr. Zimmerman hoped that the case-control study results could be presented at the next meeting.
- Dr. Paradiso asked if the VE of the live attenuated vaccine would be studied (Dr. Bridges said CDC will not) and observed the opportunity of a Phase IV study population within CDC's Vaccine Surveillance Division. The preliminary FluMist™ data are out, and a study in Baltimore of school-age children (not adults) were due to be released soon. These should help the examination of VE and drifted strains. Finally, he commented on the 19% of children in the NVSN data who were hospitalized and were high-risk for influenza. Including children with asthma, 10-15% of children are at high risk; he wondered if disproportionate rates of disease were seen within that group and they were evenly spread (without considering that high risk children are more likely to be vaccinated). Dr. Griffin had not broken that data down by age, since 46% of the children were aged <6 months and most did not have high-risk conditions. But that could be an interesting analysis for older children.
- Dr. Levin requested a follow-up on these studies, perhaps in June if they are ready.

**Rapid Assessment of Influenza Response Capacity**

Presenter: Dr. Michele Pearson, NCID

Overview: Preliminary data of a rapid assessment to determine healthcare facility capacity during the recent influenza season.

Since studies suggest a potential of >200,000 excess hospitalizations during severe influenza seasons, the last season's impact on healthcare facility resources was investigated with the Association for Professionals in Infection Control and Epidemiology.

*Methods:* From December 22, 2003 through February 13, 2004, infection control professionals at a convenience sample of 221 healthcare facilities in 41 states, were surveyed (Web-based) on: facility demographics, laboratory-confirmed influenza cases reported, staffing and bed shortages, facility diversions (i.e., ED), availability of vaccine, ICU beds, and rapid diagnostic kits, and employee vaccination rates. The sample ranged from a single facility in a state to 20 in Texas; 42% were from the southern region. Over 80% of facilities delivered general acute care, 3% were pediatric, and 17% were "other" (e.g., nursing school, long-term care, or rehabilitation facilities). Compared to the American Hospital Association database, the participant hospitals were larger, but the demographic distribution of the respondents were similar.

The results were:

- Laboratory-confirmed influenza cases per facility: 20 (range of zero to 1778); from a high of 30 in the south to a low and median of 2 in the northeast.
- Influenza vaccine shortages: 40% overall; only in the west did only 27% report that.
- Rapid diagnostic tests shortages: 58% overall; only the northeast had only 30% with shortages.
- Staffing shortages: 35% overall, from a high of 47% (west) to 23% (northeast).
- Bed shortages: 28% overall; slightly higher (32%) only in the west.
- ICU adult bed shortages: 43% overall.

- ED diversions: 9% overall, in a range from a 5% low (Midwest) to 19% (West), for a median of 6 days, but as long as 80.
- Proportion of vaccinated employees: 53% overall (up from 45% median coverage last season) in a range of 12-100%.

*Study limitations* included the convenience sample and questionable extent of generalizability of the responses, unvalidated self report responses, and lack of baseline data for comparison.

*Conclusion:* The 2003-2004 influenza season appeared to compromise the capacity of healthcare facilities in many parts of the country. Rapid assessments such as these may be beneficial in the future to determine resource needs and contingency plans for future influenza seasons.

*Discussion* included:

- *Continue to collect these very helpful data and add data on equipment and drug shortages (e.g.,. antivirals, masks) and investigation of nosocomial outbreaks, for pandemic planning*. About 90% of hospitals provided surveillance data on nosocomial influenza cases to CDC and 15% had reported nosocomial transmission in their facilities. CDC also received data on the patients and healthcare workers involved, but those were not available at this meeting. And, while this survey did not collect data on equipment, resource assessments have been done as part of other preparedness efforts, and those data are available.
- Dr. David Fedson suggested collecting data on hospitals' vaccination of inpatients who were discharged during the fall vaccination season, something apparently rarely done. CDC is very interested in inpatient vaccination programs.
- There is no explanation yet of why the northeast, with significantly fewer lab-confirmed influenza cases, had about the same resource impact.
- The 53% percent of employees vaccinated cannot be delineated to show the proportion of ED personnel. Dr. Katz advised that this be done, since anecdotal evidence indicates a poor vaccination rate for them. It was also not asked if active programs were in place to promote their healthcare workers' immunizations, but that could be added in future. However, anecdotally, the hospitals with high immunization rates seemed to have such programs.

**Summary of Vaccine Supply Issues**

Presenter: Dr. Ray Strikas, NIP

Overview: Update/summary of influenza vaccine supply for the current influenza season; vaccine produced, shortages experienced, NIP assessments of healthcare workers and institutions in the field; future plans to avoid shortages.

Charted influenza vaccine production from 1993 to 2003 showed an increase in doses produced, although not steady, from 77.2 to 87.1 million, respectively, and doses distributed from 76.8 million to 83.2 million. The provisional 2003 dose numbers included both inactivated and live attenuated vaccine production. Except for 1999, >10% of the vaccine produced was not distributed. Most the vaccine distributed or produced but not used this season was the live attenuated. The earlier trivalent influenza vaccine lot release this year served as a surrogate for distribution. This appeared to be very timely, due in part to an unchanged vaccine formulation from last season.

The recommendation of influenza vaccine annually for the U.S.' ~185 million people poses a potential for shortage upon a great demand, which was seen beginning in late November. This was borne out by an NIP survey of pediatricians and family physicians in early/mid-December, who reported small vaccine stocks in their offices (<50 doses). Most reported ordering vaccine and having difficulties in getting it by mid-December.

Two surveys of public health centers showed zero vaccine inventory by December 10 in 21 of 45 state immunization programs, 70% of local public health agencies out of vaccine, and 32 of 47 states actively redistributing vaccine in their jurisdictions. They indicated a need for another 600,000 0.5 ml doses of vaccine for those aged ≥•″ℓℓ°•ℑ ℑ×∫ℏ 4 years and another 240,000 0.25 ml doses for younger children.

In April 2003, CDC's routine influenza vaccine contract ordered and distributed 4.1 million vaccine doses (~5% of production) and another 100,000 doses of the 0.5 ml older child/adult formulation on December 8, as well as 213,000 of the 0.25 ml vaccine. Four days later, an additional 363,000 doses of the adult vaccine were ordered. It was received in early January, but the vaccine demand had declined somewhat; only 253,000 doses of that product were distributed. CDC's contracted 3 million doses of Wyeth/MedImmune's FluMist™ live attenuated vaccine were available in late December/early January, but only 62,000 doses of that were shipped. Another 250,000 doses were donated in January, again when demand was low, and only 49,000 doses were ordered by public health departments, while 42,000 doses of vaccine donated by the Department of Veterans Affairs (DVA) to CDC were all used by public health departments.

*Future plans* include development of a pediatric influenza vaccine stockpile using Vaccines for Children funds of $40 million for the fall of 2004 and for 2005. Discussions are underway on how best to use that vaccine and to develop guidelines for reserve vaccine (e.g., second doses for children) or targeting it to children at high risk versus children who are contacts of high risk persons. And, since demand drives supply, NIP will continue to aggressively promote vaccination.

*Discussion* included:

- Mr. Philip Hosbach of Aventis Pasteur, reported that about two million doses of pediatric vaccine were distributed this year.
- Dr. Birkhead commented that, although no one could have predicted the early season or the resulting demand, some preparation for such an eventuality should be readied. He also wondered if the decision to relax the recommendation to hold only high-risk clinics in October had been a mistake. Fewer doses were manufactured than in previous years, resulting in vaccine shortages for high risk individuals.
- Mr. Dennis O'Mara described NIP's collection of manufacturer information to ensure that inactivated influenza vaccine production would be at least 90% of the amount distributed the previous year, and that projected timing of production/distribution would be adequate to support the recommended ACIP schedule. Since an estimated 16 million doses of the 90 million produced went unsold in 2003, NIP estimated 71-75 million were actually administered. Since in July 2003, the projected production of inactivated influenza vaccine totaled about 82 million doses, NIP suspended the tiered vaccination approach. The vaccine was available by August and did last throughout the optimal period for influenza vaccination (i.e., October through November).
- Dr. Birkhead wished to keep the high-risk recommendation protocol in the future, especially if vaccine demand remains high. This would mean that public health can ensure the vaccination of those at high risk. Having FluMist™, which is not licensed for

high risk individuals, frustrated the public health department mission. While operationally, people should not be turned away, he felt that the outreach should focus on those at high risk.

- Dr. Zimmerman wished for a clear definition of "high risk" (e.g., a smoker, COPD) and of "close contact". Vaccinating selected individuals in a "high risk" family could get very tricky.
- Dr. Nichol commented that this season should be viewed as unique. The demand surge was coming from a rare panic that maintained a demand which generally drops off after Thanksgiving (and which wasted an estimated 20 million doses in 2002-03). Even a tiered vaccination system would not have helped such an unpredictable surge in December. She advised against moving to a much more controlled vaccine delivery approach because of a unique event.
- Mr. Hosbach confirmed this opinion from the manufacturer's perspective. Aventis anticipated throwing away several million doses before Thanksgiving. In his 17 years with Aventis, he had never seen all the influenza vaccine distributed. Dr. Paradiso agreed, but added that next year the field should foster vaccination through December. Then, an epidemic in January or February would meet a vaccinated population. But, if December/January vaccinations are above normal, the challenge is to estimate how much vaccine to make without have to dispose of millions of doses. Expanding the immunization period would also expands the amount of vaccine available and cover as many people as possible. Dr. Clem Lewin, of Chiron Vaccine, agreed. Paradoxically, he noted, future years' supply could end up being reduced if the manufacturers adjust their supply to match the tiers and avoid stock destruction.
- Dr. Steven Cochi, of NIP, expressed CDC's wish to see more supply *and* more demand. One option being seriously explored is to create a stockpile that could attenuate the potential for later season surges through staged vaccine release over time (i.e., over the course of the year to protect against such surges).

**Summary of Antiviral Purchases**

Presenter: Dr. Benjamin Schwartz, NIP

Overview: CDC development of an antiviral drug stockpile and related future plans.

A national antiviral drug stockpile would help response to annual influenza outbreaks and other public health needs (e.g., outbreaks in nursing homes/extended care facilities [prophylaxis or therapy], containment of new health threats [avian influenza], and, in a pandemic, maintenance of essential community services and prevention of mortality.

The antiviral drugs currently licensed in the U.S. fall into two classes:

1. Adamantanes (e.g., Amantadine, Rimantadine) are both produced generically by multiple manufacturers and are relatively inexpensive. But antiviral resistance may develop, such as seen with the avian H5N1 outbreak. Amantadine also may risk common neurological adverse events, particularly among the elderly or those with compromised renal function. That could limit adamantanes' use within certain high-risk populations.
2. Neuraminidase inhibitors such as Oseltamivir and Zanamivir have demonstrated impact on severe influenza outcomes, especially on hospitalization rates and lower respiratory infections (e.g., bronchitis, pneumonia).

No studies have analyzed the impact of antiviral drugs on mortality because the sample size would have to be huge. Other than that, these two drugs' high cost limits their use, and a single manufacturer produces each one.

CDC developed an initial stockpile of antiviral drugs as concern over influenza grew. It includes several hundred thousand courses of Oseltamivir (Tamiflu™) in blister-packed capsules for a single ten-dose course, as well as a small amount of pediatric suspension. It is in both a hard inventory in the strategic national stockpile as well as in a vendor-managed inventory that can be rotated for fresh drug stock. CDC has drafted guidelines for the stockpiled antiviral drugs' use, which were outlined. They include release on a state health department's request to CDC, supply that is unavailable from the private sector, the ability to use the drug within 48 hours of symptom onset, and effective monitoring of the drug's disposition and associated adverse events. It could also be used as chemoprophylaxis for government personnel investigating an outbreak, as was done for the Asian H5N1 outbreak.

The current small stockpile is inadequate to address a pandemic which would rapidly deplete supplies. Only a national stockpile could ensure prophylaxis for healthcare personnel in order to keep our hospitals working and to treat those most at risk of adverse outcomes. But establishment of a larger stockpile begs some answers to the following questions: what drugs to store; what should be rotated by the vendor versus stored in real time; strategies for the drugs' use in a pandemic; and in particular, the cost of neuraminidase inhibitors.

CDC's strategy to address and resolve these issues was to model the health impact and cost effectiveness (CE) of different antiviral drugs and their use strategies. An expert panel was assembled to estimate the impacts of therapy and chemoprophylaxis with each drug in each of the populations, after which the drugs' impact and CE was modeled based on the pandemics of 1957 and 1968. CDC is collaborating with antiviral drug manufacturers in this work, after which options will be sent to DHHS for a decision. Other countries are doing similar work.

A slide showed the estimates developed by the expert panel for the impact of prophylaxis and therapy on mortality. Prophylaxis with either neuraminidase inhibitors or adamantanes would prevent ~70% of deaths by preventing ~70% of infections. Using neuraminidase inhibitors for therapy could prevent about a third of the deaths if they are used early, after the onset of symptoms; the adamantanes were estimated to be less effective in preventing death.

*Discussion* expressed concern about the group with the highest hospitalization rate, children aged <1 year. Those aged <6 months have no vaccine or drug.. Some clinicians will use Amantadine and Rimantadine, but without any information on dosing. Dr. Schwartz thought this should be addressed in clinical trials, which could be discussed with NIH. Prophylaxis could use up antivirals more quickly than would therapy.

## LIVE ATTENUATED INFLUENZA VACCINE

### LAIV-Related Issues

Presenter: Dr. Scott Harper, NCID

Overview: Discussion of issues of live vaccine virus transmission risk in the context of healthcare workers, hospital visitors, and students in primary and

secondary schools; who should be allowed to administer this vaccine; vaccine storage issues.

The ACIP's September supplemental guidance document based its language on transmission risk on data from a single unpublished (but presented) pediatric study assessing transmission in a daycare population in Finland. Those data spurred the package insert's direction that, due to possible transmission of vaccine virus, those vaccinated should avoid close contact (e.g., in the same household) with immunocompromised individuals for at least 21 days. ACIP's recommendation preferred the inactivated vaccine for healthcare workers and others with such close contact.

Public health and the manufacturers received many calls about different scenarios for application of the recommendations. Specifically, it was asked what to do about healthcare workers who received LAIV anyway. CDC and the ACIP's Influenza Workgroup discussed this and estimated that, based on the shedding of wild-type virus and previous iterations of this vaccine, a period of 7-10 days should be sufficient for healthcare workers to refrain from care of immunosuppressed persons. However, the ACIP had to vote on this before CDC could issue that guidance, since it differed from the package insert's directive of 21 days.

Anecdotal reports were received that hospitals prevented patient contact by healthcare workers who received this vaccine for three weeks and limited hospital visitors who had received it (in some cases, barring them from the hospital). There were questions about such vaccinated children attending school and about who should be able to administer the vaccine (i.e., not by those at high risk for influenza complications). Other issues included last season's need for special freezer storage for this vaccine, and the high vaccine cost for those paying for it out-of-pocket. Those who were aged 5-49 years with no underlying medical conditions would be ineligible for any reimbursement. Finally, all this occurred in the context of public health discussions and public worries about smallpox vaccine, which linked the different issues of the two in the public's mind. This all will be addressed in the single annual influenza recommendation document to be published at the end of April.

**Vanderbilt University Adult Shedding Data**

Presenter: Dr. Thomas Talbot, Vanderbilt University

Overview: An NIH-funded study of the live attenuated influenza vaccine FluMist™ and potential transmission issues to healthcare workers.

The 21-day recommendation for no patient contact was based on the case of a single child in daycare who had shed virus to day 21. A Vanderbilt trial investigating gene expression of peripheral lymphocytes in individuals receiving either the inactivated vaccine or the live attenuated vaccine provided an opportunity to examine shedding in adults after receipt of the live attenuated vaccine. This study involved 40 healthy adults aged 18-49 years with no contraindications to either vaccine. They were randomized to receive either the live attenuated intranasal vaccine (FluMist™) or the inactivated trivalent influenza vaccine (TIV) and were followed for three weeks after vaccination. Sera were drawn to investigate markers for gene expression.

*Methods*. A sub-cohort of 20 individuals (mean age of 31.6 years in a range of 19-49) received FluMist.™ Most of the subcohort was female (55%) and white (90%) and 55% had been vaccinated for influenza, most in the last three years. They provided nasal wash samples at baseline before vaccination and on days 3, 7, 10, and between 17-21 afterward. The specimens were cultured in RMK cells to explore cytopathic effects. Routine hemadsorption was done on days 5 and 10 after inoculation. Indirect immunofluorescent assay testing was done on those found to be positive to determine the exact strain of influenza isolated, A or B. Only 50% of the subjects who shed had baseline immunity (defined as baseline titer >1:32) to the type they shed, either A or B.

*Results* showed shedding from nasal wash at day three (50%), day 7 (5.5%) and none at day ten or days 17-to-21. One person shed at both day 3 and day 7. In three of eleven individuals, influenza A alone was isolated; five of eleven had influenza B, and three had both A and B. The person shedding on days 3 and 7 shed B on day 3 and both A and B on day 7. Serotyping of the influenza A strains is being done to determine H3N2 or H1N1, and mucosal IGA analyses are also being done.

Significantly more of the younger participants shed than those older. Self-reported influenza vaccination was almost significant, but the numbers were small. Unlike in children, in whom seropositivity has been shown to reduce shedding and duration, the baseline H3N2, H1N1, and baseline B immunity to the vaccine strains were not significantly different between the two groups. The timeline of shedding coincided with vaccination. One individual seroconverted to the wild H3N2 strain and then to the vaccine's as well.

*Study limitations* included small sample size and study power, restricted number of specimens collected, and samples collected at the start of the influenza season in Tennessee.

Their *conclusion* was that LAIV virus is shed in adults who receive live attenuated influenza vaccine in the first few days after vaccination, but is markedly reduced by one week after vaccination. The recommendations for live attenuated use in healthcare workers could be modified to reduce their period of separation from patients.

*Discussion* included:

- *Were there any differences in any clinical symptoms between those shedding virus and those who did not?* Only eight reported any clinical symptoms, evenly divided between those shedding or not shedding. The symptoms reported in the first week are also seen in placebo trials. On day 19, none tested positive for influenza.
- *Could the antineuraminidase antibody titers of the shedders and non-shedders have influenced the patterns?* That was not examined, but could be, with the remaining specimens.
- *Is there a relationship seen with nasal IGA and protection against shedding?* That is not yet known, but will be examined to see if the non-shedding individuals developed mucosal IGA.
- Dr. Decker noted that the upper 95% limit rate of shedding in the underlying population at 17-to-21 was 16.7%, a reflection of the small sample size. The data about previously immunized versus previously non-immunized both makes common sense and fits with the study findings. If that same statistical analysis is applied to these two subgroups, the upper 95$^{th}$ percent confidence limit for shedding among the not previously immunized group would be 33%. As a hospital epidemiologist, that would worry him. He suggested

that Vanderbilt break out sub-analyses for the previously immunized and not previously unimmunized. He also asked if more work to expand the data was planned. Dr. Talbot reported a planned larger-scale study that he would like to participate in, but nothing specifically designed at Vanderbilt. He agreed to the need for more data to answer such questions as a hospital epidemiologist might ask.

- Dr. Poland urged that the nosology not equate shedding to transmission, which is not at all clear among adults.
- Dr. Paul Mendelman, of MedImmune Vaccines, reported that these data are consistent with the data and literature on master donor viruses for specific reassortants as well as the data generated with FluMist.™ Eight FluMist™ studies (three pediatric, five adult) are published, involving >329 persons, 85% of them healthy and 15% HIV-positive children (n=180) and adults (n=147). The very intensive analysis of the Finnish daycare trial found that nearly all the children shed in the first 14 days, but only one of 98 children shed on day 21. After day 10, only 0-2% of the most vulnerable population obtainable shed vaccine virus on any day thereafter. Adults did not shed after day 7 seven, and the children shed to days seven-to-ten. There is no expectation of later shedding. MedImmune will do a post-licensure study of FluMist™ in the off season to avoid wild-type virus that could have been a confounder in the Finland daycare study. This May-June, it will involve 100 5- to 8 year-olds, 100 who are 9-17, and 100 aged 18-49. They will be cultured 17 times in the 28 days after being dosed, every day for a week and then approximately every other day through day 28. Baseline immune status as well and their new status will be determined on day 28. In previous assessments of vaccine take rate, the vaccine virus was either shed or showed a 4-point rise in seroconversion. The post-vaccination reactogenicity did not correlate to either vaccine virus shedding or immune response to the vaccine.
- *Do you think that the 17 nasal washes were sufficient for qualitative and quantitative reasons?* Dr. Mendelman confirmed that. He added that in the HIV populations studied, only one of 23 HIV-positive children aged 1-7 years shed on days 7-10, and one such adult of 28 shed on day 3-5, but not thereafter. There was no prolonged shedding. In the NIH trials done by Jim King, there was no difference between the safety profile in the non-infected HIV children and adults and the infected HIV children and adults. Dr. Traenor added the caveat that all the subjects in those studies had CD-4 counts >200.
- Dr. Plotkin stated that, in relation to evaluating a live virus vaccine, not only the titer material being excreted, but also the genetic stability of the virus being excreted, is important. He understood that the flu virus is attenuated in each of six segments and remains stable after excretion. In that, it differs from OPV, rubella or varicella vaccines.

**Manufacturer Perspective; MedImmune Presentation**

Presenter: Dr. Peter Patriarca

Overview: The challenges of MedImmune's FluMist™ vaccine launch experience, future plans for the product, and considerations of an ACIP recommendation.

FDA approval for FluMist™ was not granted until June, which required its previous manufacture to be done at risk. They elected to do a partial launch of 5 million doses, ~25% of their current capacity. With no manufacturing or testing issues encountered and the cooperation of the FDA's Center for Biologics, FluMist™ was available from in September.

The MedImmune Medical Affairs department did a broad disease-based, non-branded campaign to educate the population about the importance of FluMist,™ not only for healthy individuals (the indication), but also for those at high risk. They also made a special effort to make the special freeze boxes available, and "dormitory freezers" for pharmacies to increase the number of access points.

The early season and media attention were expected to encourage the use of FluMist™ as an alternate for TIV, and perhaps to avert a TIV shortage. A campus campaign to prevent school absenteeism was successful, but the overall uptake was very slow, and reports of some real or not-so-real associated problems began to circulate. One was the wholesale cost, but another was price gouging by some physicians (e.g., $120-to-$150). To rectify that, a well-publicized rebate program began in November. Three million doses were sold to CDC at $20 a dose, but only ~75,000 were distributed, as were only ~40,000 of a later donation of 250,000 doses to CDC. Of the 5 million doses produced, four million were unused and were to be destroyed.

In analyzing the situation, MedImmune is seriously considering future pricing options. This is like a chicken and egg problem, because FluMist™ is very expensive vaccine to manufacture, but is progressively cheaper after a critical supply point. Without high volume, it will remain expensive. Other problems to be addressed include the special storage required and a relatively narrow indication for use.
ACIP's help was requested in addressing the persisting misperceptions, particularly to reassure a skeptical private physician market. They need to be convinced that FluMist™ does not cause "the flu", nor will it transmit it. He agreed that a distinction between shedding and transmission must be made clear. The MedImmune study is similar to that in Finland and the seminal Gelfand study of OPV transmission, in terms of being optimized to detect transmission. Essentially, the data presented to the FDA for package insert text was a worst-case scenario, which now must be interpreted. The Vanderbilt and other data demonstrate that most people shed virus at a lower, noninfectious titer, making the probability of a transmission risk very low in a normal community setting, or even a household setting. Dr. Plotkin also pointed out that even after passaging between individuals, the virus sequence is unchanged from the original vaccine strain. The probability of a simultaneous mutative vaccine strain reversion on all the gene segments is ~$1:10^{-20}$. And, when classic ILI and adverse events were compared between FluMist™ and a placebo group, ~2% of both developed ILI.

So, the public and the medical professionals need clarity that FluMist™ causes an infection; that is how it works; but it does not cause classical influenza. It *could* be transmitted, but the risk is low to rareness. With those misperceptions in place, the ACIP's vote of preference for TIV, which is reasonable, was misinterpreted to mean that FluMist™ is either not recommended or even contraindicated for healthcare workers. That spilled down to the general population, especially if medical settings had signs telling them to stay away for 21 days if they received FluMist™

Among the possible resolutions is to segregate healthcare workers into different categories; those who contact relatively healthy populations or even high-risk populations who are not severely immunocompromised, and those in contact with the severely immunocompromised. Even severely immunocompromised people infected

with wild-type influenza can recover; the concern is that the replication could continue over a prolonged period and produce mutations down the line.

He requested that the committee consider:

1. Clarifying the existing recommendation for vaccination of persons in close contact with high-risk persons; that is, stating no vaccine preference for close contacts of immunocompetent high-risk persons. Preferring inactivated vaccine for close contacts of immunosuppressed, high-risk persons is reasonable, but the risk-benefit of no vaccine at all and FluMist™ would seem to advise that healthcare workers get FluMist.™
2. Consideration of the likelihood of transmission, intensity and duration of contact, and the consequences of transmission.
3. Consideration that FluMist™ this year was actually held to a higher standard than wild-type influenza. The hospital infection guidance provided procedures for symptomatic (from wild-type influenza) healthcare workers to follow, but those who received FluMist™ were prohibited from working and taking care of patients.

*Future plans*. Several Phase IV studies are in progress. A cohort of 60,000 people in different age groups are being followed over several influenza seasons and data on reactogenicity events are also being collected to some degree. This spring, shedding and immunogenicity will be explored with wild-type influenza confounding. MedImmune clearly wants to expand the indication for pediatric use and out to 50-64 year-olds. They believe that FluMist™ is the future pediatric influenza vaccine, so they are gathering more data on this target group, particularly to understand the asthma signal reported in the initial FluMist™ trials.

They will also assess the economic impact and secondary impact of vaccination of school children (e.g., on family members, creating herd immunity and any related economic impact). To make FluMist™ easier to use, discussions with FDA are underway to bridge the frozen formulation to a liquid refrigerator-stable formulation. It has already been tested in about 20,000 people abroad, mostly children. Finally, they are looking further at transmission by linking recovered virus from vaccine recipients to the HID-50, to establish a baseline of infectiousness. They are also considering study of FluMist™ use among immunocompromised people, not so much to gain that indication as to prove the low risk of ILI. They believe they will prove that all the attenuated mutations within the vaccine virus will remain stable even after going through an immunocompromised host.

*Discussion* included:

- Ten predecessor studies to those for FluMist™ are published, among studies of college roommates, spouses and daycare settings, with no observed transmission. In the precursor data on the human infectious dose, adults shed less than two logs, and the HID-50 concentration was five logs, so an adult cannot infect another adult. It takes less virus to infect a child, so an adult with daycare contact for a few days after dosing could potentially transmit.
- Dr. Levin commented on the statement that even if shed, the virus will not have sufficient titer to infect someone else or revert back to a more virulent form. This assumes that the attenuated virus in the milieu of an immunocompromised person could not be more virulent by itself. But he asked if it would have virulent

potential in a severely immunocompromised persons, even without reverting back. That is, would this crippled virus somehow have more potential to cause harm in someone who did not have a normal immune response? Dr. Patriarca responded no. MedImmune is now mapping out the four mutations responsible for attenuation. They are in different parts of the gene segment and probably are independent of each other. For that reason, when doublets or triplets of the same mutations are made, there is no reversion back to virulence. That infers that an independent mutation at every one of these sites would be necessary, a highly unlikely ($10^{-20}$) event. In addition, Mr. Jim Young, of MedImmune, reported that the temperature barrier is sufficient to ensure that this virus remains safe. Of the four mutations mapped for attenuation, all are temperature sensitive. Reversions of all four of those temperature-sensitive mutations would be required to revert the attenuation phenotype.

- Dr. David Fedson reported that as-yet unpublished Japanese data showing that the 20 years of the Japanese vaccination (inactivated vaccine) program for school children eliminated winter season mortality in children 3 years of age until the program was discontinued, when it returned. This can serve as an empirical demonstration that vaccinating children aged >4 years, either with inactivated vaccine or with FluMist™, can prevent mortality and the serious consequences of influenza in the very young who cannot be vaccinated, particularly in the absence of antivirals. This same approach is being argued for acellular pertussis vaccine.
- Dr. Jim Turner reported his university's nursing staff's experience that getting the informed consents and screening recipients for FluMist™ took them 4-6 times longer than for the TIV. He asked about plans to shorten that process. Dr. Patriarca said no, but related a protocol in which the vaccinees read over all the related material and reviewed a checklist to help them determine their own contraindications while waiting for the vaccination. Dr. Mendelman reported a CDC time-motion study with the University of Wisconsin to assess FluMist™ vaccination time needs, and found it to be <2 minutes. Most of the time was spent instructing them, but there is no informed consent required for a licensed commercial product, unlike an IND study. But the questions and issues of immunocompromised status take time to address, making the ACIP's help in vetting shedding and its ramifications so important.
- Dr. Mendelman reported their literature search, which produced the case of a 7-year-old with AIDS who shed wild-type virus for 9½ weeks, based on the antigen detection culture, and one adult with cancer who did so for 58 days. Both survived. Belshe's data on transmission, from the FluMist™ efficacy trial, compared the attack rates for the placebo children with a vaccinee sibling with singleton vaccinee children and found about the same attack rate, ~18%. Of the children in the immunogenicity substudy, no placebo recipient with a vaccinee sibling showed a fourfold rise to antibody to any of the three viruses.
- Dr. Gilsdorf commented that, at her very large medical center, there was no area without immunosuppressed patients.

Prior to the next presentation, Dr. Zimmerman stated the Influenza Workgroup's focus was on the health of the American people and practitioners' issues in administering the vaccine. The presentation of the manufacturers' perspective was provided to inform the ACIP's discussion.

**Revisions to the LAIV Recommendation**
Presenter: Dr. Scott Harper

Overview: Updates to the 2004 influenza document, pending the ACIP's approval.

*Updated references and a description of the 2003-04 season.* Deleting the latter was suggested, but text was desired to reassure providers that efforts are being made to ensure that there is no problem with the vaccine supply. The manufacturers also appreciated this as a message to the field to get their orders in as early as possible.

*A new table of influenza vaccine coverage rates* among U.S. adults in ACIP target groups, based on the data of the 2002 National Health Interview Survey. It contains both crude and weighted sample sizes and the influenza vaccination rates with associated confidence intervals.

The text of changes to address LAIV and non-LAIV issues is appended to this document in Attachment #2.

*LAIV issues* involved:

- Transmission: In addition to the 2003 language referring to the transmission study in Finnish daycare children, the Talbot shedding study at Vanderbilt is cited. When information is available, titer information could also be added. The title should be changed from "Transmission of Vaccine Viruses" since the second paragraph now adds transmission.

*Discussion* included: 1) advice to insert a clear statement for the busy nurse or clinician about the lack of a relationship between shedding, transmission, and disease; 2) to add some interpretation of what these data mean; 3) to change "Because there is the potential" to "Although there is no known risk for transmission" and in fact, to put this in context, 4) insert that transmission is probably *good* to anyone except the immunocompromised; 5) add that since it is cold adapted, even if transmitted, lower airway disease would be unlikely to occur, and that the titer shed is less than the titer needed to cause infection. For example, the end of the additional paragraph could simply state that the observed risk has been zero.

*Contacts* of persons at high risk receiving the vaccine. The word "severely" was added to modify "immunosuppressed" and examples were provided. Additional text advised healthcare workers and hospital visitors to refrain from contact with such patients for seven days after vaccine receipt. Related issues were: 1) to define what "severely immunosuppressed" is (e.g., SCIDS, bone marrow transplant) and is not (e.g., asthma patient on steroids); 2) whether to retain the preference for vaccinating healthcare workers with an inactivated influenza vaccine (which risks the erroneous perception that LAIV could be contraindicated); and 3) to vote on the 7-day period; the package insert says 21 days, a severe barrier to vaccination of healthcare workers.

The discussion to this point had noted the unlikelihood that the vaccine would spread or be problematic if it did spread. Opinions offered were:

- With the seven day restriction to contact with severely immunosuppressed persons, a preference is not needed; the vaccine program can decide for itself.
- If the LAIV is received, aside from not treating the severely immunosuppressed, stress the use of PPE (mask, gloves) since some shedding does occur. Clarifying severity is key, as is clarifying "close" contact (as affected, e.g., by wearing a mask).
- The Influenza Workgroup supported keeping the preference due to the presence of

vulnerable patients throughout a hospital and due to the likelihood that furloughs would exacerbate existing staffing shortages, potentially compromising patient care. The data presented allow the new language relaxing the previous recommendation, but there are no data to support dropping the preference entirely. When those data are in hand, this could again be modified.

- The definition of "severely immunosuppressed" should be clear, and be preceded by an "i.e.," not an "e.g.", as done in the MMR and varicella recommendations. For example, it should not include people with HIV who have adequate CD4 counts.
- Practically speaking, a hospital will choose the least expensive vaccine. A preference is doable if there is an alternative, but if there is not, the LAIV is preferable to wild type disease.
- Rather than screening for LAIV receipt, hospitals should screen for respiratory infections.
- As was seen with the smallpox vaccine recommendations, there is no site in a hospital that could not contain immunocompromised patients

*Personnel administering the vaccine.* This new paragraph cited the likelihood of environmental contamination with vaccine virus when the vaccine is administered. It recommends against any severely immunocompromised person from doing so, but allows that other persons at high risk of influenza complications may do so. Discussion noted that the previous definition of severely immunocompromised probably means the personnel would not be working. Also advised was to clarify either "at risk for complications" or "likely to be at risk for complications", because healthy people aged 50-to-64 are not so.

*Non-LAIV issues* involved:

- Implementation of the already ACIP-accepted full recommendation of vaccination for 6-23 month-olds.
- Possible extension of that to a full recommendation for vaccination of the household contacts of children aged 0-23 months, who are at substantially increased risk for influenza-related hospitalization. The committee agreed to this language.
- Clarification of vaccination recommended, optimally in the second or third trimester, for women who are pregnant at any time of the influenza season. This was felt to not be practical, since it would negate vaccinating women who are pregnant during the traditional vaccination season – a trimester before the actual influenza season occurs. The second/third trimesters were cited because the risk from influenza rises with time, but is not statistically significant until >14 weeks. However, the first trimester may carry a risk to the fetus from a high fever in the mother. Thimerosal in the vaccine is an issue in all trimesters, but the disease risk is higher. Ultimately, the committee agreed that, with the low immunization rates, including in pregnancy, the first sentence could stand alone, recommending vaccination for women pregnant during influenza season. This also would harmonize this recommendation with others (e.g., hepatitis B and TD) as regard pregnant women. The need for research in this area is critical, however, particularly with the incidence of spontaneous abortion in the first trimester, to reassure that there is no cause and effect with vaccination. The Workgroup could review the data of the 1976 swine flu campaign, when pregnant women were also vaccinated (although the production process differed then). The data to come from Dallas should also inform the discussion of first-trimester vaccination. The WHO Global Advisory Committee on Vaccine Safety also discussed this recently and decided that there was no evidence that influenza vaccine would pose a safety concern to either the woman or the fetus. In view of that, stopping at the end of the first sentence made

sense.

- Pediatric dosing schedule, for children not receiving two doses at <9 years. The text clarifies that a child aged <9 years who is receiving vaccine for the first time and does not receive a second dose of within that season, needs only one dose of vaccine administered the following season. Two doses are not required at that time.
- Additional language on adverse events among children after vaccination, stating that healthcare professionals should promptly report all clinically significant adverse events after influenza vaccination of children to the Vaccine Adverse Event Reporting System, even if it is not certain that the vaccine caused the event. The text also cites the IOM's recommendation to report potential neurological complications, despite no proven causal relationship between the vaccine and those outcomes in children. *Discussion* included a suggestion to move "of children" down to the following sentence about the IOM recommendation that neurological events in children be reported to VAERS. The first sentence should just recommend reporting all adverse events to VAERS. In fact, perhaps some explanation should accompany this, to avoid any misperception that ACIP has some safety concern.
- A stronger statement supporting influenza immunization of healthcare workers, stressing that this involves issues of the healthcare workers' safety as well as the patient's issue. This is a quality issue. It was thought that a "strongly recommended" would encourage institutions currently considering mandatory influenza vaccination.

**Sensitivity and Specificity of Self-Reported Vaccination Status**
Presenter: Dr. Zimmerman

The ACIP's General Recommendations do not accept self-report of childhood vaccines because of the related inaccuracies, but they are silent about influenza vaccine. Related data were presented from four different studies, two showing a 78%-97% sensitivity for reported receipt of the polysaccharide pneumococcal vaccine (PPV), and 92%-100% for influenza. Specificity ranged from 25%-72% for PPV. But he thought the 25% to be an anomaly and that it was more likely to be 49%-72%; and the 22%-98% for influenza was more likely to be 40%-98%. If self-report is accepted for PPV, and influenza report's sensitivity and specificity in adults is better than PPV, it should be formally as well as informally accepted in the General Recommendations.

*Discussion* included a request by Dr. Levin that Dr. Harper make the suggested changes in the document and present it to the committee on the following morning. Dr. Paradiso raised the Vaccine Information Sheet's (VIS) recommendation for vaccination from October-November. A statement will probably be needed in order to change behavior to take the vaccine after November. The vaccine was available early in 2003 (August/early September) but most people waited until October-November. He asked that the statement language make the point that people can be immunized at any point during the season. Dr. Siegel asked if the document's short infection control section commented on respiratory hygiene and cough etiquette. Dr. Harper agreed that this should be done, based on the trend in CDC recommendations in general across the board.

During the ensuing break, Dr. Deborah Wexler, of the Immunization Action Coalition, presented awards to Dr. Thomas Vernon and Dr. Walter Orenstein, both of whom were retiring from their

positions.

**Universal Influenza Vaccination**
Presenter: Dr. Keiji Fukuda, NCID

Overview: The Committee's opinion was asked about the need to discuss: 1) universal recommendations for influenza vaccines and 2) beginning the production of H5N1 vaccine; and if so, how much.

*Universal recommendations for influenza vaccines.* After the 1957 pandemic, the recommendations for influenza were designed to protect those at high risk of developing serious complications, including death, from influenza. This included those with high risk conditions and their close contacts, the latter to reduce transmission to them. Since the condition-based recommendations were not widely taken up, ACIP expanded its recommendation to all persons aged 50-to-64 years, in order to improve coverage in the high-risk groups of that age group. More recently, based on data indicating an increased risk for hospitalizations, ACIP recommended influenza vaccination for children aged 6-23 months of age. Since then, the risk of deaths and serious complications such as encephalopathy have been suspected to be higher than thought.

Universal vaccination may now be warranted, because:

- It could significantly improve the protection of individuals, as seen in the data presented at this meeting on children who develop severe complications including encephalopathy and death. However, these also occur in some children for whom vaccination would not currently be recommended. But the Montos study, followed more recently by the Reichert and Simonson studies, explored whether higher rates of vaccination would confer herd immunity or benefits of herd immunity, specifically to those who are more vulnerable (e.g., the elderly).
- Universal vaccine recommendations may improve vaccine coverage, now way below the recommended vaccination of ~185 million Americans. The rates among the elderly, in fact, have plateaued on average at ~66% and at ~33% in those aged <65.
- Universal vaccine recommendations could help significantly strengthen the vaccine supply system, since a larger market needs more vaccine from the manufacturers, and may attract more manufacturers into the marketplace.
- However, universal influenza vaccination may be affected by production of an H5 vaccine, which would add stress on manufacturing capacity, which could in turn affect pandemic vaccine preparedness.

Other issues include the unprecedented nature of such a change, in recommending a vaccine which changes in composition almost every year. And, even if it is agreed that this should be done, many complexities remain, such as ensuring that those at high risk continue to maintain their priority for vaccination, especially in the change-over period. And, aside from the risk of causing vaccine adverse events among people at lower risk from the natural disease, there is the issue of preventing any vaccine shortages when the ramp-up begins.

Dr. Fukuda proposed that the Influenza Workgroup convene in late summer or early fall and form subgroups to address and to research in some depth all the related issues. They would review and summarize the available data and bring that back to the full Committee for discussion. The Committee could be asked to vote on this issue in the fall of 2005 in preparation

for the following season. It probably could not be done any faster, and may be significantly later, depending on how the H5 influenza outbreaks evolve. If that escalates, "everything is off the table, at least in the near term," and CDC would address that fairly exclusively.

*Discussion* included:

- Dr. Plotkin called for concurrent consideration, with the issue of universal vaccination, of the production of vaccine in cell culture, since an egg allergy is a contraindication.
- Dr. Nichol wondered if ACIP should be clear that ultimately, it will recommend universal immunization for the prevention and control of influenza in all segments of the population. Dr. Paradiso agreed, unless this is not feasible or useful. This also is important to the manufacturers' projections of production one to five years hence.
- Dr. Womeodu raised the issue of patients who have health literacy issues and other problems which might impeded immunization (e.g., fear of vaccination risks). Particularly for such persons who are at high-risk but still refuse vaccination annually, documentation to read in the waiting room would not work. They would need videotapes, for example, to understand the importance of immunization.
- Dr. Katz agreed with Dr. Plotkin's comments, and added the need for a major public education program that the vaccine does not prevent the many influenza-like illnesses, but only one particular form of acute febrile respiratory illness. Otherwise, the public will think that the vaccine failed.
- Dr. Wexler encouraged the ACIP to pursue universal vaccination to move away from the complex current recommendations.
- Dr. Finger wondered if herd immunity to influenza had been demonstrated in any population. Dr. Fukuda said no, this is still theoretical on a population scale. The Montos study was done in a small town, and the Japanese data can be variably interpreted. The potential benefits of herd immunity are frequently raised and are one of the driving ideas for larger scale vaccination. But it is not comparable to measles, for example, where ~95% coverage would be needed to erase the influenza curve. Measles is much more infectious than is influenza. The Montos study estimated a need for ~80% coverage to achieve herd immunity, but no one knows whether vaccinating 40% of the entire country would significantly affect disease in other groups.
- Dr. Poland pointed out that influenza is the only currently vaccine-preventable disease left that everyone gets, and it is neither a benign nor minor illness.
- The Arnold and Reichert studies involved school children. A phase-in of the universal recommendation could begin by expanding the 6-23 month group to 6 months to 18 years
- Dr. Fedson suggested study of the experience of Ontario's three year-old universal immunization program, which may answer many of the questions raised here and that would inform policy in this country.
- Dr. Abramson commented that, since the vaccine is already recommended for ~60% of the U.S. population, a universal recommendation would not be a big change, and age-based recommendations have repeatedly been shown as more effective than those risk-based.
- Dr. Zimmerman agreed, summarizing the Workgroup's wish to expand the recommendation, based on the data of hospitalizations among children aged 2-5 years and the excess hospitalizations for those to age 23.
- Dr. Naus reported discussion of this issue two weeks earlier among the Canadian National Advisory Committee on Immunization. Currently, they encourage influenza

vaccination annually for healthy individuals, but they were evenly (and strongly) split on advancing that to a universal recommendation. Ontario does not yet have good evaluation data, at least in part due to the light influenza seasons of the last three years, which would prevent any meaningful assessment of morbidity and hospitalization differences from baseline. There may also be issues of access to data. The Ontario program was introduced to reduce pressure on emergency rooms, but that may not have occurred; they are pressed continually. So, even Canada has concern at insufficient information to make this extra step. Another downside considered was opportunity costs. Many jurisdictions immunize through public health, and if they immunize for three months of the year, other things will not get done. A teleconference in March is planned to discuss this further.

- Dr. Mendelman cited the mortality of the past season, despite the availability of four million doses of FluMist™, due to the absence of a recommendation. The company takes great risk in continuing to produce it with no recommendation, limited reimbursement without that, and the need to educate the 5-to-49 year-old population to go get it. At the least, an ACIP recommendation for its use to prevent influenza in children would go a long way to convincing parents and to work out the pricing costs for the public sector. If the market is secure, a public sector vaccine price can be established.

*H5 Influenza Issues.* Dr. Fukuda then raised the immediate question, when seed viruses are available, of whether the U.S. should produce influenza H5N1 vaccine. He described the outbreak of avian influenza in Asia, as well as an H7N7 outbreak in Pakistan which affected 4-5 million birds. The concurrent density of the H5N1 outbreaks and high density of poultry were mapped. The H5N1 outbreaks in Cambodia, Japan, Laos, South Korea, Indonesia, Vietnam, and Thailand are highly pathogenic, and have also been documented in several wild bird and animal species.

It is likely that hundreds of thousands of people there are directly exposed to diseased birds through culling operations, living on farms, direct dealing in live markets, etc. As of the previous day, 32 human H5N1 cases had been identified and 22 patients had died. Examination of human isolates showed their sensitivity to antiviral drugs to be resistant to the adamantanes used for prophylaxis or treatment, but they still are sensitive to Oseltamivir.

The two human cases of H5N1 that were the vectors of the 2003 Hong Kong outbreak were not an optimal antigenic match to the current viruses circulating in Vietnam, so even using that for vaccine production would not be helpful. This underscored the extreme need for surveillance to identify, collect, and characterize as many of these H5 viruses as possible.

Dr. Fukuda's opinion was that the elimination of H5N1, in terms of the epizootic in the short term, and probably the medium term, was very unlikely for several reasons: the epizootic is of unprecedented size, both in geography and numbers afflicted; the capacity to control it varies significantly country-by-country; the birds affected are not easily reached, as in large commercial bird operations, but are in backyard flocks; the viruses' circulation extends beyond poultry, as it did in 1997 in Hong Kong. It has infected several different species of wild birds in several different countries. This is an unfamiliar and huge phenomenon offering no information on how it developed or what factors underlie its spread.

Human influenza surveillance is poor or nonexistent in some of the countries affected. But CDC knows that regular human H3N2 viruses are circulating in Asia and are appearing with H5N1 in some hospitals. This increases the chance of an antigenic shift, either through reassortment or by infection of humans, and subsequent adaptation to humans through mutations.

The questions to be addressed included:

- How, where, and when did the epizootic start?
- More importantly, how did it spread?
- How can the legal and illegal (i.e., smuggling) movement of poultry between countries be followed? The viruses can persist indefinitely in the environment and can move on contaminated objects (e.g., vehicles, clothing).
- What is the role of large commercial concerns and backyard flocks in the epizootic, and what is the extent of spread? There are very few data on how many people are infected, or the numbers of poultry or even species involved, in many countries. There is concern about infections in zoo animals and that these avian viruses could spread to pigs, which have the receptor for both avian and human viruses.
- What are the implications of the fact that most of the current human cases have some association with diseased birds? Must there be direct touching and then autoinoculation, or is airborne transmission a danger? Why are children more affected than adults?
- When will sustained patterns of transmission emerge, suggesting that the virus can then spread through the population, beyond person-to-person transmission?
- What does “control” mean in Asia? Is it elimination, or reducing the disease to some low level of endemicity? That answer, and its feasibility, provides longer-term implications for what other people outside of that area need to be prepared for.

*Steps to take* include 1) culling, traditionally, but when should that stop, and when should repopulation begin? Many of these populations are marginally nourished, and eliminating the birds risks further malnutrition. Another option, 2) is H5 vaccination of birds. But while that is frequently associated with disease decreases, it leaves continued circulation and shedding of viruses among those birds. That could change an acute problem to a long-term chronic problem.

The U.S. will provide assistance to Asia, but cannot go much further. So now the question is, should the U.S. produce H5 vaccine? The *advantages* of doing so include: 1) that the risk of an H5 pandemic is higher than usual and it is a very dangerous virus and 2) the apparently small likelihood of controlling the epizootic in Asia in the short- and medium-term. Then, 3) stockpiled supplies of H5 vaccine could provide significant insurance if human-to-human transmission is identified and accelerates; and 4) responses before a crisis are better than the reverse.

The *disadvantages* include: 1) the uncertainty as to whether this will evolve into an H5 pandemic. It may not reassort well with human viruses, and 2) H5 vaccine produced could significantly impact the production and availability of regular, trivalent vaccine and could result in more serious illness.

A few options were outlined for the committee's discussion:

1. After identifying the appropriate viruses, produce small pilot lots of vaccine (e.g., 10,000-20,000 doses), and stop at that. That would provide experience with the vaccine and allow the conduct of immunogenicity and safety studies. But it would not indicate what kind of problems a large-scale production might involve.
2. Produce a more significant amount of vaccine (e.g., 1-2 million doses or more). This increases the "insurance," but concurrently raises the potential impact on the current vaccine supply.

*Discussion* included:

- The U.S. manufacturing experience with A viruses other than H3N2 and H1N1 includes the 1976 swine flu vaccine and other small lots (e.g., lots of H5 vaccine using an unusual process of a vector expressed protein).
- *About how long would it take to go from small pilot lots to 10-20 million, for example, if the pandemic hits?* The hope is to have a suitable vaccine candidate virus by March or April. Mr. Phil Hosbach, of Aventis Pasteur, said the difference between producing 1-2 versus 10-20 million doses is the impact on current trivalent influenza production. In a few weeks, a monovalent vaccine could move to 10-20 million doses, but normal trivalent vaccine production would suffer.
- *Are there any data on which to model antigenic change?* Some have worked to model the molecular evolution of influenza A viruses and some of the B viruses. CDC has worked closely with some of the modelers, but there is no large bank of previous data on which to base identification of antigenic sites that change significantly, to infer how the drift goes. For something like an H5, the answer is basically no. But present evidence of human-to-human transmission is not strong, outside of one small family cluster that may point to that possibility.
- *And the fear is that it will change its properties to spread readily from human-to-human?* Yes, if surveillance is insufficient to detect that while it is an early event, allowing it to escalate locally. Based on the SARS experience, this transmissible virus could quickly spread to several countries before a warning occurs.
- *Is the assumption that a vaccine that represents the hemagglutinin and the neuraminidase of the current virus will still be protective, even if the virus changes other genes that allow it to transmit readily?* Having no vaccine provides the least protection; having one antigenically different but still an H5 vaccine and somewhat related to the current viruses provides a better level of protection than none. But no one can predict if a vaccine made now will be effective against a future breakout.
- *Can the start of a pandemic be contained with a relatively small number of doses (e.g., 1-2 million doses), and what is the difference between small pilot lots and huge production?* A pilot lot could force decision makers to prioritize that vaccine (e.g., be given first to investigators or to ED medical staff). Dr. Rennels thought that, after the seed lot is accomplished, production is not the problem, but intellectual property transfer and liability protection for the manufacturer. And, since this vaccine will involve reverse genetics for the first time, there will be FDA issues with the clinical trials needed. All that will take time and money. It will require the government's economic push to lure the manufacturers through all those hoops, but that must be done to prepare for a pandemic. She supported proceeding with small pilot lots to resolve some of these problems.

- *Manufacturer response.* Mr. Hosbach stated that a pilot lot could possibly be done in a smaller product development facility, but the industrial-sized lots would have to be done in a regular industrial facility. That would then shut down the present 24/7 normal trivalent production. Dr. Clem Lewin, of Chiron Vaccines, agreed with that, and that Dr. Rennels had highlighted all the related issues. It is technically feasible, but there are liability, indemnification and regulatory pathway issues to be resolved before such production scale-up. Dr. Fred Ruben, of Aventis, wished for some information on how these outbreaks occurred. He asked if any sero surveys were done among the populations that have very close contact with live chickens to indicate if they were been primed with asymptomatic infection. That poses tremendous implications for vaccine immunogenicity, because priming in the H3 family would probably produce a booster response to a dose of vaccine, but not in a naive population like that of the U.S. Dr. Fukuda reported that there are no serologic studies from the current epizootic. But studies were done after the 1997 Hong Kong outbreak, where the population's seroprevalence to H5 was essentially zero. It was ~5% among the poultry cullers, but ~23% to another avian virus (perhaps H9).
- Dr. Fedson commented that the small pilot lots will answer important questions about serologic response when they are put into the vaccine trial units' studies (e.g., what should be the hemagglutinin content of an individual dose). An important question is whether or not an adjuvant (e.g., alum) could boost the immune response in a totally naive population and allow the antigen content to be reduced four-to-eight fold. If feasible in production, one of the viruses could be placed in the current trivalent vaccine if the H5 risk was found to be greater than the population risk of H1N1 disease. And, H5 vaccine that might be produced in multiple million dose lots could be expanded to 50 million doses of a similar H5N1, H1N1, with an added alum adjuvant. If the aim is to protect the American population, the production would have to go from 1-2 million up to enough to immunize 250 or 270 million people; nothing in between would make political sense. The question then would be, what happens to the rest of the world without this vaccine? The political dimensions of pandemic influenza are quite different than those of the HIV epidemic. With influenza, the vaccine needs of all of those other countries will have to be addressed simultaneously. And so, the international issues on reverse genetics, intellectual property, adjuvant use, etc., apply to all vaccine manufacturers in all countries. This must be addressed as a global issue, not one of the U.S. alone.

  Dr. Fukuda responded that some of the possibilities that make sense on paper would not do so in reality (e.g., make only H5 vaccine, not H1). Since the vaccine companies make vaccine components at risk, they could not now remove the H1; that vaccine has largely been produced already. And, while the adjuvant vaccine is a good idea, it also raises issues of how quickly approval could be obtained.
- Dr. Zimmerman asked if the problem was that other vaccine could not be made during production of the 1-2 million doses, or if contamination concern would shut down whole plants and restrict them to H5. Mr. Hosbach responded that they would shut down, run the H5N1 through, produce it, and then shut down again to clean up the facility.
- Dr. Katz commented that this vaccine would require a BSL-4 facility, not a normal production venue. He also knew that North Carolina monitors the state's large poultry and the pig production facilities, and they are studying poultry and swine workers. The resulting data could be helpful. They are also immunizing the turkeys against H5. Mr. Hosbach was unsure that maximum containment would be required. The type of containment needed would depend on how the seed virus is prepared.

- Dr. Nichol suggested quantifying the opportunity costs under various scenarios (e.g., from the small lots all the way through large production). Dr. Fukuda reported that underway, but the situation changes almost daily. The costs and available resources change depending how far into the season it is.
- Dr. Curlin thanked the CDC for bringing this before the Committee, which will ultimately make recommendations. The science and technology are already ongoing world-wide, including the biosafety requirements.
- Dr. Plotkin thought the answer to be clear. Two companies said that pilot lots would be made in pilot facilities, but larger lots will require production facilities. He supported making the pilot lots to inform what is unknown about introducing H5, and then testing it clinically. Since no one knows if an H5N1 vaccine will be needed in the future, to go beyond pilot lots would gamble the vaccine supply for current viruses.

**FDA Perspective on 2003-04 Influenza Vaccine Production**
Presenter: Dr. Norman Baylor

There are two TIV manufacturers licensed in the United States, one here and one in the U.K., as well as MedImmune's live attenuated influenza preparation, and support activities that go on throughout the year. To select the vaccine strain, FDA examines vaccine efficacy, which relates to its immunogenicity (potency) and its match to the circulating wild-type viruses. Antigenic drift is continuous for Influenza A and B viruses.

In 2002-03, the vaccine composition for 2002-2003 was A/New Caledonia for the H1N1 and a Hong Kong-like B strain, and an A/Moscow-like strain for the H3N2. Several questions are asked about the strain selections each year: the presence of new, drifted, or shifted influenza viruses; if these new viruses are spreading in people; if the current vaccines induce antibodies against the new viruses; and if the strains suitable for vaccines are available.

For the 2003-2004 season, the FDA's VRBPAC found that no new strains were present for influenza A/H1N1. The hemagglutinin (HA) in all strains were similar to the current vaccine strain which went back to 2002-2003. There also were no new strains for influenza B, the HA of most of the strains were similar to the current vaccine strain, and that of a few (<1% of the viruses) were similar to an older vaccine strain.

But the answer was yes for the H3N2. The HA of most of the strains were similar to the current vaccine strain, but ~10% of the HA was antigenically distinguishable from the previous season. Genetic changes in the signature amino acids suggested a potential emerging variant cluster. New variants, now termed A/Fujian-like, were spreading in Asia, Europe, and North America and were first identified in late January or in February of 2003. They were largely inhibited by the current vaccines, but some strains were poorly inhibited.

The timing was poor for suitable strains to be available for manufacture, focusing on the H3N2. They were identified too late, and there were no H3N2 variant egg isolates until April of 2003. And, as mentioned earlier by Dr. Cox, while there was a cell-culture base variant ready for the H3N2, the requirement of an egg isolate also was not available until April. The high growth reassortants for this strain were not available until June 2003.

So, based on the data on hand in March 2003, VRBPAC decided to recommend for the vaccine composition this year keeping the H1N1 with the New Caledonia strain and selecting a B/Hong

Kong-like strain for B, and an A/Panama for the H3N2. That allowed the vaccine preparations to proceed on schedule, making doses available in quantity similar to previous years' demand. The vaccine strains used gave very good yields, the manufacturing issues were well understood, and potency reagents were available, in part because the vaccine did not change for the 2003-2004 season.

But as the new variant H3N2 began to predominate, reports arrived of associated morbidity that would significantly increase demand for the vaccine. The vaccine's effectiveness to protect against the A/Fujian H3N2 became important. Effectiveness studies are ongoing and some of those studies were presented by CDC at this meeting.

For the coming 2004-2005 season, the global surveillance is ongoing, as are the avian H5N1 pilot lots discussions. The WHO made recommendations for the 2004-2005 season in February and the VRBPAC had recommended on the previous week. The H1N1 would remain focused on the New Caledonia strain; the H3N2, A/Fujian-like would mirror this year's. The B strain would be from a Yamagata lineage, perhaps the Shanghai rather than the Sichuan; that is to be decided at the March VRBPAC meeting.

So, the inactivated influenza vaccine changes annually according to current circulating viruses. The selection time lines are somewhat inflexible, but FDA believes them to already be streamlined to accommodate surveillance and the timing of influenza appearance and manufacturing.

There were no further questions or discussion, and the meeting adjourned at 5:55 p.m. and reconvened at 8:00 a.m. on the following morning.

**FEBRUARY 25, 2004**

**NVAC Discussion of Influenza**
Presenter: Dr. George Peter

Where the ACIP discusses the technical issues relative to immunization, the National Vaccine Advisory Committee (NVAC) discusses policy. Dr. George Peter, NVAC Chair, described their discussion of influenza issues at their February 3-4 meeting. They reviewed the lessons learned in the past season to be applied in the future; the current season's vaccine strain selection process and regulatory issues; public perceptions; compared the national child and adult immunization programs; public sector roles in adult and childhood influenza vaccination, the issues relevant to CMS, health plans and insurers, NIH vaccine research, and pandemic influenza preparedness.

An Influenza Vaccine Workgroup is being formed by NVAC to evaluate the strategies and capabilities to reduce the impact of influenza disease in the U.S. A preliminary report will be provided at the June meeting. Its objectives are as follow:

Objective 1: To make recommendations and propose feasible interventions to improve influenza prevention and to reduce the disease burden. The workgroup will question and consider new strategies, paradigms, infrastructures, and technologies, as well as incremental changes in the current program. Major issues to be addressed include 1) disease burden (accurate quantification, adequate VE measurement, surveillance needs); 2) vaccine (having those most appropriate or improving/developing them); 3) immunization recommendations (appropriateness

and effectiveness to reduce/prevent disease burden); 4) vaccine production (speeding development, assuring adequate production/supply); 5) vaccine acceptance and demand (enhancing that by the public and health professionals); and 6) adult immunization (adequacy of current private/public programs and enhancements of programmatic infrastructure).

Objective 2: To review and develop recommendations to improve the current U.S. influenza program by identifying programmatic strengths, weaknesses, gaps, limitations and barriers affecting the ability to prevent influenza and reduce disease burden.

Objective 3: To identify areas where additional information is needed.

The considerations include the Healthy People 2010 goals:

- 14-29B: Increase the proportion of noninstitutionalized adults who are vaccinated annually against influenza. Target: 90% influenza vaccine coverage by 2010.
- 1-9: Reduce hospitalization for persons 65+ through influenza vaccination. Target: reduction of admissions/10,000 population from 10.6 to 8.0.
- 14-24A: Increase the proportion of young children who receive all vaccines that have been recommended for universal administration for at least 5 years.

The Workgroup's Chair will be Dr. Charles Helms. The next steps will be to appoint the workgroup members. Consultation with different stakeholders, including ACIP, is very much desired.

Finally, Dr. Peter described NVAC's unanimous passage of a resolution recognizing the contributions of Dr. Walter A. Orenstein for his outstanding leadership to the NIP. During his term, he oversaw major developments and progress, which were detailed, including the growth of the NIP from a $40 million budget to >$1 billion. The ACIP committee and all present provided a standing ovation for Dr. Orenstein. Dr. Levin **moved that the ACIP adopt the NVAC statement on behalf of the ACIP.** The motion was seconded and **unanimously approved**. After citing his contributions to the WHO, the CDC, the NVAC and ACIP, the resolution read as follows:

> "Dr. Orenstein, a pediatrician, teacher, and leader, has been a tireless champion of immunizations and has had an extraordinary impact on the health if children, both in the United States and around the world. On the occasion of his retirement from CDC, the National Vaccine Advisory Committee acknowledges his countless contributions and thanks him for a job well done."

NIP's Dr. Steven Hadler also lauded Dr. Peter, who is leaving the NVAC Chair position. He summarized Dr. Peter's long and distinguished career on vaccine advisory committees at all levels, including within the AAP as its Red Book editor, as the NVAC liaison to the ACIP, and as NVAC chair. He affectionately termed Dr. Peter the "Cal Ripkin" of the immunization advisory group, who has contributed extraordinarily to the immunization of children. Universal applause was also awarded to Dr. Peter.

**Presentation by the National Foundation of Infectious Diseases**
Presenter: Dr. Kristin Nichol

The National Foundation of Infectious Diseases (NFID) released a "Call to Action" for influenza immunization among healthcare workers. It was developed with the representatives of 24 of the

nation's top immunization experts and organizations. It highlights the measures that must be taken to improve the rates of healthcare workers' immunization and to ensure employer commitment to patient care in the workplace. Healthcare workers have been indicated as sources/vectors of influenza transmission in the workplace, seriously affecting not only patient health but also the capacity in the healthcare system. The NFID document calls for ensured, convenient access to immunization and education of healthcare workers about the consequences of influenza to themselves and their patients, and their education about the safety and benefits of immunization. The NHIS data indicate influenza immunization rates among healthcare workers to be an inadequate rate of ~38%. All healthcare workers should function under the dictum of "first do no harm" and be immunized. The Call to Action will be followed by a more comprehensive summary of the roundtable that developed this document. More information is available at www.nfid.org.

*Discussion* included:

- Dr. Poland saw this as a leadership opportunity for ACIP as well as an integrity and trust issue. For ACIP to potentially recommend immunization of wide spectrum of population, and not recommend the highest possible protection of healthcare workers and patients would be counter intuitive. He suggested adding a sentence to ACIP's General Recommendations: "Eligible healthcare workers should be immunize against influenza annually. Ideally, this should be required and facilitated by the institution in which the healthcare worker works. This protects not only the healthcare workers but also their patients, and will reduce disease burden and transmission." A footnote would provide the NFID definition of healthcare workers.
- Dr. Siegel thought that the ACIP's and NFID's support would help in gaining the administration's encouragement. The Joint Commission on Hospitalization and Healthcare Accreditation were represented at the cited meeting. An analogy was made to hospital mandates to offer the hepatitis B vaccination. Dr. Abramson reported that OSHA cannot mandate that all hospitals require influenza immunization of healthcare workers, since data in the literature cannot prove that transmission is high enough. No one has led on this issue, but needs to, in order to get the field to adopt the practice. He asked if ACIP or NVAC should lead.
- Dr. Peter asked if such support could be in the influenza recommendation or a separate statement by the ACIP, or one partnered with HICPAC. The recommendation is currently buried in the ACIP statement, but a specifically entitled statement (e.g., "Influenza Immunization of Healthcare Workers") would be more effective. It could include demonstrably successful immunization strategies.
- Dr. Nichol said an expanded statement, as done by the "Call to Action" and the following monograph, could cite the many issues deserving of further exploration, such as current immunization rates, barriers, current knowledge about successful strategies, etc. The current recommendations may not have enough space to address all of them, but an extended discussion of this is warranted.
- Mr. Fred Rubin, of Aventis Pasteur, said that the Ontario program has data on hospital and nursing home employee immunizations. Mandating those reports doubled the rates. Ms. Marcy Jones, of the California Immunization Program, related that the status of healthcare workers as a vector in their family and community was the compelling argument in California.
- Dr. Baker agreed that ACIP should take the lead on this, but since few read the ACIP documents, the hospital infection control and prevention groups should be made aware of this and facilitate an implementation and education strategy.

- Dr. Neuzil expressed the ACP's support for this. Partner organizations will be important, but if ACIP takes ownership, its actions need to be decided. In addition to a strong statement, it should specifically track and advertise healthcare workers' immunization rates, as was done for measles immunization. Dr. Tan thought that the AMA would use the Call to Action as a tool to continue to educate its membership. The National Immunization Summit also distributed this to its ~60 participants and has committed to use this report as a ongoing tool.
- Dr. Wexler urged that not just a sentence, but a paragraph with a title, be inserted in the influenza statement to draw maximum attention to this.
- Dr. Siegel reported this to be on the next week's agenda for the HICPAC meeting. She expected that HICPAC would like to work jointly with ACIP on its implementation. HICPAC is also reviewing surveillance for healthcare associated infections, which relate to this. Dr. Levin will work with Dr. Siegel for language coordination.
- Ms. Betsy Frazer, RN, of the Alabama Quality Assurance Foundation stated that the QAF could add this Call to Action in its next scope of work to its 102 member hospitals. She called it a "no-brainer" to add this to their patient indicators.

Statement revisions offered, based on the previous discussion, were summarized by Dr. Poland:

> "Eligible healthcare workers should be immunized against influenza annually. Ideally, this should be required and facilitated by the healthcare facilities within which they work. This will protect healthcare workers, their patients, and communities, and will improve prevention and reduce disease burden. Healthcare worker influenza immunization rates should be regularly measured and reported."

Additional edits suggested were:

- Dr. Rennels: Drop "eligible" before "healthcare workers" to avoid the need for interpretation.
- Dr. Nichol: Replace "facilitated" with "provided."
- Dr. Zimmerman: Work in somewhere the healthcare worker's "ethical duty" to be immunized.
- Dr. Siegel: Add the term "patient safety" to ensure that this is incorporated into the organization's patient safety program. I.e., "... would improve prevention, patient safety, and reduce the disease burden."

**2004 LAIV Influenza Vaccine ACIP Recommendations Final Text**
Presenter: Dr. Scott Harper, NCID

The edits to the recommendation were presented as discussed previously, on: 1) the shedding and transmission of LAIV viruses, 2) LAIV use in healthcare workers and 3) healthcare personnel to administer LAIV, 4) the statement on use among pregnant women, 5) a strong recommendation for healthcare worker use (to be combined with this morning's language) and perhaps 6) expanding the recommendation. The full text discussed below is in Attachment #2.

1. *Shedding and person to person transmission of vaccine viruses*.

An introductory paragraph was read; the additions are redlined in the full edited text (see Attachment #2). *Discussion* included comment that this still implied that the transmission of vaccine virus is bad; in most cases it is not, and in fact is probably positive. That should be inserted somewhere (e.g., the end of the first paragraph or the end of the last, that "To date, transmission has not been associated with disease."). And rather than "occasionally"

transmitted, “rarely” be transmitted should be used.

1. *LAIV use in healthcare workers and close contacts of those severely immunosuppressed.* This section prompted active discussion. Much was resolved, except for choosing between the least restrictive guidance approach (e.g., relying on the institution’s understanding of a patient in a “protective environment”) or a more conservative one of listing conditions as examples of the spectrum of conditions of concern. The committee asked Dr. Harper to return with several options from which to select, since a vote was needed on this day on this time-sensitive issue. The discussion involved the following:

- Replacing “i.e.” with “e.g.” for the conditions cited.
- It was asked why the second paragraph was needed, and the different criteria from the regular infection control criteria practiced by all healthcare institutions’ staff caring for severely immunosuppressed patients. Attenuated virus can be shed asymptomatically; perhaps the titer data will show that the amount of virus shed corresponds to symptoms. Nonetheless, there was a feeling that severe restrictions should not be imposed when persons with wild-type infection could come in and pose greater risk.
- Grammatically, change terminology to “patients with diabetes,” for example, etc., rather than diabetics, asthmatics, etc.
- No one should be allowed into neonatal ICUs; every part of the preterm infant body system is as extremely deficient as that of a bone marrow transplant. Wild-type illness from anyone, healthcare workers or families, must be excluded from the nurseries.
- It was noted that many patients fall between the conditions cited and, for example, HIV infection, which itself has a huge spectrum of immunocompromised status. Perhaps rather than “low risk”, they should be in an intermediate category. For MMR vaccine, “severely compromised” is considered at a CD4 count <200. An AIDS patient with a good CD4 count cannot be compared to a preterm infant.
- It could be that this virus is so attenuated it will never affect anyone, but a conservative approach is wise. Other agencies have been much stronger about keeping vulnerable patients isolated for protection. More information was expected to be available in 4-5 months that could change these rules.
- The Influenza Workgroup chose an extreme patient example (bone marrow transplant), who are kept even from exposure to normal environmental spores. That is different from an end-stage disease patient still out in the community.
- The relative risk has to be discussed; most hospitals have 15% shortages of respiratory therapists. Removing people from patient care is a risk that has to be weighed against the theoretical risk. Every exception should not be listed; the two extremes given would suffice, and allowing the hospitals decide their course of action. There is no way to avoid the inevitable questions of interpretation.
- One suggestion was to be explicit about those so severely immunocompromised as to be in isolation to protect against all infections. The data should be highlighted that, when transmitted, the attenuated virus did not revert. The most understandable recommendation may be to cite as an example any patient who must be under strict isolation (e.g., a bone marrow or neonatal patient).
- Dr. Neal Halsey thought the text too extreme and likely to inhibit healthcare workers from ever receiving this vaccine. If effected, it would be hard to go back later. He suggested moving the 7-day furlough from the second paragraph to the first, to “healthcare workers with close contact with severely immunocompromised persons within 7 days”, and dropping HIV (as done with measles, mumps and varicella vaccines) to allow healthcare workers to have contact with those patients. Virtually all healthcare

workers in all institutions have regular contact with HIV. Dr. Katz reminded the committee that the standard CD4 count of 200 was based on only one patient who developed giant cell pneumonia a year after getting MMR. No other data indicate that those live vaccines damaged any other HIV patients.

- Dr. Siegel commented that, the more people with specific interests who read this, the more problems will be found. There is only one group of patients for whom a protective environment is recommended, the patients. Visitors with any sign of viral or respiratory infection should be prohibited hospital-wide, especially in a pediatric institution. She felt that, the less said, the better, and letting the hospitals decide. Dr. Baker agreed. She suggested adding into the first paragraph, "severely immunocompromised patients (i.e., patients with hematopoietic or severe combined immunodeficiency) for the next 7 days" and then deleting the first sentence of the second paragraph and addressing hospital visitors there.
- Dr. Paradiso asked if a better definition of "contact" was needed (e.g., "unprotected contact"), noting that there are ways to prevent infection spread other than staying away for 7 days.
- Dr. Cochi raised one theme not captured from the previous day's discussions, the issue of measuring vaccine effectiveness. The availability of that this year when the season was at its peak was very helpful. Since it involves resource issues, ACIP support of this as a priority would be very helpful, especially as the move toward expanded recommendations continues. Dr. Levin suggested this be inserted at the end in the General Statements category.
- A better sense of the committee was needed on whether or not to include patients such as those with asthma, diabetes, etc., who are at the other end of the immunity spectrum. This area could require even more clarity and the current list is very incomplete (e.g,. not mentioning cancer patients on chemotherapy or asthma patients on steroids).
- The issue of contact could be another loophole. To address the ability of masking and hand hygiene to eliminate close contact, Dr. Siegel suggested inserting, "General principles of source containment, such as hand hygiene, covering a cough/sneeze, would also interrupt transmission of vaccine virus, as it does with live virus". The problem there is that infection control staff already have trouble getting people to wear masks in even more obvious cases.
- Dr. Fukuda suggested including common examples of what the recommendation is *not* concerned about, such as asthmatics taking steroids. Dr. Cathleen Coalingh agreed to the need to distinguish that there are areas of concern and not of concern, without necessarily enumerating everything. Dr. Marcuse suggested a general statement such as ". . . but not most patients with mild or moderate immunosuppression."
- Dr. Abramson moved (to no second), to provide the example at the other end of the spectrum, "diabetics, patients with asthma taking steroids, or patients with HIV."
- The basic question was defined as whether the institution allows the patient to be exposed to other respiratory viruses or illnesses. If yes, they can be exposed to the vaccine; if no, they are already isolated and protected already. But "e.g., cancer patients on chemotherapy" could be added to set a specific bar.
- Dr. Neuzil agreed that immunocompromised patients are all over a hospital. She referred to the HICPAC/infection control term of "protective environment" for the narrow group defined by Dr. Siegel and suggested "close contact with severely immunosuppressed persons for whom a protective environment is indicated (e.g., [cite conditions] patients with hematopoietic cell transplants)". That would easily define the intent for infection control staff.

- Dr. Salisbury said that the issue is the patient, not the vaccinee. He would not specify the condition, but the risk which necessitates a protective care environment for the patient. Those patients should not be exposed to individuals (healthcare workers or visitors) vaccinated within the last 7 days. No such restrictions are necessary for patients whose conditions do not require protective environment care.
- Dr. Gilsdorf supported the suggestion to group severely immunocompromised patients, categorizing the risk as mild or moderate, and letting the hospitals decide into which category the patient falls.

3. *Healthcare personnel to administer LAIV*

This was addressed in a paragraph (see Attachment #2). *Discussion* included:

- Including terminology such as "low-level transient environmental contamination", or dropping "contamination" entirely, was discussed. Alternatives suggested included "Vaccine may be transiently isolated in the immediate environment where it is being administered". Clarity about whether a separate room is or is not necessary was suggested. Other live virus vaccines, such as varicella, do not require a separate room, but they are injected, not given as an aerosol spray that could spill into the environment, or the administrators could get the spray on their fingers and self-inoculate.
- Dr. Poland suggested saying "the risk from the environment is unknown and to date undocumented."
- Dr. Zimmerman suggested deleting the first two sentences and beginning with "Severely immunocompromised persons should not administer LAIV", but defining those persons as those hospitalized in a protective environment; no one at all should be listed. Dr. Siegel suggested citing a "theoretical risk of environmental contamination to the provider".
- It was agreed to delete sentences 1 and 2 and then to move sentence 3 ("Severely immunosuppressed persons should not administer...") to the end of the paragraph. The next sentence could indicate that, while "Other persons at high risk of influenza complications may administer LAIV," obviously, ill people cannot do so.

4. *Vaccination of pregnant women*

In this section, the first paragraph addressing influenza morbidity in pregnant women was unchanged. Paragraph 2 added text recommending vaccination of women who would be pregnant during the influenza season. Paragraph 3, addressing thimerosal, was unchanged.

4. *Strong recommendation for health care worker and others in close contact with those at high risk.*

This paragraph remained the same as it had been, except to add at the end that vaccination of such workers is "strongly" recommended. *Discussion* included consensus to replace, at the end of the paragraph "of health-care personnel and others" with "those", and to insert the three sentences summarized by Dr. Poland after Dr. Nichol's presentation (see page 41).

4. *Pediatric dosing scheduled* was clarified.

4. *Expanding the recommendations for the use of inactivated LAIV*. Text was added to paragraph 1 indicating the potential expansion of indications for influenza vaccination.

*Discussion* included:

- Dr. Cochi reiterated his suggestion of adding a statement early in the document about the

need for prospective VE measurement, such as "There will be a prospective program to continually assess the effectiveness of influenza vaccine."

- Dr. Salisbury thought the last sentence to muddle policy and strategy. He suggested changing it to: "... toward the goal of further control of influenza. The strategy may be to expand influenza vaccination. " Dr. Nichol agreed that the goal and the potential strategy should be acknowledged and suggested the following for the last sentence: ". . . goal of enhancing the prevention and control of influenza through examination of strategies such as broader indications for the use of influenza vaccine, including consideration of universal immunization", whether or not the ACIP is ready to promote that at this time.
- Dr. Jane Seward noted that the distinction of "strongly recommended" versus "recommended" is not present in any other ACIP recommendation. She asked if that should be paralleled in MMR and varicella statements, or for all vaccines in general, or in the HICPAC recommendations. Dr. Levin agreed that this could be problematic in creating another category
- Dr. Poland thought that this should be different, to highlight the magnitude of the problem. He suggested moving it up to the introduction as well. Dr. Birkhead agreed.
- Mr. Hosbach advised the changing of "indications", which is in the FDA's domain, to "recommendations", which are ACIP's.
- Dr. Abramson advocated being honest with the public about the final desired strategy of universal vaccination of all ages, whether implemented or not at this time. Dr. Levin was unsure that should be said now as a commitment.

In *miscellaneous edits,* Dr. Coelingh noted that the title should be "Expanding Recommendations for Using Inactivated Influenza Vaccine**s**", to apply to both live and attenuated vaccine. Dr. Paradiso also suggested replacing "indicated" with "recommended: since it already is indicated. Dr. Traenor requested insertion of a paragraph on strategies to improve vaccination rates.

There was also some discussion of the need for informed consent, but " . . . not *written* informed consent in the provision of influenza vaccine" to remove this as a barrier to increasing immunization rates. There is no federal regulation for informed consent, even for children in the VFC program. Dr. Evans confirmed that when the vaccine is covered by the National Vaccine Injury Compensation Program, a vaccine information sheet will be required. Written informed consent is required by some states. Dr. Harper agreed to insert that language in the most appropriate place. Dr. Mootrey noted that no other vaccine statements have any text about informed consent.

**Review of the Childhood Immunization Schedule**
Presenter: Dr. Gregory Wallace
Vote/Approval

The July-December, 2004, Childhood Immunization Schedule was presented by Dr. Gregory Wallace. The schedule showed the recommendation for influenza vaccination of children aged 6-23 months in the footnote text (in red) and graphically. The footnote referenced the April *MMWR* in which it could be published. The issue of including healthcare workers and their contacts in the recommendation was not highlighted, but they could be added to the present footnote listing people other than those cited in the General Recommendations (i.e., those at high risk, household members). Given all the changes made at this meeting, Dr. Wallace suggested waiting and publishing this schedule simultaneously with the influenza recommendation. He will work with Dr. Harper to ensure that the two documents are consistent. As usual, following

the ACIP's approval, the schedule will be sent to the AAP and AAFP for their approval.

Dr. Zimmerman **moved to approve the 2004 childhood immunization schedule** and the motion was seconded by Dr. Abramsom.

**Vote**

Since the vote was on the general schedule and not specific vaccines, conflicts of interest did not apply.

**In favor:** Levin, Zimmerman, Womeodu, Traenor, Salamone, Marcuse, Gilsdorf, Finger, Deseda, Campbell, Birkhead, Allos and Abramson
**Opposed:** None
**Absent:** Poland

**The vote passed.**

## SMALLPOX SESSION

**Smallpox Vaccine Safety Workgroup (SVS WG) Report**
Presenter: Dr. John Neff, NIP

Overview: Vaccination programs' status; sentinel case review; workgroup on dermatological aspects; pregnancy registry status; summary/conclusions, future directions.

Dr. Neff and Dr. Birkhead are co-Chairs of this committee, whose expertise covers public health, pediatrics, internal medicine, infectious disease epidemiology, cardiology, dermatology, and smallpox/vaccinia. The SVS WG's members represent the ACIP and the Armed Forces Epidemiological Board (AFEB), CDC, FDA, HRSA, and Wyeth.

The workgroup began telephone conferences in late January 2003 and has met almost weekly. Its mission is to: 1) Evaluate data on vaccine safety, and the vaccine safety monitoring and treatment system of the DHHS and Department of Defense (DoD) Smallpox Vaccination Programs, and 2) monitor the safety data of use of vaccinia immune globulin (VIG -- used once to date) and cidofovir (not used to date) for any individual under the IND protocol for the CDC smallpox vaccination programs.

An emergency meeting was held in March 2003 to discuss several deaths associated with myocardial ischemia found among vaccine recipients. Subsequently, the ACIP recommended not to vaccinate persons with known cardiac disease or >3 risk factors. At the June 2003 ACIP meeting, the SVS WG reported on the ischemic cardiac events and inflammatory cardiac events. They found that there is biological plausibility that a causal relationship exists between smallpox vaccination and ischemic cardiac events, but the data are inadequate to definitively accept or reject that relationship. Also noted was that the DoD data also supported a significantly higher risk for myocarditis after smallpox vaccination, suggesting a causal association between inflammatory heart disease and vaccination.

At the third meeting in October 2003, the Workgroup discussed the feasibility of initiating studies to search for adventitious agents in the DryVax vaccine (deciding that such studies

would be too open-ended and expensive to pursue); presented the sentinel case review process (a series of committees' independent judgment of conditions with CDC input), discussed contact vaccinia occurring outside the healthcare environment, and the status of the pregnancy registry.

*Status of Smallpox Vaccination Programs (SVP*)
As of February 9, 2004, DOD had screened 665,000 personnel and vaccinated 581,000, of whom 71% were primary vaccinees and 29% were revaccinees; 88% were male and 12% female, with a median age of 27 years. As of February 13, 2004, the DHHS SVP had vaccinated 40,000 public health and healthcare response team members, of whom 36% were primary vaccinees and 64% were revaccinees. The same proportions as DOD were male to female, but the median age was 49. Vaccinations in both programs have slowed, DOD's because it is now vaccinating mainly new recruits and DHHS' due to lessening interest and volunteers. The implications of this and the appropriate response both bear discussion.

*Adverse events* reported included no nosocomial transmissions. The screening has prevented most of the preventable adverse events. There have been no cases of eczema vaccinatum, progressive vaccinia, or fetal vaccinia. There were two cases of tertiary transmission (to family members, by vaccinees paying less attention to the dressing than taken at work) and 28 secondary and two tertiary cases in the DOD program. There have been no contact transmission cases in the DHHS program. In auto-inoculations, there have been 52 and 20 non-ocular cases, respectively, in the DOD and DHHS programs, and 11 and 3, respectively, ocular cases. In non-preventable events, the DOD program had 28 suspected and 8 probable cases of generalized vaccinia, and DHHS had 8 probable and one confirmed. In both programs, all cases were mild with no sequelae. Both programs had one case each of post-vaccination encephalitis, both of which were atypical and required no long-term follow up.

So, the good news was that the programs' education and screening succeeded in avoiding the preventable adverse event. The unanticipated events that occurred included:

- Myo/pericarditis in both programs (72 DOD [68 probable, 4 confirmed], and 21 [16 suspected, 5 probable -- perhaps all revaccinees, in the DHHS program).
- Dilated cardiomyopathy, 3 cases in each program, all among revaccinees and all within 1-5 months after vaccination.

Ten fatal events were reported to VAERS:

- Five cardiac ischemic events in spring of 2003, not included in the sentinel review. The available data do not support a causal association, but the possibility cannot be excluded.
- One case of a lupus-like illness, also counted as a myo/pericarditis case and included in the CDC sentinel review. The weight of evidence favors but is not definitive about a causal response to the immunization.
- Two cases were rejected for a causal relationship (hypothermia and leukemia).

*Sentinel Case Review Process Status*. A report was released on November 7, 2003, on two previously *unreviewed deaths*. The autopsy attributed one cause of death to pulmonary emboli and the other to an illicit drug overdose, neither felt to be associated with the vaccine or to each other. A review of four cases of chest pain/dyspnea/fever syndrome (also reported 11/7/03), one fatal, found that the cases did not present a pattern that justified recognition of a new possibly vaccine-associated clinical syndrome apart from the inflammatory syndrome already recognized as myo/pericarditis. In one case, the consensus decision was that the evidence favored rejection of a causal relationship; the second had a split decision, with two reviewers favoring rejection of

a causal association but the third reviewer unwilling to exclude a causal association. The third and fourth cases' evidence was inadequate to accept or reject a causal association with smallpox vaccination specifically.

Of the five dilated cardiomyopathy (DCM) cases reported on February 2, 2004, it was concluded that all five patients had a common syndrome, DCM, but the evidence was inadequate to accept or reject a definitive causal association. Nonetheless, a possible causal association was deemed worthy of further study. Basically, there were no good background data to which these cases could be compared. Further epidemiologic study would be needed to support this possible association, especially if the program is to be continued.

Of the 20 *dermatological* cases, most vesicular lesions were found to be hypersensitivity reactions. Generalized vaccinia was found to be very rare; only one case was so identified. Because it is greatly over-diagnosed, the definition should be re-reviewed by physicians in view of the new technologies available (i.e., diagnosis no longer based on vesicular lesions).

No potential cases of *neurological adverse events* have been yet identified as requiring sentinel case review.

The *pregnancy registry* includes 190 women of 94,218 vaccinated. The anticipated rate of exposed pregnancies in the absence of screening and education was 8–12 per 1,000 vaccinated, but a rate of only 2 exposed pregnancies per 1,000 vaccinated was found. Most (65%) were vaccinated pre- or post-conception, when pregnancy tests would not have detected it. To date, 58% of these women have delivered. The rates of spontaneous abortions and ectopic pregnancies were no higher than expected for the women's age and risk history; there was no vaccinia identified in four infants available for testing, nor any fetal vaccinia reported to date.

The SVS WG will continue to meet to evaluate ongoing vaccination programs and to monitor cardiac events and the outcome of the pregnancy registry. They will report as necessary to the ACIP and AFEB and will conduct sentinel reviews and other activities as indicated.

*Discussion* included:

- Dr. Strikas thanked the workgroup for their great help in monitoring the adverse events. He reported a slight upward turn in the DHHS program in the last couple of months (~2000 vaccinated) and the military continues to vaccinate. The SVP has been merged into the overall national response program.
- The programs' milestones have evolved over time and their activities. The DHHS is developing indicators to be implemented in states this year.
- Dr. Bob Chen reported that the rate of dilated cardiomyopathies in the general unvaccinated (for smallpox) population is being reviewed in the Vaccine Safety Datalink (VSD), and should be ready for report in the next year. He also congratulated the SVS WG for piloting a new analytical technique in these case review approaches. He hoped this will also be done with routine immunizations by the Clinical Immunization Safety Centers.
- Dr. Stan Plotkin recalled that the initial ACIP recommendation was to have primary response teams available in critical venues, but the program then slid toward more a generalized civilian population. He was unclear what proportion of the 40,000 vaccinees came under the first or second category and asked the status of preparedness for a smallpox attack. Dr. Strikas responded that the DHHS is "getting there," with 14,000

now trained as vaccinators in case of an event. There have been exercises and they continue. The continuing calls about rash illness cases in the military or civilian sector has shown a continuing need for training and education regarding the rash illness algorithm.

- Dr. Birkhead reported New York's definition of preparedness for smallpox in terms other than just the number vaccinated. Most of New York state's hospitals have ≥1 person vaccinated. While this is not the number initially envisioned, they also have people trained to do other things that were not initially a focus (e.g., what to do after recognition of the first case).
- Dr. Levin noted, the in the definition of dilated cardiomyopathy, the symptoms appeared 1-5 months after *re*-vaccination, not "vaccination".

**Considerations in Timing Smallpox Revaccination for Response Teams**
Presenter: Dr. Linda Quick, NIP
**Vote**

Overview: Issues around the interval timing of smallpox vaccine administration, specifically to smallpox response team members, for a vote on this day.
.
The smallpox vaccine was developed prior to efficacy studies of administration intervals and before valid lab measures of protective immunity. For those reasons, questions remained on how often public health, clinician and laboratorian smallpox response teams should receive the vaccinia vaccine for protection against the disease. Vaccination policy was based on the risk of exposure (endemic/non-endemic countries), epidemiologic studies, the adverse events seen, and the known success of an eradication strategy.

*Literature.* The European smallpox vaccination experience from 1950-1971 demonstrated that the fatality rate increased significantly at ten years after vaccination. Mortality data from the early Liverpool vaccination program (1900-02, In: Cohen J., *Science* 2001;294:985) showed a decrease in the immunity of vaccinated infants by age 14 years; the first deaths occurred from age 15 on.

*Policy considerations* for the present day include vaccine availability (good) and its use as an "out the door" (vaccinating response team members immediately before leaving to investigate) vaccination in the event of a confirmed outbreak or a suspicious event. But response teams are of two types: those who routinely answer rash-illness reports (public health and clinicians) and those only responding to an outbreak.

The implications of adverse events at 3-, 5- and 10-years were explored in CDC's 10-state survey of smallpox vaccination complications by Neff et al. This showed that revaccinees have ten times fewer adverse events than primary vaccinees. The screening done in the current program has been demonstrably effective, but revaccinees still showed cardiac events at a rate of 1.71 per 10,000 vaccinees. While the national and state surveys of revaccinees in 1968 and expert opinion supported the idea that the more often one gets vaccinated the less likelihood of expected adverse events, the frequency of vaccination relative to VE and risk of myo/pericarditis adverse events remained at question.

*Recommendations.* In 1966, the ACIP stated that "... vaccination with fully potent vaccine confers a high level of protection for at least three years and provides substantial but waning

immunity for 10 years or more. Protection against a fatal outcome of the disease appears to extend over a longer period, perhaps for decades." The WHO divided its guidance between endemic and non-endemic areas: For the non-endemic area, they found it ",,, desirable to maintain in the general population a level of immunity high enough to minimize the risk of serious complications when revaccination is required. Revaccination at 5-10 year intervals will generally serve to maintain adequate immunity." In endemic areas, they advised revaccination of the general population every 3-5 years. Over time, the recommendations grew: for annual vaccination of lab workers (ACIP, 1978); for animal care workers, every 3 years (CDC/NIH lab guidelines, 1984), for healthcare workers involved in clinical trials of non-variola virus vaccine, every 10 years (CDC, 1991). The CDC/NIH lab biosafety guidelines again were updated in 1993 to recommend revaccination every 10 years. Then, in 2001, the ACIP advised consideration of revaccination every 3 years for those working with the more virulent orthopox viruses (e.g. monkey pox), and every 10 years for others (e.g., cowpox, vaccinia).

Risk exposure assessment is key to the vaccination decision, and in the U.S., the earliest possible revaccination of team members would be in 2 years. To facilitate the ACIP's discussion on this day, several revaccination options were offered:

1. Vaccinate all response team members every 10 years and out the door (OTD).
   Advantages: Maintained immunity supported by an "out the door" booster dose.
   Disadvantage: Immunity wanes at ten years.
2. Vaccinate all team members every three years, and "out the door", if feasible.
   Advantages: Ensures good immunity for all response team members, and fewer historic adverse events than for primary vaccinees.
   Disadvantages: Unclear risk of myo/pericarditis with multiple vaccine exposures.
3. Vaccinate high-risk groups every three years, and low-risk groups every ten years and "out the door".
   Advantages: Ensures that those at highest exposure risk are at highest protection level while lower-risk teammates are protected, but at a lower level.
   Disadvantages: Fewer response team members with high immunity in case of an outbreak; potential confusion from differential revaccination recommendations.

*Discussion* included:

- Dr. Neff thought it possible that people who had a single vaccination could be revaccinated at three years, and then every ten years thereafter, but hard data to support that are lacking.
- *How are high- and low risk being categorized?* The high-risk group is those who investigate cases of fever and rash illness (e.g., dermatologists, infectious disease doctors). Mortuary staff have not yet been considered in this program.
- Dr. Lane expressed concern about arbitrarily distinguishing between high- and low risk, a status he expected to be blurred at the local level. In an emergency, no state or local health officer should need to distinguish the number of vaccinations on their team. He preferred a universal category and vaccination every three years.
  He also pointed out the difference between markers of immune memory and immunity as understood by the public (i.e., that one would not catch the disease). Date show that both cellular immunity and markers of humoral

immunity can last 20-30 years, and a Japanese study has shown immunity for as long as 50 years after three doses. But that does not ensure absolute protection from getting disease. Anecdotal data show no smallpox in persons vaccinated twice, but there are no denominator data for that. Epidemiologic evidence shows that mild smallpox can result after at least a primary vaccination. The etiology of the myo/pericarditis is not known, but is assumed to be somewhat similar to post-vaccinial encephalitis. The revaccinees who contracted this were vaccinated long ago, not 3-10 years ago, and may have lost too much immunologic memory. But people vaccinated 3-5 years ago have essentially no risk of post-vaccinial encephalitis.

- The much larger DOD data set showed a revaccinee myo/pericarditis incidence at 0.2 per 10,000 versus 1.7 per 10,000 primary vaccinees.
- Dr. Birkhead advocated for guidance as simple as possible and not dividing by risk. "Out the door" vaccination will not be logistically difficult, since the field is preparing for vaccination of many exposed individuals quickly. He supported Option 1.
- *In the event of vaccination six months ago or a year earlier, is an "out the door" revaccination needed? What is the appropriate threshold, considering the vaccine's risk?* Dr. Lane termed vaccinia "a great vaccine against smallpox." He would vaccinate everyone who would interact with actual or even suspected smallpox patients. There is essentially no risk from recent (6-12 months earlier) vaccination. He also expected that the revaccinations would be done with ACAM2000, whose data sets indicate it to be a gentler vaccinia virus than DryVax.
- *So, with two immunizations, minor subsequent disease is less likely, as in the past? How about people being revaccinated after three years and then every ten years thereafter, plus an "out the door" vaccination?* Dr. Lane foresaw no biologic problems with that. Vaccinating every three years would also retain the currently small cadre of trained smallpox vaccinations.
- Dr. Neff agreed with Dr. Lane that more frequent revaccinations make adverse events from the vaccinations much less likely. But he added one caveat: there are two types of adverse events, from direct viral replication and from hypersensitivity phenomena. The latter probably causes the myo/pericarditis, skin reactions, and post-vaccine encephalitis. Anyone developing such a primary vaccination should be selected out.
- Dr. Katz agreed, noting that all the current experience is based on the old calf lymph vaccine. Before ten years, the ACAM tissue-cultured vaccine and new studies on clinical reactivity will be in hand, as may a modified vaccinia Ankara vaccine.
- The sense of the urgency or risk has dropped since previous recommendations. Dr. Zimmerman wished to wait in order to base the revaccination interval recommendation on the ACAM vaccine reaction rates. The vaccinated civilian cadre of vaccinators will not face revaccination until 2006, and new and potentially very important data could emerge in 2005 when the FDA application is submitted. However, Dr. Chapman related that CDC's ~600 potential responders were vaccinated in fall 2001, so their revaccination will be in the fall of this year. Most were revaccinees.
- Dr. Marcuse listed the unknowns of most concern in revaccinees: hypersensitivity myocardia, heart and brain reactions; the unknown safety profile of the new

vaccine; and the risk of exposure.

- Regardless of the risk assessment, it was commented, it is important to maintain a cadre of vaccine administrators, so perhaps they should be the first group addressed by recommendations. In some cases, the vaccinators will be the first vaccinated (e.g., in New York state).
- Dr. Strikas agreed with Dr. Zimmerman, and expected little new data to come from the ACAM 2000 Phase III licensure trials (or, Dr. Poland noted, the VaxGen trial). They will vaccinate 6,500 people and the incidence of myo/pericarditis is one in 10,000. In view of that and the paucity of much new information since 1966, , Dr. Treanor suggested retaining the 1966 recommendation of revaccination every three years. However, Dr. Neff thought that even the small trial numbers would provide more information on hypersensitivity reactions to the ACAM vaccine. A drop in the incidence of 1:100 child/adult vaccines with Dryvax will provide indirect safety evidence for ACAM.
- Dr. Abramson asked the protection rate from one "out the door" vaccination, even if it is 1-2 days after exposure. Dr. Lane reported expert opinion contributed to a Delphi analysis at CDC which produced consensus that vaccination within four days of exposure was protective. Modern laboratory data confirm that there should be rapid, higher and more solid protection then after a primary vaccination, from the anamnestic response in both humoral and cellular immunity from an "out the door" revaccination. The major reason for a booster at "X" interval is for protection against the vaccinia's spreading on its own, rather than against smallpox. That is better conveyed after three years than ten, even with the vaccine risk.
- Dr. Birkhead added his expectation that most areas' plans for the public health response teams include the wearing of personal protection equipment (e.g., N95 masks).

Dr. Levin summarized that Option #3, with the different risk categories, had been dropped. In view of Dr. Lane's comment, he withdrew his own suggestion of another option of a three-year interval after the initial vaccination and then ten years afterwards. He asked the committee's opinion. Dr. Abramson **moved to table the proposal pending the later data** and was seconded by Dr. Poland.

**Vote** :

| | |
|---|---|
| **In favor:** | Zimmerman, Womeodu, Salamone, Poland, Marcuse, Gilsdorf, Deseda, Campbell, Birkhead, Allos, Abramson, Levin. |
| **Opposed:** | Treanor, Finger. |
| Abstained. | None |

**The motion passed.**

Dr. Poland hoped to hear from the new vaccines' manufacturers to present their data when released (~1 year hence) and continued information on these complications and their pathogens. Dr. Plotkin hoped that the vaccinees would be followed and tested for antibodies and cellular immune responses. While no one knows at what level antibody is protective or provides cell-mediated immunity, the absence of that would surely not be a good sign and would inform ACIP's decision. Dr. Curlin reported that the Dryvax dilution trials, begun three years earlier, had analyzed the data of the 36-month blood samples taken from ~50-60 people (20 with each dilution). He was not sure that any long-term immunologic assays were planned, but they could be included upon such as recommendation.

## MENINGOCOCCAL DISEASE SESSION

### Introduction

Presenter: Dr. Nancy Rosenstein, NCID

The currently licensed, quadravalent, meningococcal polysaccharide vaccine has poor immunogenicity among young children, short duration of protection, and lack of herd immunity. Due to that, and the absence of an ACIP recommendation of routine vaccination, the control of endemic meningococcal disease has been poor. However, the first quadravalent meningococcal conjugate vaccine, due on the market by the first quarter of 2005, is indicated for adolescents and adults. Development of other meningococcal conjugate vaccines is rapid.

### U.S. Epidemiology of Meningococcal Disease

Presenter: Dr. Kirk Winger, EIS Officer, Meningitis and Special Pathogens branch.

Overview: Recent trends in meningococcal disease in the United States.

Meningococcal disease appears infrequently in the U.S., but a single case invites media attention and can cause panic in a community. It is fatal in 9-12% of cases, and 11-19% of survivors have sequelae, such as hearing loss, neurologic disability or loss of limbs. Before antimicrobials and better healthcare, the case fatality rate (e.g., in the 1920s) was 70%. From 1991-2002, it was 10% for meningitis and 14% for bacteremia. However, the CDC's Active Bacterial Core Surveillance System (ABCs) cannot differentiate cases that have meningococcal sepsis with *purpura fulminans*, for which the fatality rate rises up to 40%. The ABCs data showed, of the clinical syndromes caused by meningococcal disease, almost 50% were attributable to meningitis, 33% to bacteremia, and 9% to pneumonia. The balance were the other, less frequently occurring clinical syndromes sometimes associated with meningococcal disease. The case fatality ratio increases with age and is higher among adolescents and adults with approximately 80% of the deaths occurring in persons greater than or equal to 14 years of age.

*Epidemiology*. Population risk factors included household exposure (raising the risk 400-800 times), demographic and socio-economic factors (blacks are at higher risk than whites) and crowding, the presence of concurrent upper respiratory tract infections, and exposure to active and passive smoke. About 20% of the vulnerability is due to enhanced formation of respiratory droplets and impaired natural defense mechanisms.

Outbreaks occurred in the U.S. in the early-to-mid 1900s but stabilized to the current rate of ~0.5 to 2 cases per 100,000 population. However, the rates have been cyclical over the last 40 years, and although currently low, that is not due to public health intervention. Regional differences in disease rates from 1996 to 2001 were charted on a U.S. map. They showed an outbreak of serogroup B in the Pacific Northwest that is now waning. Additional data are needed to see if the rates are cyclical or if some areas have higher rates of disease, so as to target vaccination strategies.

*Disease rates* were charted by age, demonstrating the highest rates in children less than 2 years of age. Increased rates are also seen in adolescents, young adults, and the elderly. A decline in

adolescent/young adult rates since the mid-to-late 1990s was not due to increased vaccination of college students, since the proportionate contribution of college freshmen (at moderately increased risk) to the disease burden is small.

*Burden of disease* was charted by age group. Even though rates of disease are highest in those aged <2 years, the majority of cases (59%) are among those aged ≥14 years; 23% is among adults aged 25 to 64, a difficult group to target for vaccination. By *race*, whites aged <1 or 2-4 years have more disease, but for all other age groups, blacks' rates are higher, and are higher overall when compared to whites. However, that disparity has decreased in the last eight years.

The frequency of outbreaks has declined nationally, but localized outbreaks have increased. Those from 1994-2001 were caused by groups of closely related strains that are probably new clones introduced to the population. Although such outbreaks gain great public and media attention, they are only 2-3% of total U.S. cases.

The currently licensed quadravalent polysaccharide vaccine and the new conjugate vaccine is based on capsular polysaccharides of several serogroups. There are at least 13 of those, but most U.S. cases are caused by serogroups B, C, and Y. Groups C and Y are in the currently licensed quadravalent vaccine, but the B capsule is poorly immunogenic and with no currently licensed vaccine in the U.S. Rates of serogroup Y rose from 1991-97 and then declined, along with overall national meningococcal disease rates. Data analysis done by proportions rather than rates showed that serogroups B, C, and Y rose from 1991 to 2002 among those aged <2 years old, adolescents and young adults, but serogroup Y increased among those aged >65 years. For children aged <4 months, serogroup B predominated, but C and Y were also strongly present.

In summary, there were 1400-2800 cases of meningococcal disease per year in the United States from 1991 to 2002. The highest rates of disease were among those aged <2 years, but 59% occurred in those aged ≥14 years. The case fatality ratio is higher in the older age groups; serogroups C and Y account for 66% of the disease.

Ongoing *CDC activities* related to meningococcal disease are surveillance and evaluation of the epidemiology, focusing on adolescents. A cost-effectiveness study of conjugate vaccines should be ready for presentation to the ACIP in June. A meeting on meningococcal educational activities is planned with stakeholders to address both the polysaccharide and conjugate vaccines (e.g., professional organizations, state health departments, public advocacy groups). Plans for a Phase IV vaccine efficacy evaluation are underway.

Meningococcal ACIP Subcommittee Report
Presenter: Dr. Reg Finger, Subcommittee Chair

The Meningococcal ACIP Subcommittee was formed to: 1) implement the June 2003 ACIP consensus decision to educate adolescents, parents, and providers about meningococcal disease and the vaccine; 2) analyze the currently available epidemiology of meningococcal disease (globally, but primarily in the U.S.) by age and serogroup; 3) monitor the progress of meningococcal conjugate vaccines in development for safety, immunogenicity, efficacy (normally assessed in post-marketing studies), and likely cost-effectiveness by age and serogroup; and 4) help frame the ACIP's upcoming policy discussion of meningococcal conjugate vaccines (MCV) in the next 2½ years, the period in which their release is expected.

On the previous Monday, the Subcommittee heard Dr. Salisbury's presentation of the meningococcal vaccination experience in the United Kingdom. The U.K. mostly has serogroups B and C, and little of serogroup Y. In the absence of a vaccine against serogroup B, they have successfully used a monovalent meningococcal conjugate vaccine directed at serogroup C. The U.K. had a dramatic increase in type C disease occur among several age groups over a period of about 5-6 years. They dramatically reduced incidence with the C conjugate vaccine. The basis of the program was to save lives, although they also had cost-effectiveness data. Their national immunization registry, which is linked to their national healthcare system, greatly expedited the identification of children needing immunization. It also facilitated their surveillance, which showed a herd immunity effect.

Four of six manufacturers described their candidate meningococcal conjugate vaccine products; the other two will communicate that in future.

- GlaxoSmithKline is working on several multi-combinations with other antigens such as Hepatitis B, Hib, and DTP vaccines; some had serogroup C, others C and Y, and most had been used in other countries. GSK informally asked the Subcommittee if their program should target infants to 2 months old, to toddlers, or to 12 months; how strongly they preferred combination vaccines or if stand-alone meningococcal conjugate vaccines would suffice; and if serogroup Y was requirement. The Subcommittee said yes to the latter, and that inclusion of serogroups A and W135 would be helpful for international travelers.
- Aventis Pasteur filed their license application with the FDA in December 2003, which was accepted in February, 2004. By this October, they expect an FDA response leading to the licensure of a quadravalent meningococcal conjugate vaccine with all four of the antigens. The application indicates ages 11 through 55 years. They hoped for an ACIP recommendation for adolescents to avoid the need for a child program and a catch-up program.
- Baxter was a partner in the U.K. program as well as in the 2002 Netherlands program that subdued endemic meningococcal C disease. Their work focuses on a biochemical alteration to the polysaccharide in the meningococcal group C, which the Subcommittee welcomed.
- Chiron Vaccines, also a partner in the U.K. program, asked about the desirability of marketing a monovalent serogroup C vaccine to control outbreaks.

The Subcommittee began its discussions of the related issues, beginning with how to structure the educational effort for adolescents and parents. The NVPO had funded the stakeholders' meeting previously described, which may be held in early fall. An awareness/educational program will be launched thereafter. The Subcommittee is to gather VE data for infants through senior adults from outbreak information. Seniors ware not discussed at this meeting, but will be. The impending vaccines' indication stops at age 55.

CDC is conducting a cost-effectiveness study and more will be done. Some price estimates were conveyed to the Subcommittee, and a range would be used in a CE analysis. Other than CE, the life-saving imperative will factor strongly in any recommendation, as other much less cost-effective public health interventions than this have been recommended and done.

Within the year, the first ACIP recommendation will likely be discussed on MCV-4, the quadravalent (serogroups A, C, Y, W135) meningococcal conjugate vaccine for adolescents and adults. How it would be implemented will be discussed. Among the many questions involved

are whether to place MCV in the already-loaded routine childhood schedule, which depends in part on development of combinations or stand-alone vaccine. The absence of a B serogroup in the vaccine, of great importance to infants, is one consideration. However, the Subcommittee's sense was that the release of an ACIP statement on the first vaccine released need not depend on its application to infants and toddlers.

*Discussion* included:

- The U.K. had nationwide PCR testing done on submitted samples, which revealed considerable (~40%) past under-ascertainment of cases, a critical implication to the estimated burden of disease. Dr. Salisbury asked if the U.S. would restrict its surveillance to confirmed cases "or what is likely to be the true burden of disease." Dr. Rosenstein regretted that the U.S. does not have a central lab like the U.K.'s, to process every specimen by PCR upon suspicion of meningococcal disease. But CDC has been conducting a study at the Emerging Infections Program (EIP) sites, using PCR to try to estimate the increasing burden of disease. All specimens are accepted, not just those of suspected meningococcal disease. The result was not ready, but was not expected to even approach the 40% increase found in the U.K. This may relate to how patients present in the U.K., often seeing primary care providers first and taking antibiotics before hospital admission. CDC will take the PCR data and the results of another study to the CSTE within the next year.
- Dr. Jim Turner asked about how many children aged <18 years who die from meningococcal disease every year in the U.S. Dr. Winger said that 40% are aged <14 years and the case fatality rate is ~10%. Dr. Turner quickly estimated 1400-1600 cases aged <24 years, of whom 180-200 died and another 180-200 had permanent complications. He observed that, for the young, this death equaled or surpassed that of influenza this past winter. Dr. Rosenstein agreed with his calculation and conclusion. But she noted another difference between influenza and meningococcal disease; the need to chase down close contacts, which involves enormous resources, as does addressing a panic. Dr. Peter also cited the "impressive" number of vaccine-preventable deaths due to C and Y meningococci, and huge demands on Rhode Island's public health resources during a 1998 meningococcal panic. That led the state Director of Health to recommend the vaccine for children aged 2-22 years. A 75% vaccination rate was achieved by among young, school-age children.
- Dr. Katz asked what the Subcommittee learned about the development of Group B meningococcal vaccines. Dr. Finger reported a few Group B vaccines being used in specific countries (e.g., New Zealand) to attack specific serotypes of Group B. Covering 80% of all of the serogroup B seen in the U.S., though, would require 20 different serotypes. That is at least five years away from serious discussion at the ACIP. Dr. Rosenstein reported CDC's plans to ask the companies to update the Subcommittee on their vaccine candidates and progress.
- Dr. Paradiso emphasized that the length of vaccine development ranges well past five years, so such information greatly helps the companies decide in which area they should move. For example, they would like to know if a B vaccine alone was interesting and different than the conjugates, or if a combination would be needed.
- The U.K. did not measure all manifestations of severe meningococcal disease

such as bacteremia, because they believe it to be a spectrum of disease rather than distinct conditions. But they did capture the various manifestations. The duration of immunity over time, an aspect of any age-based strategy, will have to be learned over time. In the U.K., they saw a very high response four years post-vaccination with the C conjugate, at perhaps higher antibody levels than after primary immunization, among children who were vaccinated at aged 2, 3 and 4 months, and then challenged with a small dose of the plain polysaccharide at aged four. But the duration of protection remains unknown. The U.K. is committed to intensive surveillance for many years to come.

**National Meningitis Association Statement**
Presenter: Ms. Lynn Bozoff

Ms. Bozoff represented the National Meningitis Association and had lost a college-age son to meningitis. The NMA will be part of the stakeholder meeting. They supported the education of parents, adolescents, and healthcare professionals about meningococcal disease and its prevention, and hoped for an ACIP recommendation for routine meningococcal immunization for 11-to-18 year olds when the conjugate is released. The NMA feels strongly that parents have the right to be educated about the disease and the current vaccine, so that they can make informed decisions about whether to immunize their child. She related how the previous night she had received a phone call from a mother of a 19 year-old who died January. The mother read of the vaccine two days after her son died, and asked why she did not know about it.

**ACIP Recommendations on Influenza**
Presenter: Dr. Scott Harper
**Vote**

*Avian influenza.* Ad hoc guidance issued by CDC for poultry cullers was provided for the ACIP's information. It was issued through CDC's Health Alert Network and was posted on the CDC Website. It read: "Currently, unvaccinated workers should receive the current season's influenza vaccine to reduce the possibility of dual infection with avian and human influenza viruses. There's a small possibility that dual infection could occur and result in reassortment. The resultant hybrid virus can be highly transmissible among people and lead to widespread infections. Vaccination of all residents of affected areas is not supported by current epidemiologic data. So in the future, this may be a point for discussion and inclusion in the recommendations, but not at the present time."

***LAIV use among healthcare workers.***
Four recommendation options were presented for the committee's consideration. Three variables were among them: 1) adding "protected environment" and defining the "severely immunosuppressed" population; 2) either removing or 3) keeping examples of lesser degrees of immunosuppression; and 4) either leaving the seven-day concept in the second paragraph, moving it up to the first paragraph or eliminating it altogether. The options were:

1. Added text: "Use of inactivated influenza vaccine is preferred for vaccinating household members, healthcare workers, and others who have close contact with severely immunosuppressed persons for whom a protected environment is required (i.e., patients with hematopoietic stem cell transplants) because of the theoretical risk that a live

attenuated vaccine virus can be transmitted to the severely immunosuppressed person and cause disease. Otherwise, no preference is given to either inactivated influenza vaccine or LAIV for vaccination of healthcare workers or other healthy persons aged five-to-49 years in close contact with all other groups at high risk." The second paragraph was unchanged, citing the 7-day patient non-contact period.

2. This option retained the protective environment clause and defined the "severely immunosuppressed" population, but included examples of the lesser degree of immunosuppression. "Use of inactivated influenza vaccine is preferred for vaccinating household members, healthcare workers, and others who have close contact with severely immunosuppressed persons for who a protective environment is required (i.e., . . . ) but not for persons with lesser degrees of immunosuppression, e.g., persons with diabetes, asthma, or immunodeficiency virus."

3. Option three continued to have the protected environment clause and defined a severely immunosuppressed population. It left in examples of lesser degree of immunosuppression, and moved refraining for seven days from patient care up to the first paragraph. The second paragraph then just addressed hospital visitors.

4. The fourth option was worded slightly differently than the third option, qualifying the time that the patient is in that protective environment: "...severely immunosuppressed persons (i.e., patients with hematopoietic stem cell transplants during those periods in which the immunocompromised person requires care in a protective environment) because of a theoretical risk. If a healthcare worker receives LAIV . . . " The seven-day clause was inserted and no preference was expressed for inactivated influenza vaccine use ". . . by healthcare workers or other persons who have close contact with persons with lesser degrees of immunosuppression, e.g., . . . "There is no preference expressed for vaccination of healthcare workers or other healthy persons aged 5-49 years in close contact with all other groups at high risk."

*Discussion* included :

- Option 1: Dr. Siegel explained that the term "protective environment" applies to protection from fungal infections, not viral, through a positive pressure room with HEPA filtered air and air changes. It serves as a marker for those most severely immunosuppressed; an asterisk could define that. She preferred the last option's wording of "contact with severely immunosuppressed" and the example of "those with FILL IN NAME OF DISEASES during the time that they are most at risk" (i.e., when they are in the protective environment)." There was general agreement to this change.
- Option 2: There was agreement to retain the language addressing persons with lesser degrees of immunosuppression in order to reduce potential questions.
- Option 3: Dr. Levin preferred to separate the time off from patient care (and the visitor text) from the protective environment clause. Merging the top language from option four and the bottom language from option two was suggested. Dr. Finger asked if "during those periods" pertained to close contact or the preferred use of vaccine. Dr. Harper clarified that it modified "close contact;" when healthcare workers in contact with patients in that protective environment, the inactivated influenza vaccine is preferred. He agreed to clarify the wording.

"*Strongly recommended.*" The use of this term was discussed, since an ACIP "recommended" has always carried a strong message. Dr. Abramson expressed concern about its inconsistency

with other ACIP document, so there was agreement to remove the "strongly".

*Expanding the recommendation*. Two options were offered:

1. "The ACIP plans to review data on influenza disease and vaccination toward the eventual goal of increasing measures for influenza prevention and control including expanding recommendations for the use of influenza vaccines."
2. "The ACIP plans to review new vaccination strategies for achieving the goal of improving the prevention and control of influenza including expanding recommendations for use of influenza vaccines."

In *discussion*, Dr. Cochi's suggested text was added about ". . . strengthening surveillance, including prospective studies, to monitor the impact of the expanding recommendations."

Dr. Finger **moved that the ACIP accept all of the changes described on this morning, and Option Four presented on this afternoon, modified as follows: moving "seven days" back to the bottom, that Dr. Harper clarify the grammar, selecting option two regarding expanding the recommendation, and adding Dr. Cochi's text about ". . . strengthening surveillance, including prospective studies, to monitor the impact of the expanding recommendations."**

**Vote** :
**Conflicts:** Aventis Pasteur, Chiron, MedImmune, Wyeth-Lederle.

**In favor:** Zimmerman, Womeodu, Marcuse, Gilsdorf, Finger, Deseda, Campbell, Birkhead, Allos, Abramson.
**Opposed:** None
**Abstained:** Treanor, Levin

**The motion passed.**

**Vaccine Safety Update**
Presenter: Dr. Robert Chen, NIP

Overview. The issue of thimerosal in vaccines has been reviewed by the ACIP in the past. A preliminary screening analysis from the Vaccine Safety Data Link (VSD) was presented in 2000, and the refined paper was published in November 2003 in *Pediatrics*. Presented were the VSD analysis, a more in-depth thimerosal follow-up study underway, and another of MMR and autism.

**VSD Thimerosal Screening Study**
Presenter: Dr. Frank Stefano, NIP

Overview: Status review of studies of vaccine, autism and early developmental disorder: MMR/autism case-control study in Atlanta, published in February 2004; thimerosal exposure and neurodevelopmental disorder study published in November 2003 in *Pediatrics*; planned case control study of autism.

*MMR/Autism.* This Atlanta study evaluated if there was an association between Autism Spectrum Disorder (ASD) and the age of receipt of MMR vaccine in children, and if any

subgroups were at particular risk. The cohorts were identified from the Metropolitan Atlanta Developmental Disability Surveillance Program (MADDSP), a population-based developmental disabilities surveillance system (n=~300,000) begun in 1991. Autism was added in 1996.

*Study design.* Case-control, involving 624 cases and 1824 control children aged 3-10 years (born 1986-1993), living in five metropolitan Atlanta counties. MADDSP 1996 data were used to identify the cases; sources were vaccination records of schools (public and special education) and autism and developmental disability service providers. The children were classified according to DSM-4 criteria for autism or its subtypes. The children were matched on age, sex, and the local home school, and availability of school record vaccination information.

*Results*. In general, the age of first MMR vaccination was similar between the groups, with ~70% vaccinated between 5-17 months. Some differences were significant, however, in a cut-off comparison of above or below 36 months of age. More children were likely to be vaccinated at <36 months than their matched controls (93% versus 91%). Autism is often suspected from the age of 24-36 months. The Individuals with Disabilities Education Act (IDEA) provides school-based pre-school special education programs for children with autism, beginning at about 36 months, and MMR vaccination is one that is required for enrollment in those programs. That could be one source of the difference above.

*Conclusion:* This study added to the accumulating epidemiological evidence over the past few years that there is no association between MMR vaccination and autism.

***Vaccine Safety Datalink Study*** (*Pediatrics*; November 2003). This study was an initial screen, analyzing computerized HMO data to explore possible associations between thimerosal and renal and neurodevelopmental disorders. The HMO vaccination data included vaccine type, manufacturer and often a lot number (key to identifying the presence of thimerosal); health outcomes, hospital ED clinic diagnostic codes; and patient characteristics (birth data, sex, period of enrollment in the HMO).

*Study design.* Retrospective cohort, to explore exposure to mercury from thimerosal-containing childhood vaccines; outcomes of plausible neurologic and renal disorders seen in the literature from other organic mercury exposures. Initial analysis was of two HMOs participating in the VSD (A and B, n= ~125,000), and then replicated in a third HMO (C, n= ~17,000). The birth years were 1992-1998 (HMOs A and B), and 1991-1997 (HMO C). Follow-up was done through 2000 for A and B and through May 1998 for HMO C. The children were aged from 1-8 years at last follow-up. Outcomes examined were autism, tics, ADD, language and speech delays; and sleep, eating and coordination disorders. The main thimerosal-containing vaccines were hepatitis B, DTP, or DTaP, and Hib. DTaP used towards the end of the second period was assigned a zero ethyl-mercury exposure level in the analyses. Cumulative mercury exposure was assessed at one, three, and seven months of age.

*Results.* At one HMO, cumulative exposure at three months resulted in a significant positive association with tics; at the second, it indicated an increased risk of language delay for cumulative exposure at 3 and 7 months. But these findings could not be replicated in the third HMO, and no analyses found significant increased risks for ADD or autism.

*Autism results* were presented for low-, medium-, and high-levels of exposure beginning at 3 months. The medium level produced a 1.61 relative risk, although within a wide confidence

interval (0.77-3.34) that could reflect chance fluctuations. The P value was not statistically significant if the analyses were done as a continuous variable in search of a dose response-type relationship. There was no increased risk found with increasing exposure to thimerosal by seven months of age.

Study limitations included its restriction to autistic disorder ICD-9 code (299.0), unverified diagnoses, that some of the children were too young for an autism diagnosis; limited control for confounding, no measures of prenatal exposures, and the limitation to one HMO. There was also concern about potential bias from HMO medical care utilization, and the inconsistency of the associations found between HMOs. The few associations noted were relatively weak

***IOM VSD Study Review.*** The VSD now has a data sharing program so that external researchers can use the data to conduct their own independent analyses at the National Center for Health Statistics in Hyattsville, Maryland. The first study done analyzed the safety of DTaP vaccines (four doses to children), particularly for the risk of autism from thimerosal-containing DTaP compared to thimerosal-free DTaP vaccines. This was presented at the Institute of Medicine's (IOM) Review Vaccine Safety Review Committee meeting on February 9, which reviewed the issues of vaccines and autism.

The vaccines' thimerosal content was graded at zero, 25, 50, 75 or 100 micrograms. A regression analysis indicated a relative risk >8.0 if the content reached 75-100 CORRECT $\mu$g, compared to zero micrograms from DTaP vaccines. It was of concern whether CDC had missed this in their own analysis, so another analysis was done. One important consideration was whether the independent study's analysis had included age adjustment. Thimerosal-free DTaP vaccine was used at only one of the HMOs and was introduced in 1998, so children receiving all DTaP vaccination doses could have been, at the most, only two years of age. Re-examination of the data showed that the children who received all four DTaP thimerosal-free vaccinations would be ~18 months old, but compared with children who would have received four thimerosal-containing DTaP vaccines, they were about three years of age at last follow up. The study's analysis was replicated and provided a similar fairly striking relative risk, but that vanished with adjustment for age. The risk found by the independent study was a reflection of age confounding.

But computerized databases cannot provide the last word on thimerosal in autism, so CDC plans a more comprehensive and rigorous evaluation of this issue. The case children, now four years older, will be re-evaluated with state-of-the-art research instruments for the diagnosis of autism. Prenatal thimerosal exposure (e.g., from Rogam or influenza vaccine) will be evaluated. Since autism has a strong genetic component, the neurological abnormalities are probably present at birth, so relevant exposures would be a prenatal factor. A much more detailed assessment of potential confounding factors will be done through parent interviews and medical records review.

Three VSD HMOs will participate. The protocol has been reviewed by an external group of advisers and will be submitted to the IRB for review in March. The instruments are in development. Representatives of autism advocacy groups are also involved (e.g., Safeminds).

### *Thimerosal Neurodevelopmental Follow-up Study*

Presenter: Dr. William Thompson, NIP

Thimerosal, which is 50% mercury by weight, was used as a preservative in many childhood vaccines administered in the 1990s, when autism and ADHD prevalence rates also increased dramatically. That could be due to increased reporting with DSM-4 diagnostic coding implemented in 1994, or due to mercury exposure from fish and vaccine thimerosal content. The latter was of concern since in the 1990s, many childhood vaccines with thimerosal were given in the first year of life. In 1999, the AAP and the Public Health Service recommended the removal of thimerosal from all childhood vaccines. The FDA suggested that thimerosal exposure for children in the first year of life exceeded EPA's minimum threshold for safety limits and could have caused neurodevelopmental outcomes.

A follow-up retrospective cohort study was done of children aged 7-10 years when the neuropsychological test battery was administered. Those children received vaccine with thimerosal in the first year of life and were stratified by their level of thimerosal exposure. Evaluation was done of speech and language skills, executive functioning, attention, fine motor coordination, perceptual organization, motor tics, hearing level, academic functioning, intellectual functioning and ADHD symptoms.

Thimerosal contains ethyl mercury, but the study included any outcomes from previous studies that suggested possible associations from methyl mercury exposure, which has a larger literature. Both the VSD's automated records and abstraction of medical charts (provided by the mothers) were used to check for errors. The participating HMOs were Northern California Kaiser, Southern California Kaiser, Group Health Cooperative and Harvard Pilgrim, all of whose IRBs had to approve the study plan. The study planning and data collection was done by Abt Associates, which will also do the statistical analysis. The protocol was reviewed by outside experts and advocate organizations such as Safeminds. The various changes to the protocol, upon these consultations, were outlined.

The testing began June 1 and 821 children had been tested as of the previous weekend. The 380 children remaining should be tested by the end of June. Medical abstractions had just begun. These will be the study results' time-limiting factor, but are hoped to be completed by July. Initial study results will be presented to the CDC and a panel of outside experts at the same time to reduce the appearance of the CDC's influence on the generated results, as will IOM review of the results and subsequent publications. CDC hopes to develop a model similar to that used for the Vietnam Experience Study. Abt Associates hopes to provide the final in December 2004.

## Agency/Committee Reports

*Department of Defense.* Dr. Phillips reported DOD's successful (>98% participation) influenza vaccination program. DOD also has achieved the smallpox vaccination program's goals to immunize key people against smallpox; the program is now in the maintenance phase. The anthrax vaccination program was stopped by court order in December until the FDA ruled that DOD was using the anthrax vaccination for an indicated purpose, to protect against inhalation anthrax. The DOD has administered over 3.9 million anthrax vaccinations to over 1.1 million people to date, and the program is back on track.

*Centers for Medicare and Medicaid Services.* Ms. Murphy had nothing to report.

*Food and Drug Administration*. Dr. Baylor reported on the February 12-13 meeting of the

FDA's Transmissible Spongiform Encephalopathy (TSE) Advisory Committee. They reviewed the methods to minimize the risk of TSE agents in FDA-regulated medicinal products. No new policy on sourcing from the U.S. and Canada was requested of the committee, as neither is on the USDA/FDA joint list of countries from which bovine-derived raw materials may not be imported. The FDA Website is updated on these issues in ongoing fashion. The Vaccine and Related Biological Products Advisory Committee (VRBPAC) meeting on February 18-19 selected the influenza vaccine strain and began discussion of whether tissue cultures can be used in vaccine production, especially for making reference strains which now are prepared from eggs or chick embryo fibroblasts. They also are discussing how to address the issues of adventitious agents, as related to tissue cultures that are already being used by some vaccine sponsors. Global collaboration will be required on that policy.

*National Institutes of Health/National Institute for Allergies and Infectious Diseases* Dr. Curlin outlined NIAID's Influenza Research Program, whose basic research produced the reverse genetics process discussed at this meeting. NIAID also screens new candidate antiviral drugs and develops new regimens of combined drugs against pandemic strains. Novel broad-spectrum therapies are in development which target viral entry and then attack and degrade the viral genome. Diagnostic research is in the early stages and is important since influenza control strategies are increasingly based on case load reduction rather than ILI syndrome reduction. That change will also affect the diagnostic standards addressed by the ACIP.

NIH vaccine work includes development of present vaccines to be more rapidly manufactured, more broadly cross-reactive, and more effective. The current Phase II clinical trial of a new vaccine produced in the cell culture system uses existing expression systems to produce hemagglutinins to be included as vaccine candidates. The research includes examination of increased doses of the current inactivated vaccines among the elderly (which may be more effective), as well as fundamental cooperative research on DNA vaccines with sponsor companies. Other work on influenza virus proteins that are shared by several strains is being done to help broaden the coverage.

NIH also does surveillance in the course of their research (e.g., in the Hong Kong investigations). They support and participate in the work of the National Vaccine Program Office's pandemic preparedness work. NIH labs produce and distribute the research reagents, etc., that relate to pandemic preparedness.

*National Vaccine Program Office*. NVPO director Dr. Bruce Gellin related the discussions of the recent National Vaccine Advisory Committee (NVAC) meeting. The DHHS Acting Assistant Secretary charged NVAC to examine the nation's approach to influenza. Part of this will involve discussion of the role of diagnostics and considering influenza control as a measurement of disease control rather than just vaccine coverage. Preliminary recommendations are on a fast track. NVAC also was updated on the polio vaccine stockpile and the project on lab containment of wild polio viruses. The latter's Phase I inventory of laboratories and institutions nationally was led by Dr. Walt Dowdle.

Regarding pandemic preparedness, two RFPs were issued for multi-agency work to enhance the domestic production capacity for influenza vaccine by both egg- and cell-based methods. The latter is particularly of interest since there is no current licensed cell culture vaccine. NVPO is working with the Global Health Security Action Group's Technical Working Group on Pandemic Influenza Preparedness to determine any gaps not addressed in the global agenda.

Last December, NVPO participated in the Asia-Pacific Economic Cooperation meeting to help that region's countries develop their pandemic influenza preparedness plans. Also last December, *JAMA* published Dr. Jeanne Santoli's summary of the NVAC Vaccine Supply Report.

NVPO participated in a meeting held by the Office of Public Health Emergency Preparedness on innovative administrative systems for vaccinations. These are applicable both to bioterrorism preparedness and global health activities. An upcoming meeting with NVPO participation will be the first Neonatal Vaccination Workshop in McClean, Virginia. NVPO has a new Website, www.hhs.gov/nvpo, and the transition from Atlanta to Washington, D.C. is ongoing. Dr. Ben Schwartz will leave the NIP to join the NVPO, but will remain based in Atlanta; and Dr. Sarah Landry will join from NIH.

*Vaccine Injury Compensation Program* Dr. Geoff Evans provided a handout with the pre- and post-1988 compensation program totals of case and disbursement. Now in its 15th year of operation, the VICP has processed >10,000 claims. Of 2003's high in claims received, 90% were related to the autism thimerosal proceedings; the balance was for the other vaccines covered in the program.

*Adjudications* reported included the final pre-1988 claim. Awards total $1.4 billion overall to date, almost $1 billion applied to the pre-1988 program. The Trust Fund balance is ~$2 billion and earns ~$200 million annually from interest.

*Litigation* in the civil sector is ongoing since the compensation law does not cover all the possible scenarios. Petitioners must first file with the program for vaccine-related injuries, but non-vaccine-related injuries go to civil court. The mass of claims last year were based on the vaccine's thimerosal content being alleged as a contaminant or adulterant, which therefore avoided VICP filing. The law also does not cover third-party damages (e.g., family members) or those claiming less than a thousand dollars. The latter legal loopholes allowed the formation of large class action suits in the civil sector. The family member suits are seeking monitoring in anticipation of future injuries along with the <$1000 claim.

The program's *current status* includes >350 injury lawsuits in most states, often naming multiple manufacturers and at least one naming the administering physician. Most were dismissed when the courts ruled against the adulterant and contaminant allegation, but decisions have varied regarding the other allegations. The class action suits also have been dismissed, but the derivative claims are being allowed to stand in state courts based on existing state laws. There have been no rulings yet on the merits of causation; the first cases are due to be heard in early 2005.

To handle the increase in claims (now at >3500), a two-year omnibus proceeding was established, which will probably be heard either late 2004 or sometime in 2005. Once that is concluded, the decision will be applied to individual cases. About a dozen cases have chosen to leave the VICP track and pursue litigation in the civil sector.

*Legislation.* Current congressional bills included two proposing an excise tax for the hepatitis A vaccine and "any trivalent vaccine against influenza," so both products will be covered by the VICP. The program is hoping that some much needed reform legislation will be passed to improve the program's process aspects and to close loopholes.

*Discussion* included question of whether the legislation could be changed from specifying trivalent vaccine to any vaccine, to allow for coverage of a possible monovalent H5N1 vaccine. Dr. Braga conveyed Aventis Pasteur's concern that the trivalent vaccine, as a known vaccine, has known risks. To open the VICP up to unknown risks in unknown vaccines could be dangerous. The company would not manufacture a pandemic vaccine without extensive discussion of indemnification, whether or not ACIP recommends it for coverage. Dr. Gellin noted that even a bivalent vaccine, produced for normal annual use, would not be covered either. Dr. Braga responded that Aventis would consider recommendation language that conformed to the annually-given vaccine and would cover a bi-, tri-, or quadravalent, but refrained from approving the H5N1-N2-type vaccines that could entail more risk for the manufacturer. Dr. Lewin related that Chiron had no position as yet, but they were aware of the language and were evaluating the alternatives. Dr. Chen related the challenges to providing timely safety data due to inadequate funding. The Injury Compensation Act was intended as much to prevent injuries as to compensate. He hoped that those parts of the bill and funding could be improved.

*National Center for Infectious Disease.* Dr. Mawle had nothing to report.

*National Immunization Program*. Dr. Cochi added to the commendations of Dr. Walter Orenstein, who greatly contributed to achieving the record lows in vaccine-preventable disease morbidity by the end of the 20$^{th}$ century. Record high levels also exist for vaccination coverage at two years of age, based on data through the first six months of 2003. Varicella vaccine coverage was at 82.5%, and $\geq$3 doses of pneumococcal conjugate vaccine was at 59%, despite shortages of this vaccine.

The NIP budget has been level for the past 2-3 years, putting the program under stress, particularly its grant component. Rescissions, as well as inflation, produced a net decrease in the NIP's purchasing power. The President's budget decreased the NIP's 317 program vaccine purchase budget by about $110 million, anticipating that new VFC legislation would be passed. This would include under-insured children (i.e., without immunization coverage) for vaccination under the VFC program at public clinics as well as federally-qualified health centers. The proposed VFC legislation was presented, but some fear it may not pass this calendar year. It also lifts the price caps to restore Td and DT vaccines to the VFC program, and provides $5 million to purchase Td for the pediatric stockpile. The balance of the budget was level to that of FY2004. Funding for the pediatric vaccine stockpile (to be done by FY2006) is >$600 million.

National Infant Immunization Week will be held the last week in April this year and will be a hemisphere-wide event this year. Events and one of the communication materials were shared.

CDC is heavily involved in disease elimination goals. Globally, those include total eradication of polio and a 50% reduction of measles mortality by 50% by 2005 (compared to 1999 levels). Mortality from measles has declined steadily and it is hoped that the goal will be reached before 2005. It has been 18 months since indigenous measles transmission was eliminated in the Americas. The Pan American Health Organization established a new goal last September to eliminate rubella and congenital rubella syndrome regionally by 2010. The polio eradication effort was set back by case exportations from northern Nigeria to eight surrounding countries. But synchronized national immunization days were scheduled to begin on Monday in ten countries including Nigeria (except for 2-3 states of northern Nigeria) targeting more than 60 million children.

**Public comment** was solicited, to no response. With Dr. Levin's thanks, the meeting adjourned at 3:00 p.m.

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

Myron J. Levin, MD, Chair

Date

# ATTACHMENTS

## Attachment #1: ATTENDANCE

**ACIP Members**

Jon S. Abramson, MD
Mishu Ban Allos, 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
John B. Salamone
John J. Treanor, MD
Robin J. Womeodu, MD
Richard Zimmerman, MD

Member absent: Celine Hanson, MD

Potential conflicts of interest were stated by the following members:

- Dr. Levin  Conducted clinical research with Merck and Glaxo Smith-Kline, and I'm also on a Data Safety Monitoring Board for Merck.
- Dr. Traenor: Conducted clinical trials for MedImmune and GlaxoSmithKline, provided advice to Wyeth.
- Dr. Poland: clinical research funded by VaxGen and Merck; serves on Merck data monitoring and safety board.
- Dr. Abramson: Provided a one-time consultation to Merck for a rotovirus vaccine.

**Ex-Officio Members**

***Centers for Disease Control and Prevention***

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

**Other Federal Agencies**

Norman Baylor, MD, Food and Drug Administration (FDA), for Dr. Karen Midthun
James Cheek, MD, MPH, Indian Health Services (IHS) correct??
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)

***Liaison Representatives***

JON REPLACED BY MARGARET RENNELS, MDJon Abramson, MD, and Carol J. Baker, MD, American Academy of Pediatrics (AAP), Committee on Infectious Diseases (COID)
Damian A. Braga. MD and Peter Patriarca, MD, Pharmaceutical Research and Manufacturers of America
Dennis A. Brooks, MD, MPH, National Medical Association (NMA)
Richard Clover, MD, American Academy of Family Practitioners (AAFP)
Jaime Deseda, MD, National Immunization Council and Child Health Program, Mexico

Stephan L. Foster, PharmD, American Pharmacists Association (ApharmA)
Samuel Katz, MD, Infectious Disease Society of America (IDSA)
Clement Lewin, Phd, MBA, Biotechnology Industry Organization (BIO)
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)
Georges Peter, National Vaccine Advisory Committee (NVAC)
LTC Stephen Phillips, Department of Defense (DOD) Health Affairs
)
David M. Salisbury, MD, London Department of Health
Jane Siegel, MD, Hospital Infections Control and Prevention Advisory Committee (HICPAC)
Litjen Tan, PhD, American Medical Association (AMA)
James C. Turner, MD, American College Health Association (ACHA)

**Agency Staff**

**Department of Health and Human Services (DHHS)**

***Centers for Disease Control and Prevention (CDC):***

*No C/I/O identified:* Michael Greenberg, Anna M. Likos, David Newmann, Jen Reueh, ASPH/CDC, Corine Spencer, Kathryn Teates, Eric Weintraub, Kirk Wiinger

*Office of the CDC Director:* Larry Anderson, Larry Pickering, Kevin Rieders

*Office of General Counsel:* Kevin Malone

*Epidemiology Program Office (EPO):* Richard Dixon, Andrew Kroger

*National Center for Infectious Diseases (NCID)*:

John Barson
Craig Borkowf
Caroline Bridges
Lynette Brammer
Louisa Chapman
Nancy Cox
Roz Dewart
Keiji Fukuda
Scott Harper
Guillermo Herrera
Marika Iwane
Alexander Klimov
Mehran Massoudi
Ann Moen
Walter Orenstein
Michelle Pearson
Sharon Roy
Dan Rutz
Montse Soriano
Eric Weintraub
Melinda Wharton
Jennifer Wright

*National Center for Chronic Disease Prevention and Health Promotion (NCCDPHPP: National Immunization Program (NIP):*

James P. Alexander
Lorraine Alexander
Curtis Allen
F. Averhott
Kris Bisgard
Sharon Bloom
Karen Broder
Scott Campbell
Margaret Carter
Bob Chen
Susan Chu
Gary Coil
Gustavo Dayan
Lauren DiMiceli
Dan Fishbein
Cindy Gann
Paul Gargiulio
Edith Gary
Dallya Guris
Penina Haber
Jim Harrison

Pauline Harvey
Alena Khromava
Nidhi Jain
Laurie A. Johnson
Linda Johnson
Kristin Kerryan
Maureen Kolasa
Brock Lamont
Kim Lane
Karen Lees
Peng-Jun Lu
Dean Mason
Mike McNeil
Elaine Miller
John S. Moran
Trudy Murphy
Linda Neff
Huong Nguyen
Pekka Nuorti,
Dennis O'Mara
Brian Pascual
Bette Pollard
Linda Quick
Dino W. Ramzi
Lance Rodewald
Marty Roper
Ismael Ortega Sanchez
Tammy Santibanez
Jeanne Santoli
Ben Schwartz
Jane Seward
Kristine Sheedy
Irene Shui
Jim Singleton
Nicole Smith
Vishnu Priya-Sneller
Margarita Sniadack
Ray Strikas
Tejpratap Tiwari
Claudia Vellozzi
Fran Walker
Greg Wallace
Margaret Watkins
Donna Weaver
Eddie Wilder
Carla Winston
Skip Wolfe
Weigong Zhou

***National Institutes of Health*** (NIH): Carolyn Deal, Tina Thomas

***National Vaccine Program Office (NVPO)****:* Sarah Landry, Gregory Wallace

***Department of Defense (DOD)*****:** Sarah Viera, U.S. Air Force/Institute of Operational Health

***Food and Drug Administration (FDA)****:* Lucia Lee, Douglas Pratt

***National Institutes of Health (NIH****): NIAID:* Barbara Mulach

**Members of the public** or presenters to the committee in attendance were:
Larry Altman, New York Times, NYC, NY
Bill Averbeck, Aventis Pasteur
Lynn Bahta, MN Department of Health
Bryan Bechtel, Infectious Diseases in Children, Thorofare, NJ
Joan Benson, Merck & Co., Inc.
John Boslego, Merck Research Lambs
Andrew Bowser, freelance medical writer, Brooklyn, NY
Lynn Bozoff, National Meningitis Association
Pat Cannon, Wyeth, Newnan, GA
Dan Casto, Merck & Co., Inc.
Kathleen Coelingh, MedImmune Vaccines
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
Joseph Eiden, Chiron Vaccines
David S. Fedson, MD
Joline Fortson, Merck & Co.

Betsy Frazer, AQAF, Vestavia Hills, AL
Joan Fusco, Baxter
Diana Gaskins, GA Immunization Program, Atlanta, GA
Ruth Gilmore, GA Immunization Program, Atlanta, GA
E. Greenbaum, Merck
Jesse Greene, South Carolina Department of Health and Environmental Control
Marie Griffin, Vanderbilt University
Jill Hackell, Wyeth
Neal Halsey, Johns Hopkins University, Baltimore, MD
Claire Hannan, Association of State and Territorial Health Officers (ASTHO)
Rick Haupt, Merck & Co., Inc.
Sandra J. Holmes, GlaxoSmithKline
Philip Hosbach, Aventis Pasteur
Barbara Howe, GSK
Melonie Jackson, Georgia Chapter, AAP
Rudolph Jackson, MD, Morehouse School of Medicine
Marcy Jones, State of California Immunization Program
Karen Kessnick, Acambis
Jamie Lacey, MedImmune
Dr. J. Michael Lane, Atlanta, GA
Philip LaRussa, Columbia University
Jim Lathrop, Chiron Vaccines
Jo LeCouilliard, GlaxoSmithKline
Marie-Michele Leger, AAPA
Harold W. Lupton, Aventis Pasteur
Cynthia Malcom, Georgia chapter, AAP
Sussan Malone, Chatham Country Health Department, GA
Ed McCarthy, CNN Radio, Atlanta, GA
Peter McIntyre, National Center for Immunization Research, Syndey, Australia
Maryn McKenna, Atlanta Journal Constitution, Atlanta, GA
Geoff McKinley, Baxter Vaccines
Dan McLaughlin, MedImmune
Cody Meissber, MD, Tufts University
Paul Mendelman, MedImmune
Marie Murray, Recorder, Atlanta, GA
John M. Neff, University of Washington, Seattle, WA
Karen Nielsen, GSK
Nicole Paduch, Aventis Pasteur
Peter Paradiso, Wyeth Vaccine, West Henrietta, NY
Diane Peterson, Immunization Action Coalition, St. Paul, MN
Marc Pickard, WXIA-TV, Atlanta, GA
Doug Pinnell, Powderject VAccine
Stanley Plotkin, MD, Aventis Pasteur, Doylestown, PA
Geoffrey Porges, Sanford Bernstein, NYS, NY
James Ransom, National Association of City and County Health Officers (NACCHO)
Dan Reilly, WXIA-TV
Zeil Rosenberg, Becton-dickingson, Inc.American College of Preventive Medicine, Franklin Lakes, NJ
Fred Ruben, Aventis Pasteur

Lorna Scott, Wyeth
Judith Shindman, Aventis Pasteur Ltd.
Dr. Alan J. Sievert, AAP, East Metro Health District, Lawrenceville, GA
Shawn Skelly, Wyeth
Parker Smith, PCS Photo
Vincent Sneco, MD, ACP
Jeffrey Stoddard, MedImmune
Stacy Stuerke, Merck
Carol McPhillips Tangom, AAHP - HIAA
Lonnie E. Thomas, Henry Schein, Inc.
Eric Tischler, Aventis Pasteur
Karen Townsend, GA Chapter, AAP
Ted Tsai, Wyeth
Miriam E. Tucker, Elsevier
Thomas Vernon, MD, Merck Vaccine Division, West Point, PA
Peter Vigliarolo, Cooney Waters, New York, NY
Beth Ward, Georgia State Health Departement
Martin Wasserman, GSK
Barbara Watson, MD, Divison of Disease Control, Philadelphia, PA
Deborah Wexler, Immunization Action Coalition, St. Paul, MN
Matthew Williams, Flu Central, Doraville, GA
Greg Yoder, Merck & Co.
Laura York, Wyeth Vaccines
Jim Young, MedImmune
Daniel Yu, AP
John Zahradnik, Aventis Pasteur
Thomas Zink, GSK Vaccine, Philadelphia, PA

**Attachment #2: Revisions to the LAIV Recommendation**
(Edits in redlined text)

*SHEDDING AND PERSON-TO-PERSON TRANSMISSION OF VACCINE VIRUSES*

"One unpublished study in a child care center setting assessed transmissibility of vaccine viruses among 98 vaccinated to 99 unvaccinated subjects, all aged 8–36 months. Eighty percent of vaccine recipients shed >1 virus strain, with a mean of 7.6 days duration (*17*). One vaccine type influenza type B isolate was recovered from a placebo recipient and was confirmed to be vaccine-type virus. The type B isolate retained the cold-adapted, temperature-sensitive, attenuated phenotype, and it possessed the same genetic sequence as a virus shed from a vaccine recipient in the same children's play group. The placebo recipient from whom the influenza type B vaccine virus was isolated did not exhibit symptoms that were different from those experienced by vaccine recipients. The estimated probability of acquiring vaccine virus after close contact with a single LAIV recipient in this daycare population was 0.58%–2.4%.

"One study assessing shedding of vaccine viruses in 20 healthy vaccinated adults aged 18-49 years demonstrated that most shedding occurred within the first 3 days after vaccination, though one subject was noted to shed virus on day 7 after vaccine receipt (Talbot et al). No subject shed vaccine viruses 10 or more days after vaccination. Duration or type of symptoms associated with receipt of LAIV did not correlate with duration of shedding of vaccine viruses. Person-to-person transmission of vaccine viruses was not assessed in this study." (include titer information when available), (hoped to be available in the next couple of weeks)

*Additional edits* offered and approved at this meeting were to say that to date, transmission has not been associated with disease; the observed risk has been zero; and, rather than "occasionally" transmitted, use "rarely" transmitted.

**LAIV In Healthcare Workers and Close Contacts of Those Severely Immunosuppressed**

"Close contacts of persons at high risk for complications from influenza should receive influenza vaccine to reduce transmission of wild-type influenza viruses to persons at high risk. No data are available assessing the risk for transmission of LAIV from vaccine recipients to immunosuppressed contacts. In the absence of such data, use of inactivated influenza vaccine is preferred for vaccinating household members, health-care workers, and others who have close contact with severely immunosuppressed persons (i.e., patients with hematopoietic stem cell transplants or severe combined immunodeficiency, but not diabetics, asthmatics taking steroids, or patients with human immunodeficiency virus infection) because of the theoretical risk that a live, attenuated vaccine virus could be transmitted to the severely immunosuppressed person and cause disease. Otherwise, no preference is given to either inactivated influenza vaccine or LAIV for vaccination of other healthcare workers or healthy persons aged 5–49 years in close contact with all other groups at high risk."

If a healthcare worker receives LAIV, the healthcare worker should refrain from contact with severely immunosuppressed patients for seven days after vaccine receipt. Hospital visitors who have received LAIV should refrain from contact with severely immunosuppressed persons for seven days after vaccination; however, such persons need not be excluded from visitation of patients who are not severely immunosuppressed. "

*Additional edits* offered and approved at this meeting were to:
*Edits suggested* included to: change general terminology from shortcuts such as "diabetics" to "patients with diabetes"; dropping contact with HIV patients as an exclusion category'; adding ACIP support for surveillance to achieve as real-time as possible data on vaccine effectiveness; and using the HICPAC/infection control term of "protective environment" as the indicator of the severely immunocompromised patients intended to be covered by this recommendation. Left unresolved until later in the meeting was whether to categorize the risk of contact with an immunized healthcare worker as mild or moderate, or to list specific patient conditions of concern.

**Personnel Administering LAIV**

"Environmental contamination with vaccine viruses is likely unavoidable when administering LAIV. The risk of acquiring vaccine viruses from the environment is unknown but likely to be small. Severely immunosuppressed persons should not administer LAIV. However, other persons at high risk for influenza complications may administer LAIV. These include persons with underlying medical conditions placing them at high risk or who are likely to be at risk, including pregnant women, asthmatics, and persons aged ≥ 50 years."

*Edits agreed to were* to delete sentences 1 And 2 and then to move sentence 3 ("Severely immunosuppressed persons should not administer..." to the end of the paragraph. The next sentence would begin "Other persons at high risk of influenza complications may admin LAIV. Obviously, ill people cannot do so."

**Vaccination of Pregnant Women**
Paragraph 1 addresses the morbidity in pregnant women.

Paragraph 2 adds: Because of the increased risk for influenza-related complications, women who will be pregnant during the influenza season should be vaccinated. A study of influenza vaccination of > 2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine (*129* -- Heinonen OP, Shapiro S, Monson RR, et al. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. Int J Epidemiol 1973;2:229-35).

Paragraph 3 addresses the thimerosal issue.

**Strong Recommendation for Health Care Workers and Others in Close Contact With High Risk Persons.**

"Persons who are clinically or subclinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce influenza-related deaths among persons at high risk. Evidence from two studies indicates that vaccination of health-care personnel is associated with decreased deaths among nursing home patients (*110,111*). Vaccination of health-care personnel and others in close contact with persons at high risk, including household contacts, is strongly recommended."

**Pediatric Dosing Schedule Clarification**

Page 12, Subsection: Dosage, first paragraph

2003 Language: "Dosage recommendations vary according to age group. Among previously unvaccinated children aged <9 years, two doses administered ≥1 month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December.

2004 Proposed Language: "Dosage recommendations vary according to age group. Among previously unvaccinated children aged <9 years, two doses administered ≥1 month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. If a child aged < 9 years receiving vaccine for the first time does not receive a second dose of vaccine within that season, only one dose of vaccine should be administered the following season. Two doses are not required at that time.

**Expanding the recommendations for the use of inactivated LAIV.**

The introductory paragraph to the full section on the use of influenza vaccine, at the beginning of the document, was amended (in red) as follows:

> "Influenza vaccine is strongly recommended for any person aged ≥6 months who is at increased risk for complications from influenza. In addition, health-care workers and other persons (including household members) in close contact with persons at high risk are strongly recommended to be vaccinated to decrease the risk for transmitting influenza to persons at high risk. Influenza vaccine also can be administered to any person aged ≥6 months to reduce the chance of becoming infected with influenza. "

**Influenza Vaccine Supply**
Page 16, Subsection: Inactivated Influenza Vaccine Supply, first paragraph

2004 Proposed Language: "In 2000, difficulties with growing and processing the influenza A (H3N2) vaccine strain and other manufacturing problems resulted in substantial delays in distribution of 2000–01 influenza vaccine, and fewer vaccine doses were available than had been distributed in 1999 (205). In 2001, a less severe delay occurred, although, by December 2001, approximately 87.7 million doses of vaccine were produced, more than in any year except the 1976–77 swine influenza vaccine campaign (206,207). During 2002, approximately 95 million doses were produced by the end of November, and approximately 12 million doses remained unsold by the vaccine manufacturers. During 2003, despite manufacture of approximately 87 million doses of vaccine (including both inactivated and live, attenuated preparations), the season was marked by spot vaccine shortages due to unprecedented demand, largely attributed to media reports of severe pediatric illnesses and deaths during a severe influenza A (H3N2) season.

"Influenza vaccine delivery delays or vaccine shortages remain possible in part because of the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains. Steps being taken to address possible future delays or vaccine shortages include identification and implementation of ways to expand the influenza vaccine supply and improvement of targeted delivery of vaccine to groups at high risk when delays or shortages are expected."

**Reporting Adverse Events After Vaccination of Children**
"Health care professionals should promptly report all clinically significant adverse events after

influenza vaccination of children to the Vaccine Adverse Event Reporting System (VAERS) even if the health care professional is not certain that the vaccine caused the event. The Institute of Medicine has specifically recommended reporting of potential neurologic complications (for example, demyelinating disorders such as Guillain-Barré syndrome), though there is currently no evidence of a causal relationship between influenza vaccine and neurologic disorders in children."