CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL IMMUNIZATION PROGRAM

RECORD OF THE MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

October 27-28, 2004

Meeting held at the Atlanta Marriott Century Center Hotel

Atlanta, Georgia

Acronyms Used In This Report

(S)AE	(Significant or Severe) Adverse Event (Effect)
AAFP	American Academy of Family Practitioners
AAP	American Academy of Pediatrics
ABC	Active Bacterial Core (surveillance system)
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetrics and Gynecology
AFEB	Armed Forces Epidemiological Board
ASTHO	Association of State and Territorial Health Officers
BRFSS	Behavioral Risk Factor Surveillance Survey
CAIV-T	Cold-Adapted Influenza Vaccine - Trivalent
CDC	Centers for Disease Control and Prevention
CE	Cost Effectiveness
CI	Confidence Interval
CK-MB	Creatine Kinase-containing M and B subunits
CSTE	Council of State and Territorial Epidemiologists
CMI	Cell-Mediated Immunity
CMS	Centers for Medicare and Medicaid Services
COID	Committee on Infectious Disease
DHHS	Department of Health and Human Services
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GAVI	Global Alliance for Vaccines and Immunization
GBS	Guillain-Barré Syndrome
GMT	Geometric Mean Titer
gp	Glycoprotein
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus (Vaccine)
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HPV	Human Papilloma Virus
HZ	Herpes Zoster
IAC	Immunization Action Coalition
IDU	Injection Drug Users
IM	Intramuscular
IHS	Indian Health Service
IND	Investigational New Drug
IOM	Institute of Medicine
IRB	Institutional Review Board
IVCD	Inferior Vena Cava Diameter (Dimension)
LAIV	Live Attenuated Influenza Vaccine
LV	Left Ventricular (function)

MI	Myocardial Infarction
MCV/MPSV	Meningococcal Conjugate Vaccine/Meningococcal Polysaccharide Vaccine
MMRV	Measles, Mumps, Rubella, Varicella (vaccine)
MMWR	Morbidity and Mortality Weekly Report
MSM	Men who have Sex with Men
NACCHO	National Association of County and City Health Officers
NCHSTP	National Center for HIV, STD and TB Prevention
NCID	National Center for Infectious Disease
NGO	Non-Governmental Organization
NHANES	National Health and Nutritional Examination Survey
NHIS	National Health Interview Survey
NIAID	National Institute for Allergies and Infectious Diseases
NIP	National Immunization Program
NNDSS	National Notifiable Diseases Surveillance System
NREVSS	National Rotavirus and Enterovirus Surveillance System
NSAID	Non-Steroidal Anti-Inflammatory Drug
NVPO	National Vaccine Program Office
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
QALY	Quality Adjusted Life Year
QTC	Quantitative Tip Culture
RCD	Reverse Cumulative Distribution
RFP	Request For Proposal
RIA	Rabbit Immunoassay
SBA	Serum Bactericidal Assay
SI	Serum Immunoglobulin
STD	Sexually Transmitted Diseases
ST	Stress Test
TIV	Trivalent Influenza Vaccine
U.K.	United Kingdom
USPSTF	U.S. Preventive Services Task Force
URI	Upper Respiratory Infection
VAERS	Vaccine Adverse Events Reporting System
VE	Vaccine Efficacy
VFC	Vaccines for Children (Program)
VICP	Vaccine Injury Compensation Program
VIG	Vaccinia Immune Globulin
VIT	Vaccine Injury Table
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VTEU	Vaccine Trials Evaluation Unit
VZV	Varicella Zoster Virus
WHO	World Health Organization

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MINUTES OF THE MEETING

OCTOBER 27-28, 2004

OCTOBER 27, 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 October 27-28, 2004. The meeting agenda was posted on CDC's Website (http://www.cdc.gov/nip/). The meeting was convened by ACIP Chairmen Dr. Myron Levin at 9:11 a.m. He welcomed the attendance of CDC Director Dr. Julie Gerberding and all those present. The latter are listed on the attached sheets (Attachment #1).

Opening Comments

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

- New ACIP members at this meeting, who will fill four-year terms, were Dr. Tracey Lieu, Dr. Julie Morita , and Ms. Patricia Stinchfield.
- The first attendance of new liaisons at this meeting were by Dr Amy Middleman (Society for Adolescent Medicine), Dr. Nancy Bennett (National Association of County and City Health Officials), and Dr. Peter Paradiso (Pharmaceutical Research and Manufacturers Association of America).
- ACIP Workgroups to confer at this meeting were those to address influenza, adult immunization, human papilloma virus, evidence-based recommendations, and meningococcus vaccine. On the previous day, the Workgroups on hepatitis, rotavirus, and pertussis had met.
- The ACIP home page is www.cdc.gov/nip/acip; e-mail is at acip@cdc.gov.
- The next ACIP meetings will be on February 10-11, June 29-30, and October 26-27, 2005, at the Century Center Marriott.
- 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 members) of members qualified to vote. If voting, the ex-officio members are asked to disclose any potential conflicts of interest. Meeting time is reserved for public comment at scheduled intervals, but may also occur during open discussion if a speaker is recognized by the Chair. ACIP members with potential conflicts of interest are asked to disclose all vaccine-related work and financial interests, and to refrain from any discussion or vote that is related to such matters. When needed, however, limited waivers of such conflicts of interest are granted, to enable the members to provide their expertise to the Committee. Waivers may be issued, for example, to members who also conduct clinical vaccine trials or serve on Data Safety Monitoring Boards (DSMB). Those members may provide information to the committee on matters related to those vaccines, but they may not participate in the discussion or in related votes. They may discuss other vaccines produced by the same company, but not vote on matters related to that company's vaccines.

The members and liaisons then introduced themselves (see Attachment #1). Those reporting potential conflicts of interest were Dr. Greg Poland (grants from Chiron, VaxGen, and Merck Research Laboratories), Dr. John Treanor (Wyeth, MedImmune, ID Biomedical), and Dr. Levin (clinical trials for GlaxoSmithKline [GSK], Merck, and Merck's DSMB).

AGENDA ITEMS

Influenza Vaccine Shortage

Report of the CDC Director
Presenter: Dr. Julie L. Gerberding, Director, Centers for Disease Control and Prevention

Overview: CDC response to the influenza vaccine supply shortage.

Dr. Gerberding offered her thanks to the wide variety of CDC's partners who are helping to address the influenza vaccine shortage stemming from Chiron's manufacturing shut-down: the NIP and NCID's Influenza Branch staff, CDC's communications staff, the front-line public health servants across the United States, and the citizens deferring their own immunization to ensure that those most in need are immunized.

On the day of Chiron's announcement, the ACIP assisted CDC's first round of prioritizations and vaccination target recommendations. CDC's Communications and Emergency Operations Center is in full operation. Under the lead of the Coordinating Center for Infectious Disease, Operation Influenza coordinates CDC's multiple entities' response to all the aspects of the shortage's challenges (e.g., surveillance; guidelines; informatics; supply diversion, development of worst-case preparedness scenarios and possible solutions, etc.).

The slow start of the influenza season helped the distribution of available vaccine. Early indicators suggest a good vaccine match to the current circulating virus. As of this week's end, CDC will have distributed 9.5 million additional vaccine doses. First priority for these goes to children, followed by the frail elderly, veterans/troops, and those most vulnerable to the complications of influenza. More vaccine in production by Aventis and MedImmune will be distributed equitably. This is being done based on the evidence and in coordination with state and local health officials. The manufacturers, Aventis being particularly named, have been extraordinarily cooperative in sharing normally proprietary information in order to identify gaps and to reallocate vaccine to the areas of most need. Ongoing surveys are being conducted in long-term care facilities to determine the potential number of patients needing immunization. Associations in all sectors, private, public, not-for-profit, and faith-based, are helping.

CDC will continue to refine the forecast of vaccine shipments. Currently, 61 million doses are in stock for this influenza season and efforts are underway to identify more doses. There are enough antiviral drugs to treat 40 million people, and interim guidelines for antiviral use have been distributed. The Advertising Council of the U.S. donated TV and radio spots to educate the country on the issues of the shortage.

Discussion included:

- ❖ Prospective examination was advised of orders pending with Aventis, as well as those already shipped, to aid equitable distribution. Dr. Gerberding agreed, and cited several examples of the cooperation evident in responding to the shortage.
- ❖ The CDC Website is getting >300,000 hits a day, with influenza as the primary pick. The site information addresses the needs of doctors, the business community, institutional human resources, etc. The basic message is that those sick with influenza should stay home. The support for this by employers and schools is urged.

CDC Actions/Plans

Presenter: Dr. Lance Rodewald, NIP

Overview: Program planning before October 5, 2004; distribution pattern at that time; immediate steps taken; public health challenge.

This year was the first in which universal recommendation of influenza vaccination for children was promoted by the ACIP and embedded in the schedule of the very influential childhood immunization program. The ACIP voted to include influenza vaccine in the subsidized Vaccine for Children (VFC) program to ensure its provision to the nation's under- and uninsured children. The media coverage of last season's early and aggressive course and of pediatric deaths also raised the public's interest in influenza vaccination.

Chiron had seven distributors and had also filled partial orders. Aventis distributes ~85% of its supply in a staggered fashion directly to all their end users, allowing many of them to begin vaccinating early. As of October 4, they had distributed ~33 million doses to all types of customers at all levels of disease risk, and not according to market share. Chiron expected only a month's delay in shipping theirs while some of the contaminated lots were investigated.

When it became clear that no orders would be shipped, the resulting distribution gap related to Chiron's vaccine orders. Because both companies serve the entire country, the disparities were not geographical. One local provider might have vaccine because the order went to Aventis, while the next would not because they ordered from Chiron.

Response. On October 5, Aventis stopped shipping their remaining 22 million doses., and with CDC began formulating an allocation plan for the remaining inactivated vaccine. The ACIP met in emergency session to advise CDC on reducing the targeted groups from 185 million overall to 95 million, and from 20 million children to 9 million (actually, ~13.5 million doses, since some children needed two doses).

Public health faced a challenge to allocate the 22 million doses as well as possible to fill the critical distribution gaps; to facilitate community efforts to redistribute the vaccine; to identify providers for targeted individuals and reduce inappropriate vaccination; to make effective use of the live attenuated (LAIV) vaccine in order to spare doses of the inactivated vaccine for individuals unable to receive the LAIV; and to identify any other sources of vaccine.

The 2002 vaccine distribution was charted with data from the Behavioral Risk Factor Surveillance Survey (BRFSS). Also charted was that distributed in 2004 before October 5. It showed that the vaccine in 2004 was not where people were accustomed to receiving it, as it was in 2002: primary care providers, hospitals, workplace, health departments, clinics, etc.

Information dissemination has been an essential ingredient to meeting the challenge. It also has been unprecedented, in terms of health officials' access to industry proprietary information for use in guiding whom to vaccinate, or not. Also unprecedented has been the partnerships to meet this challenge and the quality of communication involved.

Vaccine Allocation and Distribution to Date
Presenter: Dr. Jean Santoli, NIP

Overview: CDC distribution goal and approach to reach high risk patients.

CDC developed a distribution plan to reach the maximum number of providers treating priority patients, to be done in two simultaneous phases.

Phase 1 will identify Aventis' and Chiron's orders for providers and public contracts, and those pending. Distributors and key stakeholders will be identified to resume vaccine shipments as fast as possible to priority groups. The doses to be filled were charted, by provider/order groups as of October 5.

- Orders to be filled 100% were to: 1) providers caring for children: the VFC program, pediatricians, and the preservative-free Aventis orders for children aged <3 years; 2) long-term care facilities and hospitals; and 3) the Veterans Administration's federal contract with Aventis (which includes the Indian Health Service's orders).
- Orders filled at <100%: ~75% to 1) mass community vaccination providers (much of these orders were already shipped), and 50% to 2) the Visiting Nurses Association of America for their high risk patients, 3) office-based providers who ordered from Aventis, and 4) state/local public health (except for those ordering from Chiron, who are addressed in Phase II).

Phase II will work at the state and local levels to determine the pending orders to Aventis and Chiron, then work with locally-supplied information to direct the supply to high risk patients and their providers. The focus is on orders from long-term care facilities, hospitals, pediatricians and other primary care providers, and the local public health departments that ordered from Chiron distributors. Local information is being collected on the orders' magnitude and geographic distribution. Follow-up will be done with state and local public health officials about the remaining needs after their 50% deliveries and about any orders falling outside the paradigm (e.g., public health orders for high priority long-term care facilities).

Public health has secure access to CDC's Influenza Vaccine Finder system, created to monitor and manage the vaccine supply. Based on their established relationships with providers and community institutions, they may monitor the supply, directly administer the vaccine, reallocate it as needed, and most importantly, communicate and provide guidance to providers and the public.

Phase I vaccine shipments resumed in the second week of October and will continue through December 19, at ~3 million doses a week. Aventis will ship an additional 4 million doses. When Phase II planning is complete, shipment of those orders will begin. FDA and CDC are exploring purchase options abroad for availability later in the season.

Discussion included:

- Defining the process for identifying targets with state/local levels is ongoing with CDC's public health partners, including ASTHO, CSTE, and NACCHO.
- Possible other vaccine delivery methods than the 0.5 cc intramuscular (IM) injection were inquired. For example, an NIH preliminary report indicated that a 0.25cc dose might be adequate for immunity and would double the supply. Or, an intradermal dose might increase vaccine effectiveness 5-10%. But the half-dose studies were done among healthy individuals, not the targeted groups. Some of those studies, and others on intradermal injection, have been submitted for publication. However, the use of such methods is unlikely this year due to insufficient supporting data.
- CSTE suggested that CDC catalog the states' activities to assess the impact on outcomes. Through the BRFSS' random digit dialing survey, monitoring is being done in real time and through the influenza season to ensure that the vaccine goes to those in need. This is the first such real-time assessment done of influenza season strategies and outcomes on a population basis. The BioSense electronic system for collecting health information nationally will also supply data from DoD clinics to help assess the national status.
- The need to target to high risk patients has been stressed to those getting 100% of their orders.
- MedImmune developed a plan to target their orders of the FluMist® LAIV to providers, using smaller order sizes, so as to focus on (but not necessarily limit it to) the priority groups. Public health also has ordered some of that vaccine for use in the states and DoD is using FluMist® to preserve their injectable vaccine supply in some settings.

FDA Perspective

Presenter: Dr. Norman Baylor

Overview: FDA activities to identify additional vaccine sources.

FDA is exploring all possible options of vaccine access, foreign manufacturers as well as product made by Aventis Pasteur and MedImmune. It is illegal to import other vaccine to the U.S., except for use under an IND with informed consent. This is being explored with CDC. Communications are underway as well with Health Canada, SwissMedic, and the Pharmaceutical and Food Safety Bureau of Japan, etc., for information on their licensed companies for possible importation and IND protocol use. FDA is doing this under a "master file" procedure, which allows information to be gathered on manufacturing and clinical experience for expedited review. As potential sources are identified, FDA will inspect their facilities. Some inspections will probably occur in the next few days and weeks. They are discussing plans for the 2005-06 season with the current U.S.-licensed vaccine manufacturers. And as possible, are facilitating the entry of other vaccine manufacturers to the U.S. market. Particularly, they are discussing a a clearer licensure strategy to invite new influenza vaccine manufacturers in for future seasons.

Discussion included that there is no product status between licensed or unlicensed. Rapid vaccine licensing prevents FDA from thoroughly evaluating the vaccine's safety and efficacy. The public knows that a licensed product has been thoroughly evaluated, the absence of such warranty for an unlicensed/IND administered vaccine would have to be clear. However, FDA will work out the details with CDC on how to facilitate this process. One way might be to use a national IRB to govern the use of foreign vaccines, or other vaccine models (e.g., as used for the smallpox vaccine). It will be months before the shortage can be alleviated, perhaps by December

or January. Some manufacturers have been found, but they have a limited number of doses. To get a million or more, more manufacturers have to be identified, their facilities inspected, and work done with DHHS to distribute them.

DHHS/NVAC/NVPO Perspective
Presenter: Dr. Bruce Gellin, NVPO

Meeting the nation's vaccines needs is a moving target, as different companies have different vaccines available at different times. The vaccine would have to be suitable for the northern hemisphere this year, and in a quantity to be determined (but perhaps ≥2 million doses). Managing an IND is complicated by the national scope of the vaccination and the multiple products with potentially different indications. There also is the question of liability, which is being addressed and may be covered under the VICP.

A lack of information has caused long lines. That should be alleviated when it can be estimated when the vaccine will get to communities. Media attention includes articles of governments (e.g., New York, Illinois) that are seeking to buy their own vaccine. Far beyond an IND application, that raises other practical implications such as proper shipment and storage.

NVPO has had active communication with all involved since the contamination. An additional 50 (and perhaps 58) million doses is projected to be released by Aventis, and there are other discussions underway with Merck about increasing production of the pneumococcal vaccine. Antivirals have been placed in the Strategic National Stockpile as well as those already distributed. Some influenza vaccine price gouging has occurred; one Florida company has been charged with selling it for $900 per vial. A federal task force with DHHS, Justice, the FTC, DHS and the VA is coordinating efforts this year and addressing the supply for both this year and next..

- *Discussion* included:
- Mr. Phil Hosbach reported that Aventis is continuing to have unusually good vaccine yields, which will allow them to produce a total of 58 million doses. About 2.6 million will be available by the end of January 2005.
- Fortunately for this season, companies in Europe as well as the U.S. have a long history of producing more vaccine than is purchased. Some is made in monovalent bulk for final production, an excess that could be used. Many of these manufacturers also supply product globally, not just for one country, so a lower demand than predicted would result in extra vaccine. That is the situation that FDA is seeking.

Local and State Level Perspectives

Local level prioritization.
Presenter: Dr. Jody Hershey, Southwestern Virginia Health Officer and past President, NACCHO

NACCHO is receiving questions from "just about everyone" at the local level (e.g., primary care providers, nursing homes), none of whom expect to have sufficient vaccine for all their priority individuals. They find that the necessity for prioritization is pitting groups against each other, such as the elderly in nursing homes versus community residents. Local health departments are

asking if supplies should be sent to nursing homes or kept for community-based clinics. The nursing homes face the ethical implications, given only half their needed supply, of deciding whether to vaccinate the staff or the patients, or to vaccinate the staff and quarantine the patients for the winter? Community clinics ask if the healthy elderly should be vaccinated, or foregone in order to vaccinate children? And, ironically, while it appears that the VFC will vaccinate their eligible children, those with health insurance may not receive it.

NACCHO has been tracking member experiences in yet another shortage year to see how to operationalize guidelines in jurisdictions. Among the many prioritization schemes they have recorded is Montgomery County, Maryland's, which held a lottery for the 800 doses they received for priority patients. Massachusetts is reserving 15% of their allocation for high priority patients; another district is limiting vaccination to exclude healthcare workers, prenatal providers, etc. Troy, North Carolina, is only vaccinating patients with a note from their provider confirming their high risk status, and is not vaccinating pregnant women. Refined prioritization schemes would have been helpful from the outset of the shortage.

ACIP is the gold standard out in the field and most attend to their recommendations. But Dr. Hershey had to wonder how much value a further prioritization would offer this year, given the extent of local prioritizations in the last few weeks. Now may be the time for ACIP to simply support the judgments of state/local health officials. Adding more refined prioritization could just confuse the public and, if the revised standards differ from their priorities, undermine the health officials' authority to ration.

State level prioritization.
Presenter: Dr. Gus Birkhead, New York State Department of Health

The New York state health department's experience is not necessarily generalizable, but it does reflect the current challenges to provide answers. It is hard for the public to understand the health department's greater problems in controlling flu than other diseases, since it is statutorily responsible to protect the public's health.

The health department can control vaccine supply in outbreak situation (e.g., community-wide vaccination in a meningitis outbreak) and they know that the local level's community context is key to a distribution strategy. But historically, most state/local health departments have had a limited role in distributing influenza vaccine (~5-10% of the supply), and they have focused more on children's than adults' immunization in the past. So, while they are not the main supplier of vaccine, they play a key role in coordinating supply according to need. A survey of clinics, nursing homes, providers, etc., was done to determine their vaccine orders and needs. The baseline they established as of October 5 indicated that nursing homes, more than hospitals or others, had ordered mostly from Chiron. ACIP's guidelines for standards of care were presented as the state standards, which gave them "teeth." Letters were written to the vaccinating community and public education began

The Minnesota government participated with Chiron in a multistate vaccine contract. They provided each state's ordering point with a complete list of who had ordered, and arranged half-shipments to them from Aventis. But beforehand, they asked the state health department if any changes should be made, and some that was to be shipped to the general population instead went to the health department.

Dr. Birkhead thanked CDC and Aventis for the states' access to proprietary data. He hoped to have that prospectively as well, to further guide state/local distribution planning. New York had ordered 50,000 doses, based on last year's experience and now needed to decide if that should go to nursing homes or elsewhere. Managing all this closely enough to ensure the vaccine gets to those in need will be a big challenge, particularly since demand may increase due to publicity on the shortage. He agreed with Dr. Hershey that making a major change now would be confusing at least and disruptive at worst. Local determinations should be supported and guidance provided as best as possible.

The lessons learned for future influenza seasons, and for avian and pandemic influenza situations as well, are: 1) vaccine should be under the control of the public health departments, as with any other disease outbreak. And 2) a consensus is needed on who gets vaccine first in a limited supply situation. Practical guidance is needed.

Discussion included:

- The ACIP teleconference raised the issues of sub-prioritization, but such fine-tuning was not possible at that time. CDC is now including medical ethicists in their discussion of general supply considerations and what further can be done now. The Influenza Workgroup was asked to address these issues for the future as well.
- Dr. Cochi clarified that institutions such as nursing homes, long-term care, hospitals, etc., that care for high risk patients will receive 100% of their vaccine orders.
- The literature's bulk of information on various groups' risk could be useful to organizations or regions to define the relative risk even within high priority groups. But many are less familiar with that information than they should be. There are also knowledge gaps about the risks for certain groups (e.g., healthy 40- vs. 65-70 year-old individuals and risks of household contacts), and there is uncertainty about the value of immunizing healthcare workers. More information is needed for the next and subsequent years.
- Dr. Martin Myers reported that NVAC's consideration of such issues as regards a pandemic. With the importance of prioritization in planning and response, he asked DHHS to add prioritization to the pandemic plan now on its Website.
- Dr. Zeil Rosenberg, of Becton-Dickinson, reported hearing that a low-dose syringe used world-wide would be approved for use in the U.S. These are auto-disabled syringes that force dose accuracy and will help expand the supply by reducing wastage. His company is looking for guidance on the use of that and other technologies.
- Public education on how to limit exposure began during the SARS epidemic (e.g., cover a cough, stay home if ill), but was not evaluated. Other methods, such as well-described infection control measures, could be applied to communities (e.g., cohorting patients).
- Howard Bedecker, of the California Immunization Program, disagreed that ACIP prioritization recommendations now would be unhelpful. His impression was that the ACIP's goal was to decrease morbidity and hospitalization, or older patients would be prioritized over the young. He did not understand why pediatricians, who also order for healthy children, would receive 100% of the vaccine while the doses to internists, who may have higher risk patients, are reduced. California's health department is not allowed to redirect pediatricians' doses out of the VFC supply, even if they offer those for their healthy patients. This prioritization scheme also would not be protective in a pandemic, when the social infrastructure would need to be protected first. He recommended greater transparency in the rationales that support ACIP prioritization.

Current ACIP Recommendations
Presenter: Dr. Scott Harper

Overview: Review of current recommendations and questions addressed by CDC related to the influenza vaccine recommendations.

The priority vaccination groups, considered of equal importance, are: all children aged 6-23 months; adults aged ≥65 years; persons aged 2-64 years with underlying chronic medical conditions; women who will be pregnant during influenza season; residents of nursing homes and long-term care facilities; children aged 6 months to 18 years on chronic aspirin therapy (to prevent Reye's Syndrome); health care workers involved in direct patient and out-of-home healthcare; and household contacts of children aged <6 months.

For live attenuated influenza vaccine, the current ACIP recommendation encourages the use of internasally administered LAIV for healthy persons aged 5-49 years who are not pregnant. That group includes health care workers and persons caring for children aged less than six months.

Children aged ≤9 years require two doses. All children at high risk for complications from influenza, including those aged 6 to 23 months, who present for vaccination should be vaccinated with a first- or second dose, depending on their vaccination status. Doses should not be held in reserve to ensure that two doses will be available. Instead, available vaccine should be used to vaccinate persons in priority groups on a first-come, first-served basis. Nonpriority groups are persons not included in one of the other priority groups. They should be informed about the supply situation and asked to forego or defer vaccination.

Some of the questions received by CDC since October 5 include the following:

- *Does CDC recommend using partial doses of influenza vaccine?* No.
- *How is "direct patient care" defined?* The groups were not listed, but conceptually, this would be activities with the potential to spread influenza through direct face-to-face contact. The language was crafted to allow some latitude at the local level.
- *Should international travelers be vaccinated?* No, not unless they are also in one of the priority groups.
- The fact that there is no FDA-approved drug for children aged <1 year is another prioritizing factor, not only for children but also for household contacts.
- Dr. Keiji Fukuda, of NCID's Influenza Branch, stated that the complexities of this situation are still being addressed. Precedence in earlier vaccine shortages was given to people at high risk, and the long-range vaccine program goal was to protect people as much as possible. The challenge in a shortage is how to truncate the process without derailing progress in raising vaccination levels. Deciding who should get the vaccine is difficult. The federal government can provide guidelines in an ongoing manner, but the local communities and health departments have a hands-on role in implementing them.
- Schools with students who have only exercise-induced asthma have been asked not to provide influenza vaccine. A pulmonologist should be consulted to advise whether these children should be a lower priority than those with chronic asthma, for example.
- Many questions remain about how to address the different types of patients in a clinic. How is it decided what the cutoff for immunosuppression should be? Some patients take low-dose steroids; are children with fixed position congenital heart disease at risk or not?

Individual decisions will often be required.

- By statute, VFC vaccine cannot be given to children who are not eligible for that program. Those eligible are uninsured children in Medicaid, American Indian, Alaskan native, and under-funded children seen in federal vaccination programs. Since the uptake is always a little slower than desired, the VFC doses ordered (4.1 million) are unlikely to be wasted. The 9 million VFC-eligible children will require 13.5 million doses since some need two vaccinations.
- Dr. Zimmerman suggested issuing an ACIP statement that some prioritization may be needed at the local level, depending on local circumstances.
- Dr. Nichol was reassured by CDC data on the numbers of high-priority individuals and the doses needed to immunize them (40 million) at past immunization levels. A stock of 60 million doses could accommodate a 50% increase in demand, something that has not happened to date.
- However, media attention could well increase demand, and 33 million doses had already been shipped, with an unknown number given to healthy people. That makes it now uncertain that there is enough vaccine for all risk groups.
- Care was advised that the calming messages issued to the public not give the impression that the vaccine really is not needed.
- One group not listed in the priority groups was the household contacts of immune-suppressed individuals, a guiding principle of oncology. The reason was that there is no contraindication to using killed vaccine among immunocompromised populations.
- Dr. Nancy Bennett, of Monroe County, NY, stated that the country depends on the private sector to deliver most of the vaccinations in the U.S. In cases like this, physicians depend on public health's prioritizations to support their implementation of those with their patients. Now, national prioritization is too late; the local situations have already been handled. But it is critical for ACIP to address this for the future to avoid inequitable distribution.

CDC Recommendations on the Use of Antivirals

Presenter: Dr. Scott Harper, NCID

Overview: October 2004 interim recommendations on the use of antivirals to reduce the impact of influenza on those at high risk for severe complications secondary to infection; guidance on which agents to use for prophylaxis versus treatment; priority use of antivirals; when antivirals may be considered; populations to use antivirals and contraindications for chemoprophylaxis use; use of the Strategic National Stockpile's antiviral.

1. For **antiviral chemoprophylaxis** of influenza, CDC encourages the use of **amantadine or rimantadine; for treatment,** use of **oseltamivir or zanamivir,** as supplies allow. This recommendation is in part to minimize the development of amantadine or rimantadine resistance among circulating influenza viruses. That resistance to the latter two is more likely to occur than to neuraminidase inhibitors. The Asian avian influenza has also been resistant to adamantanes; in that case, neuraminidase inhibitors would be needed.

(2) Priority groups for the use of antiviral **treatment** are those with a potentially life-threatening influenza-related illness, those at high risk for serious complications of influenza and who are within the first 2 days of illness onset. **Priority groups for chemoprophylaxis** are: 1) in institutions caring for high risk persons; patients and unvaccinated staff exposed to outbreaks

for its duration, and vaccinated staff for the first two weeks of the outbreak; and 2) those at high risk likely to be exposed to persons infected with influenza, such as in a family/household setting, for 7 days.

3. Antivirals used as **prophylaxis** may be considered in communities where influenza viruses are circulating, among: 1) high risk persons unable to be vaccinated; 2) vaccinated high-risk persons during the post-vaccination period when their full immune response is building; 3) immunosuppressed persons who might not mount adequate response to vaccine; and 4) unvaccinated healthcare workers with direct patient care responsibilities. To allow leeway at the local level, treatment of persons without high-risk conditions also can be considered, but not as a priority group.

4. Antivirals are **not recommended** for prophylaxis of non-high risk individuals, since supplies of both vaccine and antivirals may be insufficient.

5. Antivirals stored by the Strategic National Stockpile serve as a resource when antivirals are unavailable through the private sector. These may be requested only by state and territorial health departments upon an urgent priority need due to an inability to procure medicine from private distributors. Rimantadine in tablets and syrup is currently stockpiled.

Discussion included:

- *ACP was concerned over how the recommendations, although good, would be functionally implemented. Antivirals would have to be immediately available to address an influenza outbreak in a nursing home. Will the distribution/allocation be more orderly than that seen for vaccine? To be prepared, should providers, who do not use these much now, order them or work with the health department?* Both. They should educate their patients that these drugs can be used when influenza symptoms begin, and they should check around for supply (e.g., hospitals or pharmacies).
- *Will there be another Website set up, as done to locate the closest influenza vaccine supply? And what is the supply?* There is no such activity to set up such a secure Website. The supply is currently projected at 40 million doses available, and 5 million in the stockpile. The tablets and syrup can be use either for treatment or chemoprophylaxis.

CDC Communications Update

Presenter: Dr. J. Anderton, CDC, Office of the Director

Overview: Summary of CDC's public health messages and public service announcements; communications outreach to and through partner organizations.

CDC's first messages upon issuing the interim guidance were to emphasize the priority groups for vaccination. In response to the long lines for vaccination, millions of added doses will be shipped in subsequent weeks. Dr. Gerberding's message to "be patient and persistent" got good media play. Recently, prevention and hygiene messages have been emphasized, such a covering a cough and good hand washing practices. CDC's media monitoring showed good attention to this campaign, and CDC's Website has received 300,000 hits a day to read the messages in multiple languages. The site (Www.Cdc.gov/flu) is updated regularly. It also has fliers and posters for physicians and pharmacists who should or should not be vaccinated.

The previous week, with the Ad Council's help, CDC recorded appeals that were sent to AM and FM stations, asking people to leave the long lines and just use the general preventive measures. Messages for business were also recorded (e.g., Walmart will air them to their shoppers in their stores). Other messages urge that the shot be deferred until after Thanksgiving. Future planned messages will focus on antiviral use when influenza outbreaks occur and related issues, such as pneumococcal vaccination information. Emphasis on the high priority groups will continue. Print ads will run in newspapers in the next 2-3 weeks.

Partner groups working with CDC include business, faith-based organizations, tribal health centers and IHS medical directors and directors of health promotion and education in the states. They will distribute a stopping-germs-at-work fact sheet. CDC issued several updates to the ~41,000 members of its Clinician Registry and conducted a Web-based conference for providers on October 14. The Clinician Information Line received >1300 calls on complex patient issues this month.

Communications plans are being developed for several scenarios, including a severe influenza season. CDC will comprehensively evaluate this communication plan for use in future events.

Discussion included:

- Concern was expressed that the vaccination message is going too far in the other direction. Dr. Plotkin's paper carried an AP story quoting "public health officials" that "… for most, getting a influenza shot is not a life or death matter," and saying the vaccine is only ~58% effective. CDC should stress that this is only an emergency curtailment and will return to promoting influenza vaccine coverage in future. Dr. Anderton responded that those opinions had been expressed in the past as well. It is hard to balance that this year is different and special, without risking declined interest in influenza immunization.
- *Do the communications distinguish between typical virus and flu, to counter misperceptions of what the vaccine will do?* The Website has basic information on influenza symptoms, how it is spread, etc., carried forward from previous years. Dr. Womeadu urged CDC to go beyond the Website to develop other measures to reach those not computer-savvy.

Issues Related To Use of the Live Attenuated Influenza Vaccine Flumist®

Presenter: Dr. Peter Patriarca

Overview: Update since FluMist® was presented to the ACIP in February of 2004; overview of major development initiatives and request for feedback on MedImmune's future plans.

FluMist® fell far short of sales goals in 2003, but post-marketing studies were consistent with the pre-licensure safety profile. MedImmune acquired all rights to FluMist® and liquid cold-adapted influenza vaccine (CAIV-T) from Wyeth. They built a $62 million state of the art manufacturing facility in the U.K., with a capacity to produce 40 million doses. Commercial pricing for FluMist® was reduced. The non-returnable form is now $16 dose and $13.50 for the government. About 1.1 million doses were released and another 2 million will be released in November. MedImmune is working to distribute it to healthy persons aged 5-49 years, within the ACIP priority groups. They also eliminated the need for a vaccine freeze box this year, and hope to do so permanently.

But confusion about CDC guidance persists. It states that FluMist® is a good option for all healthy people aged 5-49 years, but several state laws now restrict FluMist® only to contacts of infants aged <6 months and healthcare workers. Doses in physician offices are unused. Almost 40% of mothers of infants aged <6 months are nursing and therefore cannot receive FluMist.

Two postmarketing studies are underway:.

1) A Kaiser safety study in California enrolled ~9000 people to compare their outcomes to other control groups and found a similar adverse event profile to prelicensure studies. This study is in year two. Vaccine effectiveness studies are being planned.
2) Shedding and transmission was studied among 300 subjects to analyze virus recovery and immunogenicity. The results are due in May 2005.
3) The FluMist® transmission risk to those who are immunocompromised was studied in both HIV-infected adults and children (300). A new study will follow 20 children on chemotherapy. NIH is also doing a study to compare FluMist® to TIV.
4) Year two of the "SchoolMist" study is underway with Johns Hopkins University, to compare control schools in northern Maryland with schools where FluMist® is offered. A pharmacoeconomic outcomes evaluation done in year one of the children and their families was encouraging.
5) The liquid formula, CAIV-T, is a refrigerator-stable formulation (thanks to the addition of arginine and procine gelatin) with the same active ingredients as FluMist®. Developed in parallel by Wyeth, it improved FluMist® in some ways, such as enhanced purity from additional processing steps. It was clinically tested in >16,000 subjects, 10,000 of them young children. Product characterization and clinical immunogenicity comparisons were done to determine whether FluMist(r) and CAIV-T have the same immunogenicity response. That should be presented to FDA before July 2005.
6) A signal identified in the Kaiser study indicated a 0.5% increased absolute asthma risk in the vaccine group compared to the placebo group. But there was no clustering of these events and asthma was significantly decreased in older children. Two studies explored this:
    a) CAIV-T was given to ~2000 children aged 6-71 months with diagnosed recurrent respiratory tract disease, who were monitored for culture-confirmed influenza. No statistical difference emerged from the analysis, although there was a slight increase in the CAIV-T group in comparison to the TIV group.
    b) CAIV-T was given to >2000 children with asthma in Europe, who also were monitored for culture-confirmed influenza. Uniformly nonsignificant differences were found, and a very small absolute increase was seen in the CAIV-T group versus the TIV group.

Wyeth's efficacy research compared the attack rate in the TIV group to that of the CAIV-T group and showed ≤53% relative attack rate reduction. The asthma study showed a similar but lower (35%) reduction. In terms of relative risks and benefits, there could be a slight increase in asthma rates among FluMist® recipients, but that may be balanced out over the course of an influenza season. To determine that, MedImmune is doing a trial with 7000 children at 300 different sites globally. Only those who are immunocompromised or who have significant active asthma were excluded. The placebo control group will be compared to one with an injected placebo and another given an intranasal placebo; the secondary endpoint is medically significant wheezing. The outcomes in the immediate post-vaccination period will be compared to the vaccination benefits throughout the influenza season over one year.

In summary, MedImmune is aggressively pursuing additional studies outside of the current indication. They are converting to a more program- and provider-friendly formulation of refrigerated storage and have additional manufacturing capacity through a brand-new manufacturing facility. And, something related to pandemic planning, MedImmune leads in the technology and owns the intellectual property to derive vaccine strains, including potentially pandemic strains, using the plasma and rescue or reverse genetics techniques. That will enable a more rapid production of vaccine strains for the interpandemic periods, potentially providing earlier influenza vaccine to consumers.

MedImmune is looking forward to discussions beyond the CDC, with state and local jurisdictions. They want to be integrally involved in meeting the challenges of every influenza season. They hope in future to avoid the irony that, with a capacity to produce 40 million doses of FluMist ®, the U.S., is looking to import foreign vaccine.

Discussion included:

- The reduction of relative risk from 4% to ~2% was determined for influenza per se. The vaccine benefit of preventing disease was applied specifically to wheezing attacks. E-mailed Dr. Levin xpt section for clarification 3/9 a.m.
- Production of the additional doses began the day after the Chiron announcement. An additional 2 million doses will be ready in a week and testing data will be submitted to FDA for the vaccine's release. About 400,000 doses per week should begin to be released in mid-November.
- The current price is c. $16 to the distributor, down from $45 last year, plus administrative costs that would bring it up to ~$58.
- The limiting recommendations on vaccine use could reduce coverage. While CDC's clarification of this vaccine's use for "all" healthy subjects helps, it is up to the state and local end-users to ensure that this safe and effective vaccine is not under-utilized. The implications for success or failure in that regard are both short- and long-term, as MedImmune cannot lose money on vaccine production indefinitely.

Status of the U.S. Influenza Season

Overview: Current influenza surveillance update; Asian H5N1 strain; NIH studies

CDC Report

Presenter: Dr. Keiji Fukuda, NCID, Influenza Branch

A U.S. map of data from the WHO and NREVSS sentinel surveillance systems showed very low- to sporadic influenza activity to date. Visits to sentinel providers for influenza-like illness were charted for 2003-04 and showed a still-low level of activity to October 16. The activity of the H5N1 virus in Asia was similarly mapped. Avian virus cases were confirmed in poultry and in humans. An average death rate of 73% occurred among the 44 documented human H5N1 cases reported to the WHO through October 25 in Thailand and Vietnam.

Chinese studies have show the viruses to be evolving, both antigenically and genetically, and growing more lethal rather than attenuated. The virus has been found it in swine as well as poultry and also can infect cats (tigers died in Thailand). It has been isolated in people. Many of the patients were resistant to adamantane drugs and required neuroaminidase drugs. There is no

evidence yet of genetic reassortment, and no sign yet of *sustained* human-to-human spread.

The Asian countries are continuing their disease control efforts and the virus appears to have been eliminated from South Korea and Japan. Major efforts are underway in Thailand and China, but poultry vaccination remains controversial. DHHS/CDC and the WHO are continuing active human surveillance.

In U.S. response/preparedness activities, the draft pandemic preparedness plan was released for comment and state/local pandemic response planning has increased. Enhanced national surveillance includes the better ability of state labs to do quick typing for avian viruses through real-time PCR analysis. The stockpile of antiviral drugs is small but growing, and vaccine development and testing by NIH is proceeding.

NIH Studies
Presenter: Dr. George Curlin, NIH/NIAID

On May 27, NIAID announced the award of two contracts for the production of an inactivated H5N1 vaccine based on the 2004 H5N1 reference viruses. It was produced through reverse genetics by NIH, to work against the A, Hong Kong, HK1203204 H5N1 virus isolate. It will be tested in NIH-funded clinical trials in NIAID's VTEU laboratories. The two companies awarded are Aventis Pasteur in Swiftwater, PA, and Chiron Corporation in Emeryville, CA.

Two formulations of inactivated H5N1 vaccine will be produced, 1 mcg/ml and 45 mcg/ml. Aventis' will produce 4000 doses of each formulation, to total 8000 doses, and Chiron, 5000 doses of each formulation, to total ten. Chiron's production facility is in Liverpool, England (not the contaminated commercial manufacturing plant), and they have contacted the U.K. authorities about that. NIH expects the H5N1 research lot to be acceptable.

These different volumes of these two formulations provide the flexibility to clinically evaluate a wide range of dosage levels. The first clinical trials will assess the safety and dose range (7.5mcg, 15mcg, 45 mcg and 90 mcg) and the related immunogenicity of two doses of vaccines, given ~4 weeks apart, to healthy adults. Other age-specific trials will assess vaccine efficacy among the elderly, adolescents, young children, and infants. They will be based on the data from the healthy-adult study.

The NIAID intramural lab also is planning production of live attenuated influenza vaccine in collaboration with MedImmune, against viruses with a pandemic potential.

Discussion included:
- The vaccines under these contracts are egg based. Other contracts are to evaluate cell-culture-based vaccine as well as novel ways to administer the vaccine. Some other countries are also independently pursuing this.
- Dr. Gellin reported that DHHS has a contract with Aventis to manufacture on a commercial scale up to 2.5 million doses of H5 vaccine. That would be done in parallel with the NIAID studies. Presuming 15 mcg per dose, he thought that 2 million doses could be manufactured for this year before ramping production up for next year. DHHS also has a $15 million RFP out for cell culture vaccine research and the construction of U.S. production facilities. NVPO asked for $100 million for this research last year and received $50 million. They

hope that the full $100 million might be awarded this year, and anticipate that this will be a long-term area of study. The cell culture award recipients will be announced soon.

- ❖ The southern hemisphere's influenza season recently ended, and was fairly unremarkable. The H3A2 virus isolated in the vaccine was A/Wellington, which is different but related to the A/Fujian strain included in the U.S. vaccine in past years.
- ❖ There are little data on the H5N1 human-to-human transmission since the first report in 1997: only the first case was in Hong Kong in a physician infected by a patient; a family cluster was reported in Vietnam, and the Thai cluster involved a mother and her child.

Public Comment

Ms. Elissa Kanowitz's daughter Amanda was one of the 152 who died of influenza last year. She had a mild case, with a fever that was never over 102º degrees. She became ill on Saturday and died in her bed by Monday. Ms. Kanowitz begged the ACIP, in the 2005-06 season and beyond, to expand the recommendation for vaccination to all children under the age of five years. At age 4½ years, Amanda was not in a recommended group under last year's recommend, but the average age of death from influenza was among those over age 3 years. The vaccine shortage changed the dynamics of demand, which is directly tied to a CDC *recommendation,* which influences parents reluctant to vaccinate their children. And, in this litigious age, pediatricians may not recommend it unless they are backed up by a CDC recommendation.

Expanding the recommendation would have to be done at the February 2005 meeting. Amanda's case was a rare, rapid deterioration linked to the state of her immune system. She had a history of benign hypersensitive reactions, something seen in her brother's reaction to MMR vaccine as well. Three of the four children who died last year had hives, making Ms. Kanowitz wonder if a genetic predisposition to hypersensitivity is a factor. She wished the other 150 families would be polled to see if that was a factor in common. She asked that blood samples be gathered in children hospitalized for influenza to study that now, rather than later. Her family has established the Amanda Kanowitz Foundation to study these things. Given the genetic similarities in her son and other families, she thought that the influenza was an incidental cause of death; it could have just as easily have been caused by streptococcus or staphylococcus. She called for research. While she understood that privacy laws impede contact with parents, she asked that her statement be considered as her permission to contact her, and offered to help as an advocate however she can.

MENINGOCOCCAL VACCINE

Meningococcal Workgroup Update

Presenter: Dr. Reginald Finger

Overview: Meningococcal Workgroup core tasks, progress in its first year, and current topics of focus.

For over a year, this Workgroup has discussed policy options for the prevention of meningococcal disease through vaccination, while the MCV4 vaccine was under development. Their document on possible recommendations should be completed soon and could be issued quickly on the completion of the vaccine's licensure and related policy discussions. The Workgroup examined meningococcal epidemiology by age- and serogroup, vaccine safety,

immunogenicity, and the cost effectiveness of vaccination, as regards outbreak control and chemoprophylaxis of individual cases. The Workgroup has also participated in NCID's national education campaign on meningococcal disease.

Input on the recommendations document was received from the AAP, AAFP, and the ACHA. Those organizations will issue their own concurrent recommendations rather than waiting to issue a joint recommendation. The proposed scope of MCV4 use by the VFC program has been discussed with CDC, and a parallel structure for a VFC document was developed. The Workgroup recommended a broad ACIP recommendation for vaccination during the adolescent visit.

The document's focal topics were:

- A proposed recommendation for across-the-board, cohort-wide MCV4 vaccination at the adolescent visit at ages 11 or 12, and for college freshmen living in dormitories. Discussions included how to adequately respond to the meningococcal incidence peak between ages 16-19 years. The Workgroup chose to use the broadest possible recommendation to promote the adolescent visit and in favor of clarity, rather than adjusting the recommendation according to the vaccine supply. However, a stepped recommendation could be done and that probably will be debated. And, considering the incidence data relative to the logistics of implementation, the Workgroup recommended vaccination of college freshman living in dorms, as opposed to all freshmen.
- The vaccine is expensive and supply will be limited in the first year. To suggest a structure for a subnational catch-up campaign, the Workgroup borrowed from the polio campaign's subnational approach.
- Those who are medically at higher risk would be addressed separately (e.g., asplenic or immunodeficient patients).
- The Workgroup decided not to address catch-up campaigns for now, due to limited vaccine supply, in the interest of a simple and clear, easy-to-understand recommendation.

The options offered for implementing the vaccine's use were to:

- Conduct no catch-up campaign: vaccinate each cohort as they reach age 11 or 12.
- Base the catch-up on disease epidemiology (e.g., threshold of disease in a geographic area, as done for hepatitis A).
- Leave catch-up to the state health department's discretion.
- A seven-line paragraph on page 4 of the recommendation (beginning "State and local health departments…") was not inserted in the document but offered as an option for and ACIP decision.

With regard to what other higher-risk populations should be included in the recommendation, the Workgroup discussed how much MCV-4 the nation could afford. Assuming no supply issues, the Workgroup analyzed the cost per life year saved compared to several factors. If that cost is favorable to MCV-4 use, then other considerations to be addressed will include the federal budget and the vaccine's impact on the rest of the immunization schedules (i.e., competing needs).

AvP Clinical Data on Menactra™ Polysaccharide Vaccine

Presenter: Dr. David Decker, Aventis Pasteur Corporation

Overview: Clinical data from the trials of the conjugate meningococcal quadrivalent vaccine (Menactra™); immunogenicity and safety results.

The meningococcal vaccine that has been licensed in the U.S. for 20 years is Menomune®, a quadrivalent polysaccharide vaccine delivered in a single dose. It is widely used, shown to be highly effective in outbreak studies, and has an excellent safety profile. However, it does not induce a T-cell dependent response, immune memory, or provide immune persistence or protection. Polysaccharide vaccines in general provide no booster effect (rather, hyporesponsiveness has been seen), and no reduction of disease carriage or any meaningful herd immunity.

Conjugate vaccines were developed to correct those limitations. Aventis Pasteur developed Menactra™, a safe and effective quadrivalent conjugate meningococcal vaccine, also delivered in a single dose. They have filed a biological license application (BLA) with the FDA for its use among adolescents and adults aged 11 to 55 years. A supplementary application for use among those aged <10 years will follow, and then another for age >55.

The compositions of Menactra™ and Menomune® were compared. Menomune® has 50 mcg of each polysaccharide, while Menactra™ has 4 micrograms of each polysaccharide covalently coupled to 48 micrograms of diphtheria toxoid. Neither vaccine has a preservative or an adjuvant. Menactra™ is a liquid that is administered subcutaneously; Menomune® is lyophilized, requiring reconstitution for IM injection.

A noninferiority margin was set to exclude clinically important differences within a reasonable sample size, accounting for any theoretical variability in the sample (Menactra™) and allowing for control of variability in the comparison group (Menomune®).

Immunogenicity (the antibody present) can be measured by lab tests such as ELISA and RIA, but the more complex testing of functional assays (e.g., serum bactericidal antibodies, CHO cell assays) reveals how well the antibody performs to protect from disease. FDA's advisory board, VRBPAC, determined that immunological data could be used to support meningococcal vaccines' efficacy, that bactericidal antibody may be used as a measure of functional antibody and presumed protective activity, and that total antibody as measured by ELISA or similar techniques cannot be used as a serologic correlate of protection. Hence, the serum bactericidal antibody test is the standard approach for meningococcal assays. It conforms to WHO and CDC standards and is fully validated. It uses a baby rabbit complement rather than a human complement to avoid the latter's problems of consistency, availability, and standardization.

Immunogenicity endpoints were demonstrated by four-fold rises in titer after- versus before immunization. The coprimary outcome was a measured rise in the GMT of averaged post-immunization titers. Seroconversion rates were reported in a descriptive measure for initially seronegative study participants who had a four-fold or greater rise. The latter is on the VRBPAC Website. RCD curves were used to graphically demonstrate the antibody distribution of all the study populations.

Clinical trials involved 10,683 children, adults and adolescents in 9 trials. They were given Menactra™ (n=7642) or Menomune® (n=3041), the standard of care, to demonstrated Menactra's™ non-inferiority, immunogenicity, safety, and the ability to coadminister it with Td

vaccine or Typhim Vi, the polysaccharide typhoid vaccine. Menactra™ met all pre-specified criteria for noninferiority to Menomune® relative to immunogenicity and safety. It also demonstrated persistent immune response, priming and boosting, and overcame hyporesponsiveness.

Clinical trial MTA02: This multicenter, randomized clinical trial compared the two vaccines' use among two evenly-divided U.S. (N=881 healthy adolescents, to evaluate short-term (to 28 days post-vaccination) noninferiority of immune response relative to safety and immunogenicity. The polysaccharide vaccine's strength is its short-term response.

- *Immune response:* No major differences in short-term immune responses were seen between the two vaccines, as was demonstrated in data slides. The latter showed four-fold rises in SBA titer by serogroup among adolescents along the entire 95% confidence interval of the noninferiority margin. In fact, the geometric mean titers for Serogroup A in the Menactra™ vaccines were higher than those of the Menomune® recipients.
- RCD: Ascending antibody responses charted with the ascending proportions of the study population showed all achieving the minimum level GMT of 128 (the correlate of protection from invasive disease established in baby rabbit SBA assays). Both vaccines' titers well exceeded protective levels, but a higher proportion of Menactra™ recipients had high mean titers.

Clinical trial MTA19: MTA02 subset cohort (n=150, evenly divided between vaccines). A follow-up 3 years later focused on Serogroups C, Y, and W-135. The two vaccine groups were compared to 88 age-matched naive participants to evaluate: 1) antibody persistence over three years, and 2) Menactra's™ priming and boosting ability and response, three years later. All participants received one dose of Menactra™.

- *Immune response*: Again, the Menactra™ group showed a substantially higher response and better persistence of antibody than that of the Menomune® group. The antibody response of the previously immunized group was 18,000 for Serogroup C and was still at 8000 after 28 days. Those never immunized with Menactra™ showed a robust response (to 7,000), for Serogroups C, Y, and W-135, demonstrating the boost from a prior receipt of Menactra.™ But because of Serogroup A's cross-reactive epitopes, no statistical difference was seen between the naïve subjects and those immunized with Menactrai.™
- Among children previously immunized with Menomune,® rather than the hyporesponsiveness seen with reimmunization with the polysaccharide meningococcal vaccine, the response to Menactra™ was substantially better for Serogroups C, A and W-135.

Conclusion: Menactra™ demonstrated superior antibody persistence at three years and higher GMTs than seen after Menomune® or among naive controls. It primed and boosted with a rapid, high anamnestic response that far exceeded the naive controls' response. Prior Menomune® vaccinees reimmunized with Menactra® demonstrated a rapid increase in bactericidal antibody, to levels exceeding what was expected from polysaccharide reimmunizastion.

Clinical trial MTA09: In a primary safety and immunogenicity comparative trial of the two vaccines' use among healthy adults (n=2,500), ~60% were given Menactra™ and 40% received Menomune®. The primary outcome for noninferiority was met, a four-fold rise in titer, to a mean well over 1,000. The divergence curves ranged from 1000 to 8000 for Serogroups Y and W-135; the GMT differences were of no clinical relevance.

Study MTA12: An evaluation was done of non-inferiority in safety and immunogenicity with concomitant administration of Td vaccine and Menactra™ in healthy adolescents (N=1000). Half received Menactra™ and Td simultaneously, followed 28 days later by placebo; the other half received Td and placebo, followed 28 days later by Menactra.™ Non-inferiority was demonstrated by four-fold rises in meningococcal SBA titers and the same pattern was seen for the GMTs. Data were presented to show that there is no interference from simultaneous or sequential administration. Tetanus antibody response was also identical whether the vaccine was administered simultaneously or sequentially, as was the diphtheria antibody response. In the latter, simultaneous administration led to an even higher response rate among those with high preexisting antibodies.

Study MTA11: A concomitant administration of Typhim Vi and Menactra™ in adults, as a representative of travel vaccines, was done. Of the 945 healthy adults, half received Typhim Vi and Menactra® simultaneously; the other half received Typhim Vi and placebo and then the Menactrai™ 28 days later. The GMTs rose four-fold in both the sequential and simultaneous groups, proving noninferiority. The antibody responses were also essentially identical between those getting Typhim Vi and Menactra™ simultaneously, as they were for Typhim Vi delivered with a placebo.

Study MTA17: This study of young children aged two years immunized them with Menactra™ or Menomune,® similar to the Trial MTA02 among adolescents. Following up with those children two years later, at age 5, they challenged them with a microdose (5 mcg) of polysaccharide and compared to age-matched, naive controls. The anamnestic response was assessed to exposure to the polysaccharide and to measure the duration of immune response.

Results: Antibody levels among the naive controls were substantially lower than those seen in the Menactra™ recipients at age 2-3 years. For Serogroup A, C and W-135, the immune response to exposure to the microdose of polysaccharide within eight days was very high in the Menactra™ group. Six children who did not respond to Serogroup C in the original study of 2-year-olds showed excellent responses (days 8 and 28) to this 5 microgram challenge, demonstrating that they had developed immune memory.

Conclusion: Menactra™ is consistently immunogenic in adolescents and adults. It satisfied all the noninferiority criteria and produced superior antibody levels after three years to those given Menomune® or among naive controls. One dose of Menactra™ primed for memory, as demonstrated by a rapid and very high booster response upon immunization. Menactra™ was shown to be a superior reimmunization pathway for prior Menomune® recipients, demonstrating the important immunological characteristics of a conjugate vaccine.

Safety Data. *Trial MTA04* examined safety and lot consistency of the vaccine in the trial conducted among adolescents, and *MTA14* did so in the adult trial. Both trials compared Menactra's™ safety profile to Menomune's®, to: 1) characterize the overall safety profile of Menactra,™ and 2) demonstrate comparable rates of reported severe systemic reactions between the two vaccines' recipients. The reaction rate of Menactra™, being a protein vaccine given intramuscularly, was expected to be higher than the polysaccharide Menomune®, which is given subcutaneously. Information was solicited and collected on immediate systemic and local reactions for the first week, and on unsolicited adverse events reported between Day 0 and 28.

Ongoing safety surveillance was done for 6 months, and information was collected about serious adverse events.

Extremely low reaction rates caused a change in the initial hypotheses (a <0.10 difference in rates in the upper limit of the two-sided 95% CI) to a much tougher measure, a ratio <3, since the expected rate in the control group was only 1%. Pre-established systemic medical conditions with predefined scales were recorded in a diary as they occurred in the first seven days.

The safety profile showed very comparable rates between Menactra™ and Menomune® that, for all participants, all ages, for immediate, solicited local, solicited systemic, severe solicited systemic, and unsolicited AEs, and for SAEs. Solicited local reactions differed as expected. The details of these data were presented. All the noninferiority criteria were met for safety comparisons in each study.

The rate of any reactions or severe reactions among adolescents went from a low rate for the placebo group, rising through the Menomune® group and then the Menactra™ group. All were lower than the rate of the group that also received Td vaccine. For pain, the duration of any- or a severe reaction was very short (1-2 days), to a maximum of 3 days with Td for any reaction, and a maximum of one day for a severe reaction. The same pattern was seen for induration, swelling, and redness. Trial MTA12 measured local reactions among adolescents who received Menactra™ or Td, or both simultaneously (in either in the same or other arm), or a placebo in the other arm. The reactions in the Td arm were the same, whether placebo or Menactra™ was injected in the other arm, and the local reactions at the Menactra™ site were lower than local reactions at the Td site. The same was true for adults studied. The complaints of pain at the injection site went from low, for the placebo site, and then rose up through the Menomune,® Menactra,™ and Typhim Vi groups. Severity was uncommon and the rates of duration were, again, 1-2 days or at most 2.5 days for the Typhim Vi. The previously described patterns of pain, induration, swelling, and redness were repeated in this group.

Severe serious events The Menactra™ recipients reported 77 serious events (1%) and 39 were reported by the Menomune® group (1.3%) All but one of the events were found to be unrelated to the vaccine, and the one (a distal esophageal ulceration) could also have been related to a sports injury a month earlier which had been treated with NSAIDs. The two deaths in the two groups were entirely unrelated (an auto wreck and a drug overdose 79 days post-vaccination).

Conclusion: Menactra™ is safe and well-tolerated among adolescents and adults, meeting all noninferiority criteria. It produced no local reactions beyond what would be expected for a protein conjugate vaccine, and those seen were less than from Td vaccine. Menactra™ can be administered safely either concomitantly with, or one month, after Td or Typhim Vi.

Summary of the risk/benefit of Menactra:™

- The reactogenicity profile is consistent with other protein or conjugate vaccines. There is an increased rate of local reaction compared to Menomune,® but those local reactions are less than those seen with Td, a routinely administered vaccine.
- Menactra™ is highly immunogenic, providing improved antibody persistence, priming, boosting, and overcoming hyporesponsiveness.
- Administered in a U.S. program, Menactra™ is expected to show persistence of protective antibody, reduction in disease carriage, and herd immunity (as seen in the U.K.)

Menactra™ was considered for licensure by the FDA's VRBPAC on September 21. They voted unanimously that the data are adequate to support Menactra's™ efficacy and safety when administered to individuals aged 11 to 55 years. Aventis has built a new production facility to manufacture Menactra™ on a large-scale basis. Once both the Menactra™ are its production facility are licensed, the product will be available rapidly.

Discussion included:

- There was no difference seen in the diphtheria response when Menactra™ was given after diphtheria vaccination, nor any relationship between the amount of diphtheria antibody and the adverse reactions. But there was some carrier priming, demonstrated by the superior response to Td by those with preexisting high titers.
- CDC and ACIP are working with Aventis to ensure a good correlation between the size of a one-year cohort aged 11-20 and the vaccine supply. Mr. Phil Hosbach, of Aventis, confirmed that the supply is in place for that age group and for 22 year-olds and college freshman, but not if the ACIP issues a strong catch-up recommendation in the first year of production. The new production facility will be ramped up even before operations begin, so there should be no problem in supply once it is in full operation.
- *What are the 95% CI limits on the GMT for Serogroup C, the most import group relative to adolescent disease; and is there a significant group without persistent antibodies three years later?* This sample size was not selected for a 95% CI, but to provide data potentially useful without depleting the population needed for the 3-year follow up study. Aventis did not calculate a comparison. This would be a best-judgment decision after reviewing the point estimates in their full context. Menactra's™ duration of protective antibody will remain unclear until the populations can be followed over time and/or until ongoing antibody monitoring confirms that there is no need for a booster, as seen in the U.K. since the quadrivalent's introduction in 1999. The polysaccharide vaccine is protective for 3-5 years and there is every reason to expect better from the conjugate.
- *Is there any indication of what the SBA128 correlate of protection would be at 3 years?* No. That is being explored in the U.K., but the results are inconsistent. This is confounded by the herd immunity that results after population immunization efforts, which biases the necessary measurements to this question. There is no easy answer.
- The U.K. results indicate that their broad-based vaccination program reduced disease carriage by 66% and reduced disease rates 50-80% among those not vaccinated. That was not unexpected in view of the similar experience with after the introduction of the Hib conjugate vaccine. That is expected in the U.S. as well if the vaccine is used properly.
- Mr. Hosbach reported Aventis' discussions with CDC about the vaccine's cost. As with all vaccines, the volume affects the price. But Menactra™ will be comparable in price to Menomune®, which is now at $70/dose, for the 11 year-old and college freshmen cohorts.

Cost-Benefit Analysis of a Mass Catch-up Campaign to Deliver MCV-4 Vaccine

Presenter: Dr. Ismael Ortega-Sanchez, NIP

Overview: Analysis of the effectiveness and cost effectiveness of a catch-up meningococcal vaccination campaign among adolescents aged 11-17 years in the U.S., and the impacts of this campaign on the individual (direct) and potential herd immunity (indirect) of the entire population.

A Monte Carlo simulation analysis was done of a hypothetical population of about 10 million individuals, defined as proportional in an age distribution to that of the total U.S. population, with 1 million being aged 11-17 years of age. The analytical strategy assumed an initial year of a mass catch-up vaccination campaign among 11-17 year-olds, followed by Year 1 routine immunization of 11 year-olds. This continued in the analysis for ten years to assess the possibility of a heard immunity impact. The latter analysis also measured the costs and benefits of the catch-up campaign along age-specific points of a lifetime.

Assumptions for the analysis, based on the U.S. population, were:

- The catch-up provides a direct protection to the initial group itself and indirectly to the other age groups.
- For the 10-year follow-up, incidence rates for each year were calculated using the ABC surveillance data, by: age year, serogroup-specific incidence rates, fatality ratios, and by the proportion of survivors with sequelae (by condition, from different references).
- Vaccine efficacy (VE) was calculated at 93% for Serogroup C, based on from the U.K. meningococcal conjugate vaccine experience.
- Coverage in adolescents was calculated at 70%, taken from the three doses of hepatitis B mandated for middle school entry in California.
- Age-specific herd immunity impact was based on the U.K. experience (percent reduction in attack rate in unvaccinated cohorts as studied by Ramsay and Balmer). These are age group-specific and assume the most reduction in attack rates among the unvaccinated due to the catch-up campaign.
- Economic data: A two-stage cost structure is used: 1) medical cost per case (i.e., the acute infection) of ~$34,590, with ~5% attributable to indirect costs from lost work; and 2) long-term or human-capital costs in terms of medical complications (e.g., premature death or disability, permanent disability, dependency). Total costs were societal costs, delineated by the proportion of work time lost in immediate and lifetime productivity, in terms of permanent disability or premature death.

Analysis results for serogroups C, Y, and W-135, assuming replication of the 100% incidence reduction from herd immunity seen in the United Kingdom, were:

- Number of cases prevented: a) with no vaccination program: <1700 cases per year; b) with no herd immunity (direct impact only): 148 cases per year (~9% of total expected cases); c) with herd immunity's indirect protective impact: 528 cases/year (~32% of expected cases).
- Cumulative impact over 10 years: a) without vaccination: >16,000 cases; b) with a catch-up campaign and routine immunization every year of the 10 years: ~ 5,263 cases prevented at a societal cost per case prevented of >$531,000; c) with a catch-up campaign: ~470 deaths prevented of the expected ~1480, at an annual societal cost of ~$6 million per death; d) 24,246 life years saved of the expected 68,000 lost, at a cost of ~ $116,000 per life year saved.
- Cost to society with no vaccination: $2.8 billion. Cost with a catch-up campaign and routine immunization program: $1.9 billion ($928 million saved).
- Program costs over 10 years: ~$3.5 billion, of which 45% would be needed in year one to introduce the catch-up campaign; the balance of 55% would be disbursed in installments.
- Net present cost was ~$2.5 billion to do this program, or, for each dollar invested in this program, >30 cents in return.

A Monte Carlo analysis was done to calculate the net cost per life year saved, including only medical (direct) costs. It assumed 70% coverage in the 11-17 year-old group and an $83 vaccination cost. From a baseline of only 20% percent of the herd immunity impact achieved in the U.K. and a cost of $272,000 per life year saved, the analysis was calculated up to 100% coverage and a cost of $138,000 per life year saved.

Another important variable was examined by changing the cost to vaccinate an adolescent. Two vaccination cost scenarios were examined relative to their direct and total costs: 1) a catch-up campaign plus routine immunization of 11 year-olds and a catch-up campaign for those aged 11 to 17 years old; and 2) only routine immunization among those 11 years old. At an $80 cost to fully immunize an adolescent (including administration cost and wastage assumptions), the direct and total cost relationship was 2:1. The two catch-up strategies were only equivalent only when the cost to vaccinate is ~$20. The Lieu et al study found a cost per life year saved of $80,000 for the pneumococcal conjugate vaccine at a dose cost of $58, but did not include the possibility of a 100% herd immunity impact.

Another scenario explored was of conducting a targeted catch-up campaign to high (i.e., incidence almost 100% higher) endemic areas. Using the ABCs data, the top 25% endemic counties were identified and the costs per life year saved were compared to an approach targeting all counties. The analysis showed almost the total societal cost for the catch-up campaign, plus routine immunization in all the counties, to be almost three times higher than that of a targeted strategy in counties with high endemic rates. In some cases, targeting was even cost-saving.

Conclusion:

- Catch-up vaccination of healthy adolescents should have a substantial impact (~32% reduction) on the burden of the vaccine serotype disease, accompanied by reductions in associated costs.
- Compared to preadolescent routine vaccination, a catch-up campaign would cost twice as much in terms of cost per life year saved.
- Targeting high endemic counties might decrease the cost per life year saved.

Perspective: Economics of a Catch-Up Campaign

Presenter: Dr. Martin Meltzer, NCID

Health economists struggle to include all the epidemiological data available in analyzing the effects of herd immunity. But in this case, there is only one datum point to use: the U.K. experience from vaccinating ~80% of children under age 17 in about 2 years, which generated an estimated herd immunity of ~70%. That makes the context of the analysis, the meaning of "dollars per life year saved," even more important. At the dawn of the 20th century, infectious disease caused ~800 deaths a year per 100,000 population. This was reduced by the 1950s to about 100-150 per 100,000, but not by the introduction of vaccines. Public health has many domains of work and its investment priorities compete for dollars to support that work. As a example, the rise in mortality since the 1970s/80s was charted, attributable mostly to HIV/AIDS.

Children under age 11 comprise ~35% of all U.S. children under aged 17 years. If all the rest were vaccinated, the epidemiology indicates that some herd immunity would be generated, but by how much no one can estimate. That is important, since both price and the degree of herd immunity generated produce large impacts. For example, if 35% of all children aged <17 were

vaccinated at a total cost of ~$100 per child, and that produced 50% herd immunity, the cost would be ~$200,000 per life year saved. By any measure, in terms of dollars per life year saved, that would be the most expensive U.S. vaccination campaign ever.

The 1995 Tengs et al study demonstrated that there is a wide range of the median cost per life year saved according to both the type of intervention and whether it is a primary (e.g., vaccine), secondary, or tertiary (e.g., screenings) intervention. Among the traditional methods of analyzing the economics of vaccine is determining its ultimate cost savings to society. Although that is not essential to its value, cost-saving vaccines have created a tempting economic standard. But, as shown in the Stone et al study in 2000, interventions that have been adopted have cost different amounts per life year saved (e.g., the cost of having smoke detectors in homes was $210,000 per life year saved in 1993 dollars). The thresholds of cost acceptability for interventions vary.

Another metric used in judging the value of an intervention is the quality adjusted life year (QALY). This estimates the quality of life years or quality lost due to long-term sequelae. Immunizations are the cheapest in this regard, even without the cost-saving vaccines, at a median cost of only $1,500/QALY. The ranges per QALY are enormous. For example, blood donor screening's median cost per QALY is $355,000, in a range from cost-saving per QALY to $8.7 million/QALY. But it should be noted that, while the latter is expensive, no one would stop doing it because of that.

To compound the discussion, while vaccination's value is accepted by most, some would balance vaccine-related adverse events against that. The Prosser et al study (submitted for publication) analyzed parents' opinion of the value of the time traded off to avoid an uncomplicated influenza case and its adverse events (e.g., a severe allergic reaction or Guillaine-Barre Syndrome). In the median value, the parents would not trade a single day of their life so their one-year-old could avoid an uncomplicated case of flu. But they would trade 30 days to avoid a severe reaction in their one-year old, and three years to avoid GBS, even knowing that the risk of the latter is very rare (1:1 million). The U.S. has a history of avoiding adverse vaccine events (e.g., the switch from DTwP to DTaP vaccine, or from a live- to an inactivated polio vaccine).

But there are some absolutes. One is that the term "cost effective" is subjective; it need not equate to cost savings. Procedures, programs, or technologies can be adopted at a net cost to society if they are valued. Oregon's unsuccessful attempt to firmly set a value for every service demonstrated that societies are reluctant to judge all interventions according to one threshold of acceptance and rejection. Another absolute is that the term "cost effective" does not equate to "affordable." Budget limits demand that society prioritize what it is willing to pay for.

Discussion included:

- The model assumes that the U.S., at best, would immunize everyone to age 18. The protection of herd immunity decrease disease among ~67% of those unvaccinated. The model also generated scenarios for attack rate reductions of 20, 40, 60, and 80%, and explored the likelihood of each scenario.
- The dollars per life year saved were discounted at 3%. The $83 base vaccination cost included dose plus administration and the cost of adverse events, as was done for the introduction of the pneumococcal conjugate vaccine. That cost figure will probably decline, as it did for PCV. The calculation also tried to estimate the administration costs of a catch-up

campaign of ~70% all children aged 11-17 (~20 million) in 1-2 years, something never done before.

- Dr. Nancy Rosenstein of NCID noted the analysis' assumptions of adolescents as the primary transmitter of *Neisseria meningitides*. If only a cohort of 11 year-olds are vaccinated, the analysis would make the cost per life year saved look better, but the population level impact would likely be small. But if the U.K.'s herd immunity impact is replicated by a catch-up campaign, there would be a more dramatic impact on disease burden in the U.S.
- Productivity costs were included in the analysis of acute infection. About 5% of the medical costs calculated in many studies, or $34,000, is of indirect costs from time from work lost. And, while the societal cost did not include medical costs, it did include public response costs (~$4000/case) as well as costs for specific single and multiple complications, which were calculated to cause a 30% reduction in lifetime productivity. That would produce a total 37-48% productivity reduction in terms of indirect costs.
- This duration of this vaccine's immunity (e.g., when given to pediatric recipients) was not calculated. The analysis was limited to age 11 and up; only the herd immunity effect to children under 11 was considered.
- The single-dose cost effectiveness to vaccinate 11-year-olds was calculated at ~$61,000-$69,000 per life year saved, which is comparable to PCV. But it was re-emphasized that the catch-up campaign assumes that the U.K.'s herd immunity can be replicated. The less of that, the more the cost.
- At the last meeting, CDC presented infant and toddler vaccination strategies. Although they were basically equivalent, the infants involved the highest cost per outcome prevented due to the necessary three doses, which greatly multiplied the analysis' metrics.

ACIP Meningococcal Workgroup Recommendations

Presenter: Dr. Oleg Bilukha, NCID

Overview: Data on the immunogenicity and safety of MCV4; use of MCV4 and MPSV4; recommendations for chemoprophylaxis; Workgroup's preliminary recommendations for prevention and control of meningococcal disease among selected groups: adolescents 11 to 12 years, adolescents 12 to 19 years, college freshmen living in dorms, other groups; recommendations for revaccination and for chemoprophylaxis.

Studies of military recruits in the 1960s confirmed that naturally-acquired bactericidal antibodies (measured by SBA) conferred protection from invasive meningococcal disease. SBA titers of ≥4 in human sera became the gold standard for a protective threshold against meningococcal disease. The U.K.'s licensure in 1999 of Serogroup C conjugate vaccines was based on safety and immunogenicity data, but not on clinical efficacy. The immunologic data came from SBA testing of baby rabbit, not human, serum, and the threshold values were determined by comparing rabbit SBAs to human SBAs. The latter titers of ≥128 were considered by experts to reliably predict protection for Serogroup C and those ≤8 were accepted as predictive of disease susceptibility. However, there were few data on the protective thresholds for Serogroups A, Y, or W-135. The polysaccharide vaccine Menomune™ (MPSV4) also was licensed (in 1981) based on its safety and immunogenicity data. It showed high efficacy to the existing Serogroup A/C meningococcal polysaccharide vaccine as measured by a ≥4-fold titer elevation, rather than any specific level of itself. That same criterion was applied to license MCV4 as compared to the polysaccharide to prove noninferiority.

Immunogenicity data were summarized on charts that showed the four-fold or greater rises in SBA titers among 11-18 year-old subjects at 28 days after vaccination with either MCV4 or MPSV4. The same results were demonstrated for subjects aged 18-55 years.

SBA titers measured three years post-vaccination showed higher titers for all four serogroups among the MCV4 vaccinees than the MPSV4 vaccinees, and at levels of statistical significance for serogroups A and W-135. However, the mean SBA titers for those previously vaccinated with MPSV4 were lower than the titers achieved by naïve vaccinees given MCV4. Those vaccinated and re-vaccinated with MCV4 had higher titers than the naïve subjects, except for serogroup A.

Safety data on local reactions (e.g., pain, induration, swelling, injection site redness) showed more common reactions after MCV4 than after MPSV4 injection. But reactions to the MCV4 were similar or slightly lower than those to tetanus diphtheria or typhoid vaccines administered to adolescents. Systemic or severe systemic reactions were similar between MCV4 and MPSV4.

ACIP Meningococcal Vaccine Workgroup recommendations were offered for the ACIP's consideration after the vaccine is licensed:

- *Vaccinate adolescents as early as possible, at age 11-12 years (during the adolescent visit), to achieve the maximum individual benefit by covering the adolescent years of increased risk*. This was based on meningococcal disease's significant incidence from age 11-18 years, the vaccine's expected duration of protection for 8-10 years, and the ability to concurrently vaccinate MVC4 with other vaccines
- *Do not initiate a national catch-up campaign in the year after MCV4 licensure.* Neither vaccine quantity nor immunization infrastructure to vaccinate multiple cohorts of adolescents is likely to be in place.
- *Recommend routine vaccination of college freshmen living in dormitories,* among whom the incidence rates and disease risks are substantially higher. Colleges might target all matriculating freshman to ensure that all dorm residents are vaccinated, and offer MCV4 to students already enrolled who want the vaccination, supply permitting. MCV4 is preferred for the latter group as well, but the MPSV4 could also be used.
- *Recommend vaccination for other groups at risk who are already targeted for vaccination with MPSV4,* such as microbiologists working with meningococcal isolates, travelers to epidemic or hyperendemic countries, military recruits, and patients with terminal complement deficiency and with anatomic or functional asplenia. MCV4 is again preferred; MPSV4 is acceptable.
- *Routine vaccination for adults aged 2-55 years is not recommended, but if demanded, can be given,* due to this group's low disease risk. Neither vaccine is recommended for those <10 or >55 years, but they can be used for outbreak control. Again, MCV4 is preferred for use among the age groups for which it is licensed; MPSV4 is acceptable.
- *Continue the current revaccination recommendations for MPSV4 (every 3-5 years for those remaining at high risk), which are applicable also to MCV4.* In fact, revaccination with the latter was preferred due to data suggesting that it can better overcome the immunologic hyporesponsiveness that occurs after repeated administration of polysaccharide vaccine. However, MCV4's duration of protection requires further study.
- *Continue the current MPSV4 recommendations for postexposure chemoprophylaxis.* Rifampin, ciprofloxacin and ceftriaxone are used; azithromycin can be used in children and is

available in suspension form. However, further exploration of its effectiveness in eradicating meningococcal carriage and its not causing microbial resistance is needed.

Discussion included:

- Several ACIP and audience members expressed concern at the focus on vaccinating a group at the lowest risk in the hope of achieving increased immunity over time, when the highest rates are among 17-18 year-olds. Either pursuing the higher risk cohorts or going after two rather than one was suggested. The concerns cited specifically were:
  - The 11 year-old recommendation was discordant with the morbidity and, more important, the mortality data. While the vaccine supply and feasibility issues cited were valid, the preference was still to first immunize those most at risk of death and then later drop the outreach to another platform.
  - Vaccinating 11 year-olds offers very little public health impact, preventing only 10-11 cases with 60% coverage in year one.
  - While the vaccine prompts a memory response, whether that is memory-protective remains unknown. A recent *Lancet* article indicated that very young children were not protected after a year.
  - An 11 year-old strategy would provide little herd immunity for the primary carriers, adolescents.
  - How would the immunization be done? The adolescent visit at age 11-12 for the TD booster, MMR, etc., reaches that cohort, but it would take "a couple of" years to build the infrastructure to mount an effective 18 year-old campaign. The field has trouble even getting the currently-recommended college immunization done.
- Dr. Neal Halsey recommended the simplest path to avoid the cost of an added visit. As much as possible, he would tie this vaccination to existing recommendations, such as the ACIP's recommendations for children going to college and some state mandates. Dr. Modlin agreed. His recent review of adolescent health visits to practitioners for HBV vaccines indicated than <25-30% of adolescents visit a practitioner after age 11-12. Vaccinating 30% with a vaccine with 50-60% efficacy would provide a limited outcome.
- Suggested avenues through which to reach another cohort included a high school departure senior year dose, such as done for the adolescent hepatitis B catch up vaccination. A school/college entrance requirement vaccination for all students should reach a major portion of the targeted cohort. The importance was stressed of the hepatitis B strategies (school mandates and demonstration projects) to this immunization.
- Dr. Lou Cooper advised consultation with clinicians before the ACIP issued its recommendation.
- Several encouraging factors were noted:
  - The vaccine supply constraints should last only one year, with Aventis doubling the supply in the next two years to an unlimited capacity within 5 years. About half of all high school graduates go to college, and most state laws call for meningococcal vaccination. New York State also targets 11-12 year-olds through summer camps and prep schools. A high school entry requirement would catch people at about the right age for disease susceptibility and create another entry point to health care to adolescents. However, that would raise the costs from those presented at this meeting.
  - Almost 70% of adolescents make a health care visit annually, usually for acute, urgent care; the meningococcus immunization could be emphasized then. After 4 years, the catch up for those missed could be done.
  - The emotion attendant to this vaccine provides a good opportunity to construct a new

catch-up visit platform for a certain age. Parents want this.

- The appropriate time to vaccinate age groups will probably be discussed again for other vaccines. Perhaps entry to any school should be the approach.
- Dr. Nancy Rosenstein, of NCID, understood that the 11-12 year-old recommendation was frustrating, but remarked that it would at least allow a feasible "baby step" in the right direction. The Workgroup's recommendation to change the college recommendation for those in dorms would also aid the catch-up.
- Dr. Deborah Wexler, of the IAC, supported the high school entry suggestion. Even an uptake of ≤20% would offer a start, and may not greatly affect the vaccine supply issues.
- If only ~30% of 11 year-olds are seen, high school as well as college entry should be doable with the projected supply. However, high school entry could be too early to catch the peak at 17. Thought is needed on the best entry point.
  - One downside raised to the recommendation was that, if the AAP and the AAFP recommend another cohort to reach, practitioners would have to implement that with no supportive infrastructure to reach those children. The Workgroup was reluctant to commit a nation of pediatricians, family practitioners and health departments to do something until they can do so.
- Dr. Rosenstein expressed the program's need for more guidance and asked that those wanting another model than the one proposed joint the Workgroup to craft that. Of particular interest would be to do the modeling for the inclusion of another cohort, such as 15 year-olds, to present at the February meeting.
- Dr. Chapman suggested that the other three active ACIP vaccine workgroups focusing mostly on adolescents (HPV, pertussis and HIV), assign a representative to coordinate their discussions with those of the Meningococcal Workgroup. Dr. Middleman volunteered to do that.
- Mr. Howard Bedecker, from California applauded the integration of programmatic costs to added mandates. It must be ensured that costs are factored in (e.g., for the school to check each student's immunization record) in a consistent fashion over time.
- Citing the spike in meningococcal disease around age 18 years, Dr. Orenstein was confident that family practitioners would implement a recommendation by the ACIP to ensure vaccination by that age, and promote the 15-16 year-old visit. Having that additional cohort would also address the highest risk groups immediately, instead of waiting more years.
- Dr. Abramson reiterated the Workgroup's decision to not recommend this college-wide, and that there may not be enough vaccine for two cohorts if demand is high.

Dr. Levin asked the Workgroup to explore possible other solutions to recommend to the ACIP in February. Another entry point could be considered if the cost is calculated.

Public Comment

Ms. Lynn Bozoff, Executive Director of the National Meningitis Association, thanked the ACIP for the opportunity to raise awareness of meningitis, the availability of a safe and effective vaccine, and the opportunity to have been part of the Workgroup. If routine recommendations had been in place, her son Evan would still be alive. Everyone should have the opportunity for protection from this disease. She urged the ACIP to recommend this vaccine to all traditional college freshmen, not just those in dorms; they also die who live in fraternity or sorority houses, apartments, or who commute. She often hears from affected parents, and more recently, from a 12 year-old girl who had lost her 9-year old friend, Dylan. She read her e-mail. She asked the

committee to issue strong recommendations so that she need no longer receive such phone calls and e-mails.

Ms. Carol Waghorn, a founding member of the National Meningitis Association, lost her son at age 17. In his dorm, he came down with a headache after track practice. Thinking he had the flu, the health center sent him back to his dorm. The next morning, seriously ill, he was entered into the health center and, when seen by a doctor several hours later, his rash was recognized. He was rushed to the ER across the street from the health center. Several hours later, when his parents got there, he was in a coma and she barely recognized him. He died that night, with them holding his hand. She learned several months later that there was a vaccine available and wondered why it was not available or known to her family. Her son had serogroup C, which the vaccine could have prevented. She was delighted to hear of the new vaccine and was certain that its use would make a big difference.

Mr. Mike Kefferly related being one of three people who had spoken to the FDA the previous month, along with his daughter and an anti-vaccine advocate. His daughter cried as the latter speaker discussed the costs versus the benefits of vaccination, and judged that the vaccine should probably be limited to dorm residents. His son Pat was an 18-year-old dorm student. While Mr. Kefferly understood the policy complications, he also knew the impact to colleges when CDC does not recommend meningococcal vaccination. They place lesser emphasis on the availability of a vaccine if the student wants it. He offered to help the Workgroup to craft the right language, or to educate college administrators and parents, so that no other parent has to learn that their child could have been vaccinated but died instead. He already is working with a Maryland legislator who has committed to write to all the state governors to encourage their work with their legislatures on bills to support the work CDC and NGOs such as the National Meningitis Association.

Ms. Lynn Knockrouse related having lost an aunt who was not vaccinated against tetanus, stepped on a nail, and died awaiting a liver. She is now the mother of three boys. She related how she learned, upon her son's 4-year-old visit, that he had apparently missed his MMR shot at 18 months. Since her other son may have celiac disease, her 4-year old also was tested, revealing a severe allergy to a particular vaccine component. He was also IgA deficient, as is she and her 2 year-old. Her son received his MMR vaccination and other routine shots. On returning home, he collapsed several times, but recovered each time. The next day, he developed a rash and a big welt on his lip. The physician recommended warm compresses and sent him home.

Her son began to respond differently, such as excessively crying at a time out, becoming hypersensitive to noise, or stopping bowel movements days at a time. She called the doctor every day and took him to an allergist. By the fourth week, he was butting her and the walls with his head, walking in circles, biting and growling, and did not want to be touched. She continued to call the doctor, who finally said that vaccines do not cause such severe reactions and asked if she wanted her son referred to a psychiatrist.

She found the Defeat Autism Now Website and a doctor who ran tests. They found that her son had a bacterial infection in his intestinal lining (apparently from antibiotics taken for an ear infection) and a 5.97 titer for measles (a high level is 1.34). With treatment, he has begun to write and call her "Mama" again. She asked for screening and research, to determine if an IgA

deficiency should be a contraindication for vaccination.

Dr. Levin responded that hers was a very complex story and offered to talk to her about it on behalf of the committee at the break time.

Agency Updates

Department of Defense (DoD). Dr. Phillips reported that DoD is following ACIP-defined priorities for vaccination, particularly as related to military family members. Normally, influenza vaccine is mandatory for all those in uniform since the disease is famous for decimating armies. The latter has made it difficult to turn away people seeking the vaccine in favor of delivering it to the deployed field personnel. DoD is also emphasizing education on influenza prevention and for the first time ordered ~250,000 doses of the LAIV FluMist.® They are negotiating with DHHS to return inactivated vaccine in exchange for more LAIV, which is targeted for use among new recruits. They have received ~30% of their total vaccine order, almost all of which was sent to the deployed forces. They expect to have all vaccine delivered by late November/early December. DoD's Health Care Center, under Dr. Renata Engler, will conduct a half-dose vaccine study with NIAID to generate data that should be useful in future.

Food and Drug Administration (FDA). Dr. Baylor related VRBPAC's discussion of post-licensure safety studies of the Aventis Pasteur meningococcal vaccine as well as those on concurrent vaccination among travelers and adolescents. FDA is working with DoD and NIAID to review the half-dose influenza vaccine study and is looking for more influenza vaccine for the nation's supply. VRBPAC also heard an update on the Phase III HIV vaccine study in Thailand.

National Institutes of Health (NIH). Dr. Curlin reported NIAID's focus on influenza vaccine and H5 strain challenges. Clinical trials of biologics and vaccines are the most rapidly growing segment of their institution.

National Vaccine Program Office (NVPO). Dr. Gellin reported that most NVPO activities also are focused on flu. An NVAC Task Force is examining the influenza vaccination system and its strategies and capabilities to reduce the impact of influenza in the U.S. and reduce the disease burden. Preliminary reports were given in June and at the last meeting and included eight recommendations: 1) develop a system for influenza vaccine delivery in all settings or medical homes; 2) work with payers to make influenza purchase less of a burden and financial risk for providers; 3) explore options for supporting a comprehensive adult vaccination program; 4) consider expanding the influenza vaccination recommendations; 5) develop a better understanding of the U.S.' influenza disease burden, implement new surveillance systems for a better ongoing assessment of program impact and VE; 6) reinforce the importance of influenza vaccination for health care workers; 7) conduct a comprehensive review of the influenza vaccine research program across the departments; and 8) identify gaps for additional support.

The lessons learned will be incorporated to the pandemic plan. As called for by the IOM's 2003 Vaccine Financing report, a stakeholders meeting was held in June. The response to that report now is working its way through DHHS. That report is pertinent to the current situation in its assessment that the IOM's degree of "fix" was not sufficient to the degree that the system is "broken."

Vaccine Injury Compensation Program (VICP). Dr. Evans reported that two new vaccines will be added to the VICP, and perhaps a third (meningococcal) within the next year. He described the two-step process for in which the influenza vaccine will be added to the Vaccine Injury Table (VIT). Perhaps the most important part of the process is the excise tax legislation, which levies a 75 cents per "dose", or case prevented, tax (i.e., so the cost for a trivalent vaccine preventing three diseases includes a $2.25 tax). The date of the tax statute begins a time line that includes an 8-year period of retroactive coverage for claims. In step two, the CDC publishes in the *MMWR* its recommendation of the vaccine for routine administration to children. The DHHS Secretary then publishes a Federal Register notice of the vaccine's coverage and placed it on the VIT in a provisional category. The rule making process then adds injuries or conditions relevant to the vaccine, another notice is published for public comment, and the VICP consults with its advisory committee, the ACCV. The final rule is then published and the vaccine is listed separately on the table.

The 2004 American Jobs Creation Act imposed an excise tax for both trivalent influenza vaccines and hepatitis A vaccines. The Secretary will publish separate notices of coverage in the Federal Register to provisionally list them on the VIT, and begin rule-making with ACCV consultation. For hepatitis A, Congress established the effective date as the first day of the first month beginning >4 weeks after the enactment date, which will be December 1, 2004. When hepatitis B will be added is still not determined. In view of influenza's seasonality, rather than the normal effective date of the day after the President signs the law, the DHHS Secretary was authorized to set that date. DHHS will discuss and announce this in the Federal Register.

National Center for Infectious Disease (NCID). Dr. Mawle reported on the NVPO-funded meningitis stakeholders meeting held in Atlanta, which was chaired by Dr. George Peter. The 50 participants represented a broad range, including traditional health care providers to public health, advocacy groups, and organizations (e.g., of school nurses). The meeting's goal was to launch an education campaign to raise awareness of meningococcal vaccine. This was before CDC learned of the vaccine's impending licensure. But even the vaccine is not the "final answer" to end this disease. It does not cover meningococcus B and its age range is not all-inclusive. Therefore, the focus is to reach and educate the community, particularly parents, on meningococcal disease and to promote health-seeking behaviors. Two breakout sessions were held to discuss public health messages and communication strategies to different targets, such as health care practitioners, public health, and students (including older students taking more responsibility for their own health. CDC expects to follow up on this and be funded to implement an education program.

In 1999, CDC was mandated to set up an anthrax research program to address the risk factors for adverse events, explore the immune correlates of protection and to discuss the routes and strategies of administration. Regarding the latter, a clinical trial begun in 2002 completed its enrollment in March 2004. The data of the interim analysis is likely to be completed in January 2005. Two possible alternatives being explored are to change the route of administration and to drop one of the six priming doses. CDC is working with FDA on this and will report to ACIP.

Center for Medicare and Medicaid Services (CMS). Ms. Murphy reported CMS' issuance of a statement that all children on Medicaid who qualify under the ACIP recommendations are entitled to a influenza shot if the vaccine is available. Medicaid provides that through VFC. States that have run out of vaccine can get it from the private supply, if available, and payment

will be worked out later. No child should be turned away and no parent should be required to pay for it. CDC has ensured delivery of 100% of the VFC vaccine ordered, but that does not cover all of the children in the VFC. CMS has a mechanism for states to reimburse providers for their private stock used, but the health departments all differ in how they do this. For that reason, she could not predict how that would be done.

Pandemic Influenza Plan Update
Presenter: Dr. Ben Schwartz, NVPO

The Influenza Pandemic Plan was released on August 26 and the period for public comment had expired, but the NVPO still will consider comments. DHHS will continue to consider issues such as indemnification for vaccine manufacturers, vaccine purchase and distribution, and target groups for the use of antiviral drugs. NVPO formed a committee that will include the stakeholders to influenza issues (public health, healthcare organizations, etc.) to gather their input. ACIP input, especially through a representative on the Workgroup, will be appreciated.

The vaccine shortage had emphasized what would happen, in the event of a pandemic, if the U.S. had no domestic production. Vaccine security, defined as U.S. vaccine production, is now a major focus. RFPs have been issued to secure the egg supply for egg-based vaccines and to diversify the U.S. vaccine supply by licensing U.S. produced cell-culture vaccine. a small stockpile of H5N1 vaccine also has been acquired, and investigational lots of H5N1 vaccine are being tested by NIH. NIH and CDC are exploring the potential of using lower antigen levels per dose, to further stretch the national vaccine supply.

National Immunization Program. Dr. Cochi deferred the NIP's report in view of the late hour, and the meeting adjourned at 6:22 p.m.

OCTOBER 28, 2004

UNFINISHED BUSINESS

Interim and 2004-05 VFC influenza vaccination resolutions
Presenter: Dr. Greg Wallace, NIP

Overview: Prioritization language for this year's vaccine supply; VFC resolution.

Interim VFC resolution *(revising resolution 6/02-1); vaccine supply prioritization.* If approved by the ACIP, this interim recommendation would revise the recommended use of influenza vaccine in the current shortage, to prioritize among certain groups. Once approved, the recommendation would be immediately effective and would expire automatically on this season's June 30 vaccine expiration date.

The interim recommendation provided additional vaccination prioritization for pregnant women in any trimester as well as household contacts and out-of-home caregivers of children aged <6 months, since the latter cannot be vaccinated. The other groups already specified and continuing as priority recipients were:

- Children aged 6-23 months;
- Children and adolescents aged 2-18 years:

- Those with chronic pulmonary or cardiovascular disorders (e.g., asthma)
- Those who had regular medical follow-up or hospitalization in the preceding year due to chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including that caused by medications or by HIV).
- Those who are receiving long-term aspirin therapy and may therefore be at risk for developing Reye syndrome after influenza
- Those who are residents of nursing homes and other long-term care facilities that house persons at any age who have chronic medical conditions.
- Those who are household contacts or out-of-home caregivers of children aged <6 months.

❖ Adolescent females aged <19 years who will be pregnant during the influenza season.

2005-06 VFC resolution. Upon the ACIP's recommendation, this VFC resolution would become effective on July 1, 2005, for the next influenza season. It clarified the risk groups, incorporated the live attenuated influenza vaccine (FluMist®), and updated the pregnancy recommendation for inactivated influenza vaccine.

Risk groups specified remained the same, but the age groups for chronic disorders were changed to 6-23 months and 2-18 years; HIV was specified under those with immunosuppressive diseases, and specified all pregnant women aged in any trimester.

Eligible Groups for the inactivated influenza vaccine included children and adolescents aged 2 through 18 years who are household contacts or out-of-home caregivers of persons in the following high-risk groups: 1) any children aged <2 years; 2) children or adolescents in any of the other groups listed above; 3) any person aged ≥50 years; 4) adults with chronic disorders of the pulmonary or cardiovascular systems; and 5) adults who have required regular medical follow-up or hospitalization during the preceding year for chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]).

Live Attenuated Influenza Vaccine (LAIV. The eligible Groups to receive LAIV were:

❖ Healthy children and adolescents aged 5 years through 18 years who are household contacts of persons in the following high-risk groups provided that the contacts are not severely immunocompromised (e.g., patients with hematopoietic stem cell transplants) and requiring care in a protective environment:
- Any children aged <2 years
- Children or adolescents in any of the other groups listed above;
- Any person 50 years or older;
- Adults with chronic disorders of the pulmonary or cardiovascular systems
- Adults who required regular medical follow-up or hospitalization during the preceding year for chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]).

Groups who should not be vaccinated with LAIV were listed. Those with an asterisk were specified to receive inactivated influenza vaccine if they were older than 6 months:

❖ Children aged <5 years

❖ Persons with asthma, reactive airways disease or other chronic disorders of the pulmonary or

cardiovascular systems; persons with other underlying medical conditions, such as the metabolic diseases diabetes, renal dysfunction, and hemoglobinopathies; or persons with known or suspected immunodeficiency diseases or who are receiving immunosuppressive therapies*

- ❖ Children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza infection)*
- ❖ Persons with a history of GBS
- ❖ Pregnant women*
- ❖ Persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs.

On the vaccination dosage schedule and interval chart, FluMist™ was listed as approved for those aged 5-49 years, while specifying that the use of brand names was "not meant to preclude the use of other licensed influenza vaccines." Dosages also recommended reference to the manufacturer's package insert.

Contraindications and precautions were amended to specify that either inactivated or live attenuated vaccine can be administered in the presence of minor illness. The groups listed in the second bullet above were again listed as contraindicated for vaccination with LAIV. A history of Guillain-Barré Syndrome after vaccination with influenza vaccine was also added as a precaution against vaccination with the inactivated virus vaccine.

Discussion included:

- ❖ The insertion of an allergy to "chicken" eggs will be one of the word-smithing edits considered.
- ❖ While the contraindication or precaution about the use of inactivated virus vaccine with a "history of GBS within six weeks following influenza immunization" was retained to remain consistent with the ACIP recommendation, the Workgroup was asked to consider the necessity of stating that.

Dr. Stinchfield **moved to accept both of the VFC resolutions as presented** and Dr. Birkhead seconded the motion.

Vote
Conflicts: AventisPasteur, MedImmune, Chiron
In Favor: Womeadu, Stinchfield, Salamone, Morita, Marcuse, Lieu, Gilsdorf, Finger Campbell, Birkhead, Allos, Abramson, Levin.
Opposed: None
Abstained: Treanor, Poland, due to conflict.

The vote passed.

HEPATITIS

Hepatitis A Vaccination Recommendations
Presenter: Dr. Beth Bell, NCID

Overview: Rationale for revisiting the recommendations on hepatitis A vaccination; relevant

data on coverage and current disease burden; next steps for the Workgroup; ongoing cost effectiveness analysis.

ACIP has incrementally recommended the routine vaccination of children, beginning in 1996 with children living in communities with high rates of hepatitis A and routine vaccination of all adults at high risk. This was extended in 1999 to states and communities with consistently elevated hepatitis A rates, which covered ~30% of the entire population and accounted for >50% of hepatitis incidence. Implementation was variable for this new stepped and voluntary vaccination strategy approach. The permissive 1999 language advised states and communities to determine the recommended vaccination age groups according to their community disease patterns (e.g., vaccination of children according to age or setting [e.g., daycare], or when presenting for medical care).

When mapped, the impact of this vaccination policy to date graphically demonstrated unprecedented declines (76%) in the targeted areas, well below any rates previously recorded. The largest declines occurred among children, but there was also good evidence of a herd immunity effect. With overall national rates at a historic low, the epidemiology of the disease has changed; most incidence now occurs among adults. In the pre-vaccine era, most hepatitis A occurred in children, primarily among those aged 2-9 years, whose rates were followed by those aged <2 years. Maps again demonstrated the elimination of the regional epidemiology that existed before routine vaccination was implemented.

With the passage of sufficient time to demonstrate the impact of the recommendations' implementation, and with possible changes in the vaccine's labeling, NIP has considered two strategic options, to 1) continue the current regional strategy, focusing on providing more guidance to improve coverage, or 2) extending the recommendation to children nationwide.

As of 2003, one-dose coverage among young children ≤35 months varies according to the recommendation decided by the state, as was expected. While it is high in some states, there is a big range nationally. The overall average coverage in the 11 states that recommended vaccination was 51% in a range 6-73% (highest in the states with vaccination mandates), and 25% in the states where vaccination is "considered." The limited data of coverage of older children also suggest a very wide range, and coverage among adults is likely to be very low.

In general, all data suggest a modest coverage at best, below that of other routinely-recommended vaccines. The current wording of the recommendation does not specify a preferred approach. While incidence has been declining overall, prevalence rates have risen, with more disease concentrated in adults. Of the 7653 cases reported in 2003 (down from 25-35,000 cases in the mid 1990s), ~80% were in adults. A map also demonstrated that, for both adults and children, most of the cases had occurred in the regions with no recommendations for vaccination of children.

Between now and the February meeting, the Workgroup will discuss a recommendation to vaccinate all children nationally. They will consider the objective of a hepatitis A vaccination policy (i.e., lower incidence or transmission elimination) in the context of sustainability of the current approach, the feasibility and acceptability of a national recommendation, and the cost effectiveness of that strategy. They also will review CE studies and those of coverage in older age groups.

Discussion included:

- The vaccination was begun to prevent hepatitis A in children. But now that the rates are higher in adults, the CE will evaluate the lowered vaccination age from 2 years to 1, and will model possible resulting herd immunity.
- The available data on infected adults indicate the largest proportion coming from outbreaks among risk groups such as gay men and drug abusers, especially methamphetamine users. There have also been some food borne outbreaks and cases brought home by returning travelers.
- One challenge already seen to a sustainable routine vaccination strategy, is that states achieving lowered rates are tempted to stop the vaccination and begin again only with rising rates.
- The epidemiology of food borne hepatitis A makes it hard to quantify the effect of vaccination on food borne illness. The large outbreaks in 2003 from food contaminated before entering the U.S. would not have been prevented by vaccinating food handlers. There is no evidence that vaccination has affected food borne transmission rates, but even if it did, that would be hard to demonstrate. CDC is trying to determine the effect on fulminant hepatitis as part of a comprehensive analysis of vaccination effect. A study of fulminant hepatitis in transplant centers suggests that a smaller proportion of fulminant cases are attributable to viral hepatitis, as compared to the pre-vaccination era. A few large national chains are vaccinating food handlers, but the success rate is low due to the turnover among such staff.

CE Analysis of Expanded Hepatitis A Vaccination in the U.S.

Presenter: Dr. Gregory Armstrong, NCID

Overview: Proposed methodology to evaluate from a societal perspective the economic impact of expanding routine childhood hepatitis A immunization beyond the U.S. areas specified in the 1999 ACIP recommendations.

Much of the previous CE research on expanded hepatitis A vaccination in the U.S. has been done by the pharmaceutical industry. CDC contracted for a independent CE assessment with the Research Triangle Institute (RTI), which won a competitive RFP. The parameters of the analysis will be cost effectiveness (cost per case prevented, cost per year of life saved and other measures); cost-utility (cost per quality adjusted life year [QALY] gained); and cost-benefit (net present value of costs and benefits).

The principle immunization scenarios posited for both the baseline measurement and the expanded recommendation were *"counterfactual" scenarios* (no- or full implementation), and *intervention scenarios*. For the latter, the baseline analysis will assume full implementation of the 1999 recommendations. For intervention, the analysis will assume: 1) nationwide routine childhood immunization starting at age 1 or 2 years and 2) routine immunization *plus* catch-up immunization at age 5 *or* at ages 5 and 12. Other scenarios may also be considered.

The Markov model structure will be used to follow one cohort, aged 1 to death, over a period of one year. The analysis will focus on those vaccinated, those without vaccine-induced immunity, and those with hepatitis A virus infection. The latter will be analyzed according to the costs of asymptomatic infection, mildly symptomatic infection without icterus, and acute infection

(uncomplicated, fulminant, and fatal).

The vaccination costs calculated will relate to the cost of vaccine acquisition, its administration and the cost of work loss by the caregiver. The costs associated with acute hepatitis A infection will be direct medical costs, cost of lost productivity, and the costs of public health intervention for reported cases. Three sensitivity analyses will be done: univariate, probabilistic (multivariate sensitivity), and threshold analysis.

The cost analyses will proceed in five phases:

1. *Cost of Incidence* of acute hepatitis A. This will consider reported incidence to calculate age-specific pre-immunization incidence reported, from 1990 to 1995 (assuming the NNDSS overall incidence rate of 10.2/100,000). It will use the published multiplier of 4.3 (Armstrong GL. *Pediatric*s 2002;109:839) to factor in under-reporting, and will use an age-specific multiplier to factor in anicteric infections (ibid). The yearly change in incidence without immunization will be calculated in a range of 0% to -2.1% (Jacobs RJ. *Ped Infect Dis* 2003;22:904).
2. *Cost of Vaccine* given as a 2-dose series (but with lower coverage for two than one dose). It will be analyzed using the same immunization rates as other childhood vaccines, assuming a VE of 94% after 1 dose and 100% after 2 doses (1 Innis BL. *JAMA* 1994;271:1328). Long-term efficacy, an area without much data as yet, will be modeled based on the distribution of titers after 1 or 2 doses, the rate of decline in antibody titer over time, and an assumed threshold of 10-20 mIU/ml (Van Herck K. *J Med Virol*;63:1). The cost of mild adverse events, in view of the vaccine's minimal reactogenicity, will also be calculated.
3. *Hospitalizations and deaths.* Based on the rates reported by the NNDSS and the 1990-1995 NHDS, a total of ~5700 hospitalizations for acute for hepatitis A will support this calculation. Since hospitalization data is not reported by all states, the age-specific hospitalization rates of those reported will be applied to all cases reported from 1990 to 1999. The cost of liver transplants attributable to acute hepatitis A will be estimated from a number of different data sources. The NNDSS data indicate ~100 deaths from acute hepatitis A annually, an estimate support by the Sentinel County Study of Viral Hepatitis. Also to be factored in is that mortality rates from acute hepatitis A increase with age.
4. *Other selected costs* to be analyzed include the costs of vaccine acquisition ($11/dose, public sector; $28/dose private sector), administration ($15/dose), caregiver work loss (0-0.125 days/dose, depending on if the child's visit was for another reason); direct medical costs ($780, outpatientl; $7000, hospitalized/uncomplicated; $24,000, hospitalized, fulminant hepatitis; $270,000 for the first year, liver transplant, $25,000 for subsequent years); work loss (age-dependent, as older workers generally earn more than those younger; 7-16 days for outpatient acute hepatitis A: 12-40 days for hospitalized acute hepatitis A).

Finally, 5) *herd immunity* is important to the economics of hepatitis A immunization, since >50% of the benefits derive from preventing secondary infections and infections in family members and other contacts of those immunized. The evidence for a herd immunity effect is theoretical, but strong. Most HAV infections occur in young children, and studies in both the U.S. and Israel of children's immunizations showed simultaneous incidence declines in adults alongside >90% declines in children. Recently published data (Samadari T. *Vaccine* 2004;22:4342) also indicate that for every 1% increase in vaccine coverage among children, there is a resulting 3.9% decrease in incidence in other children, and a 1% incidence decrease in adults.

Therefore, the likely CE impact from herd immunity will be assessed for:

- Cohort-specific effects, assuming no impact with 100% vaccination coverage and no loss of immunity, and increased CE with decreasing vaccination coverage. This will be assumed in the base model, as will a modest increase in CE overall.
- Population effects, assuming a large impact in year one that eventually declines over time with subsequent cohorts to a negligible impact. These effects will not be factored in the base model, so the latter's results will represent cost-effectiveness after several years of immunization. But RTI will estimate the impact of population effects from the first cohort's immunization, which are expected to decrease progressively with subsequent cohorts.

Upcoming anticipated milestones of this project include RTI's December presentation of the analysis results to CDC. These will be discussed with the ACIP Hepatitis Workgroup and presented to the ACIP at the February meeting.

Discussion included:

- Since disease incidence and vaccine costs are the main drivers of CE, Dr. Lieu suggested also assessing the CE of universal vaccination at the current incidence rates, for which data are available to 2003. Dr. Armstrong clarified that the incidence rates used in that part of the analysis assume the lower coverage in the states that have not recommended the vaccination, rather than the overall U.S. incidence rates. The analysis will examine declining rates over time, factoring in hepatitis A's periodicity as well as vaccination. To this point, with the exclusion of imported cases, the declines in incidence rates in the states without a recommendation have remained within historic limits.
- The Markov model's structure, moving from vaccination to hepatitis susceptibility, was based on assumptions leading from antibody titer declines.
- Since the U.S. hepatitis A antibody levels are ten times higher than the reported incidence would indicate, under-reporting is factored into the analysis. That is estimated using the most accurate disease burden data available (enhanced NHANES reported rates).
- Dr. Hadler noted that the analysis focused more on children, even though ≥66% of the current burden is among adults. He urged the Workgroup to carefully consider adults, the other half of the immunization strategy. This is more of a challenge to meet, with no federal or insurance support for adult vaccination, but it should be considered as part of the strategy for improving hepatitis A control.

Updating the Hepatitis B Virus Transmission Elimination Strategy

Presenter: Dr. Eric Mast, NCID

Overview: Update on implementation of ACIP strategy to eliminate Hepatitis B Virus (HBV) transmission; draft ACIP hepatitis B vaccine recommendations (new and consolidation of previous recommendations); plans for finalizing recommendations.

Before hepatitis B vaccination programs began, the HBV incidence was 200,000-300,000 annually, a rate that has declined to ~73,000 new infections. However, one in 20 Americans (~12.5 million) have been infected with HBV during their lifetime; 1 in 200 (~1.25 million) have chronic (lifelong) HBV infection, and 4000-5000 deaths per year are related to HBV chronic liver disease.

Since most of HBV's morbidity and mortality occurs in those with chronic infection, the primary goal of hepatitis B immunization is to prevent chronic infection. A slide of the estimated age at infection for individuals with chronic infection, before childhood vaccination programs, showed 59% among adults and 24% among children (mostly child-to-child transmission) and adolescents. Another 18% was perinatally acquired by newborns. Those statistics supported ACIP's 1991 recommendations to vaccinate adults in high-risk groups and to conduct universal infant vaccination and catch-up vaccination of all children and adolescents aged <19 years.

Strategy for Prevention of Perinatal Infection. Data were presented from emerging infectious disease surveillance sites in eight states (2001), as well as data from 10 other states from 1991-1999. Overall, >90% of women in the U.S. have been screened for hepatitis B surface antigen status, and the 2001 (the last data) rate was 96.5%.

However, preventing perinatally acquired HBV still faces a number of challenges.

- Less than 50% of expected infants born to HBsAg-positive mothers are reported.
- Infants born to mothers with unknown HBsAg status often are not managed appropriately.
- Tracking errors have lost infants born to known HBsAg-positive mothers.
- A recent Alabama Department of Health study of births 1990-2002 showed that, of 982 infants identified born to HBsAg-positive mothers, 92% received hepatitis B immune globulin and HBV vaccine within 24 hours of birth, and 89.8% had three doses by age 8 months. But another 318 (22%) were not identified until a registry of surface antigen positive mothers was linked to birth certificates. Only two-thirds of these received hepatitis B immunoglobulin (HBIG) and vaccine within 24 hours of birth and only ~60% had three doses by eight months.
- Hospital-based surveys of maternal and infant records suggest inadequate policies and procedures in place to identify and provide a birth dose to infants of mothers with an unknown HBsAg status. Fewer of the latter infants are given hepatitis B vaccine at birth versus the infants of HBsAg-negative mothers, nor are they properly managed. A case was described of an infant girl who died in 1999 of fulminant hepatitis B due to inadequate recording, tracking and follow-up procedures.

In response, the consolidation of several recommendations were proposed: the 1984 recommendation for postexposure prophylaxis for infants born to surface antigen positive mothers and the 1988 recommendation for routine testing of all pregnant women. In addition, new recommendations under consideration by the Workgroup include policies and procedures to ensure surface antigen screening and reporting of surface antigen positive pregnant women. Specifically, these address policies and procedures to ensure HBsAg screening and the reporting of HBsAg positive women:

- The incorporation of HBsAg testing/results into prenatal testing panels, all pregnancy forms, standing orders for testing mothers without an HBsAg test result, and electronic birth certificate or newborn metabolic screening.
- State laws are urged to test all pregnant women for their HBsAg status, to report HBsAg-positive women to the health department, and to certify that all women are so tested before hospital discharge.

Additional recommendations under consideration include:

- The maintenance of health department programs to ensure case management for infants born to HBsAg-positive mothers and infants born to mothers with unknown HBsAg status.

- ❖ Standing orders to ensure case management in hospitals, to: 1) review HBsAg test results for all pregnant women at the time of admission for delivery; 2) provide hepatitis B vaccination at birth for all infants born to HBsAg-positive mothers (with HBIG), all preterm infants <2000 grams born to mothers with unknown HBsAg status (with HBIG), and all medically stable full-term infants (≥2000 grams).

Strategy for universal infant and catch-up vaccination ***of children/adolescents (<19 years)***. Routine infant vaccination is now at the highest rate ever (92.4% coverage), even with the thimerosal controversy of 2000. Adolescent vaccine coverage is also increasing, now at ~70%, largely due to elementary (45 states) and middle (35 states) school entry laws HBV vaccination mandate. The overall decline of hepatitis B incidence among children aged 2-18 years is 89%, and racial/ethnic disparities in children's rates have been eliminated. Several serosurveys have shown a dramatic impact in the prevalence of both hepatitis B virus infection and in chronic infection in populations with previous high rates of infection. Data were presented from studies in Hawaii and Atlanta showing dramatic declines. After 99% vaccine coverage was achieved in 2001 in Hawaii, chronic infection rates fell from 1.6% to 0.4%, and from an overall prevalence of 4.5% 0.2%. In Atlanta, the children of Asian immigrant parents had an overall antigen prevalence of 11.7% in 1986 and a chronic infection rate of 6.6%, both of which dropped to 0.6% with 98% vaccine coverage.

The primary challenges now for infant and adolescent hepatitis B vaccination are to maintain or increase vaccination coverage in infants and to fully implement elementary and middle school mandates. The Workgroup's proposed recommendations were to:

- ❖ Consolidate/update the 1991 recommendation to routinely vaccinate all infants and the 2002 recommended preference for a birth vaccine dose.
- ❖ Include hepatitis B vaccination in standing orders for routine care of medically stable full-term infants.
- ❖ Urge states to adopt regulations or laws requiring hepatitis B vaccination for entry into child day care, kindergarten, and/or elementary school.

For previously unvaccinated children and adolescents, the Workgroup recommended:

- ❖ Consolidation of the 1982 recommendations to vaccinate children in ethnically-defined high risk groups and adolescents in high risk groups: the 1995 recommendation to vaccinate children aged 11-12 years on routine visits to a health care provider, and the 1999 recommendation for universal vaccination of all children and adolescents.
- ❖ Routinely provide hepatitis B vaccination in juvenile correction facilities and in programs serving youth at high risk for STD, HIV/AIDS, and those in substance abuse treatment and prevention programs.
- ❖ State adoption of regulations or laws requiring hepatitis B vaccination for entry into middle school or its equivalent.

Strategy for Vaccination of Adults in High Risk Groups. The groups at high risk of hepatitis B infection include heterosexual persons with sexual risk factors (42%), men who have sex with men (MSM – 19%) and injection drug users (IDU – 18%). Other groups include the 5% who are household contacts of individuals with hepatitis B, those who are institutionalized, or those on hemodialysis (a risk factor of blood transfusion) or with occupational exposure to blood. The latter two have high vaccination coverage and dramatically reduced HBV rates. Another 16% have no identified risk factor. But vaccine coverage still remains very low among the groups of

MSM, IDU and STD clinic clients, where estimated coverage ranges between 6-16%. The ~65% overall decline in incidence has plateaued since 1998, and racial and ethnic disparities remain. The declines also have masked the increases of some groups (e.g., +5% in men aged 20-30 years and +30% in men and women aged >40 years).

The reason that the adult risk group outreach has not succeeded as well as that to children is the absence of mechanisms provided by the childhood immunization program: vaccine purchase and delivery. The Workgroup recommended:

- The update of the 1992 recommendations for the vaccination of adults with risk factors for HBV infection: 1) persons at risk of sexually-transmitted HBV infection; 2) MSM, 3) IDU, 4) sexual and household contacts of HBsAg-positive persons, including family members of HBsAg-positive immigrants and international adoptees; 5) persons at occupational risk; 6) dialysis patients; 7) patients receiving clotting factor concentrates; 8) international travelers; and 9) inmates of correctional facilities.
- Vaccination for any person desiring protection from hepatitis B virus infection.
- Routine availability of hepatitis B vaccination in high risk settings (e.g., STD clinics, HIV/AIDS testing and counseling programs, drug use prevention treatment clinics, correctional facilities). The previously mentioned Sentinel County Study of Viral Hepatitis found that >50% of persons with acute hepatitis B had past vaccination opportunities in STD clinics or in correctional facilities.

Other recommendations:

- No change to past recommendations for pre- or post-vaccination testing.
- No change to the past recommendation for no booster doses.
- Assessment of the immunity in persons with reliable vaccination history.
- Development of methods with which to manage persons with unknown or uncertain vaccination status, immigrants and international adoptees.
- Acceleration of vaccination schedules (i.e., when travelers must leave before completing the normal vaccine series schedule, data support administering it at weekly intervals). The recommendation should formally state that if this is done, a dose should be given at six months after the initial dose to ensure long-term protection.

The time line for generating recommendations was outlined. Ad hoc Workgroup conference calls to discuss outstanding issues will be held through January 2005. The revised draft will be distributed by mid-December for Workgroup member comments, which are due in mid-January 2005. The final draft will be distributed to the ACIP and the Hospital Infection Control Practices Advisory Committee (HICPAC) on February 1 and discussed at the February 10-11, 2005 ACIP meeting. If the committee approves the recommendations, the final draft will be distributed for stakeholder review and comment and published in the June 2005 *MMWR*.

- Issues remaining for the Workgroup's discussion include those related to: 1) case management to prevent perinatal HBV transmission, including how to highlight the importance of birth dose for all infants; 2) recommendations to prevent HBV transmission in adults; 3) addressing the issues of long-term protection/booster doses (review published and unpublished data on long-term protection, assess scientific basis for existing booster dose recommendations, propose future studies to assess the need for booster doses).

Discussion included:

- Dr. Levin asked the Workgroup for send the information to the ACIP members earlier than now planned.
- As much data as possible to support the birth dose is desired to give pediatricians the comfort of that as the standard rather than the preferred method. The AAP's Committee on Infectious Disease is aware of that; many think that the birth dose is necessary.
- CDC is aware that some health care workers vaccinated for hepatitis B in the late 1980s or early 1990s now have negative titers. While hepatitis B surface antibody titers decline over time (with ≤50-60% losing antibody after ten years), the protective levels are thought to remain. This is supported by population-based studies showing the absence of infection as well as booster-dose studies showing a prompt anamnestic response in these individuals. Those data will be presented to the Workgroup. An ACIP statement to that effect will be helpful to those whose employment now requires boosters, and is in the document.
- An initiative by three CDC centers (NIP, NCID, NCHSTP) demonstrated, as does this project, the need for an adult immunization program. The tricenters' initiative experience may be shared with the Workgroup.
- The HBV vaccine is among the most successful, yet adult immunizations lag. The recommendations were last updated 14 years ago. Another 14 years must not pass before a feasible and workable adult immunization structure provides the vaccine purchase and delivery mechanisms for adults to lower that primary area of disease burden.
- The Workgroup's attention was suggested to the issue of genetic escape mutants and the potential impact on vaccination programs and strategies. A recent report indicated a surprising number of unimmunized children with gene variations that could lead to vaccine resistance. Also suggested for Workgroup discussion was the issue of the combined hepatitis A-B vaccine, and the potential need for longer needle lengths for obese patients to ensure that the vaccine is not deposited in fat, causing decreasing immunogenicity.
- There was agreement that the data support an anamnestic response, except among those who became immunocompromised after their series of injections but before their exposure; this has been documented in HIV-infected patients. Such individuals may need a booster. For that reason, the existing recommendations for testing and boosting of immunocompromised individuals will remain in the recommendation.
- The document could discuss the need for some adult version of the successful elements that raised childhood coverage, such as school entry or requirements for testing of pregnant women. For example, correctional settings hold people at risk, but there is no funding to conduct outreach there. Vaccination requirements or at least screening encouragement should be proposed. Another area of opportunity is vaccination of health care workers.
- Representation of ACOG on the Workgroup was suggested to profit from their experience with GBS or the Group B streptococcus screening and recommendations.
- Thirteen or 14 states now have laws for screening pregnant women, but no analysis was known of whether their implementation produced any differences in screening rates. However, states that report newborn metabolic screening have demonstrably greater success in identifying surface antigen-positive mothers.
- To address the disparities of adult HBV immunization, as much information as possible beyond race/ethnicity is needed about those at risk so that they can be reached in the health care system.
- The recommendations are specific with regard to international adoptees and immigrants, both for testing and vaccination, but illegal immigrants have not been discussed. More information about that would be needed.
- The Workgroup's review was suggested of the IOM reports on the safety information

gathered for hepatitis B since the recommendation's last revision.

Agency Update: NIP Report. Dr. Cochi updated the committee on the strategic vaccine reserves. To avoid supply disruptions, the intent is to have a 6-month supply (based on the birth cohort) of the universally recommended pediatric vaccines on hand in the national stockpile. With VFC funding, this should be accomplished by 2007.

However, several factors complicate stockpile assembly and maintenance, such as changing vaccine market share and that the selection of vaccines for storage involves combination vaccines and overlapping combinations. Another issue is revenue recognition; the vaccine companies cannot declare the value of the stockpiled vaccines on their revenue sheets, since the Enron and other accounting scandals. However, the Senate Appropriations Committee recently requested more information from the DHHS Secretary regarding this so that they may discuss and perhaps resolve that problem. DHHS and CDC are working with the SEC to resolve this issue.

Polio eradication and polio vaccine stockpiles. After eradication, vaccine-associated paralytic polio (VAPP) will be the sole cause of polio. In September 2003, a WHO expert consultation on polio vaccine concluded that due to that risk, OPV use should be discontinued after wild polio is eliminated. Recently, the WHO's ad hoc advisory committee on polio eradication endorsed and reaffirmed the cessation of OPV as WHO polio policy.

Current population immunity and surveillance sensitivity are at their highest, something particularly important for detecting the emergence and circulation of any VAPP variants. OPV use will end upon: 1) appropriate containment of all polioviruses; 2) global surveillance and notification capacity; 3) the establishment of stockpiles of monovalent OPV and some trivalent vaccine; and 4) creation of a response mechanism. The Global Alliance for Vaccines and Immunization (GAVI) has allocated up to $200 million to begin building the stockpile and the WHO has approached several vaccine manufacturers about working with their national regulatory authorities to relicense their OPV or to license a new monovalent OPV.

Discussion included:

- Mr. Salamone thanked the ACIP for its leadership on polio vaccine issues. CDC had announced polio eradication in the U.S. two weeks earlier and, with the use of inactivated polio vaccine, no VAPP had been reported in the U.S. since 1999.
- Mr. Phil Hosbach of Aventis confirmed that the major impediment to filling the stockpile is the accounting issue. Once that is resolved, Aventis anticipates no problem in providing the product on time. Aventis does have its own strategic stockpile, but that cannot be considered a "virtual stockpile" for the government.

VARICELLA

Introduction

Presenter: Dr. Jane Seward, NIP

In the nine years of varicella vaccination program, vaccine coverage has grown from ~27% in 1997 to at least 85% in 2003. That number was the rate among 12-month-olds in 2002, and so is likely to be an underestimate. Varicella coverage approaches that of MMR vaccine and not

surprisingly, varicella cases and severe outcomes have dramatically declined. Having achieved a 90% disease reduction, the program is considering setting a new goal, varicella elimination.

Varicella Epidemiology And Future Program Goals
Presenter: Dr. Dalya Guris, NIP

Overview: Background, varicella vaccination program and its goals; program achievements; lessons learned from recent school outbreaks; post-licensure vaccine effectiveness data; new goal under consideration; next steps.

Varicella vaccine, licensed in the U.S. in 1995 under the brand name Varivax®, is the only one licensed and approved for preventing illness caused by human herpes viruses. ACIP published its recommendations for varicella vaccination in 1996 and updated them in 1999. Currently recommended is routine vaccination at children aged 12-18 months, as well as susceptible children and adolescents. Vaccination of adults is also given priority for those at high risk for exposure and transmission. The prelicensure data indicated a vaccine efficacy (VE) of 70-90% from one dose of vaccine to prevent varicella of any severity, and >95% efficacious in preventing severe disease.

Varicella's pre-vaccine disease burden was considerable, with ~4 million annual varicella cases annually, causing 11-13,500 hospitalizations and 100-150 deaths. More than one child and adult died due to varicella every week. The main risk factors for severe disease were extremes of age and immune deficiency. Congenital varicella syndrome also occurred in 1-2% of pregnancies within the first 20 weeks of pregnancy.

The two Healthy People 2010 goals pertinent to varicella disease and vaccination coverage were adopted by the program: a 90% reduction in varicella (which would be 400,000 cases in 2010) and ≥90% vaccination coverage for children aged 19-35 months. Significant progress has been made toward these goals. The 1997 coverage of 26% among children aged 19-35 months rose in 2003 to 85%. However, there is a range of coverage between states from 67% to 93%; 32 states had levels of ≥80%. As of June 2004, 44 states mandated varicella vaccination for one or more levels from day care through high school.

Data were presented illustrating the program's progress:

- *Case rates.* Four states (Texas, Michigan, West Virginia and Illinois) have consistently reported varicella cases to the CDC, with vaccination rates between 77-89%. They showed 70-87% case reductions in 2003 versus the average reported from 1993-1995. Similar reductions were charted in case rates at two CDC surveillance study sites (Antelope Valley, CA and West Philadelphia, PA).
- *Hospitalization rates* at these surveillance sites since 1995 dropped from ~3/100,000 population to <1/100,000 in 2003. That was also reflected in data for children aged <10 years, taken from the national Medstat data base maintained for insured healthcare utilization: 17/100,000 in 1994-1995 to 1.6/100,000 in 2001. A less apparent reduction was observed in older age groups as well.
- *Varicella mortality.* NCHS data show an average of 107 deaths annually from varicella before the vaccine, which dropped dramatically to only 26 in 2001. Rates dropped 78% from 1990-95 versus 2001; 100% in children aged 1-4 years and 88% in those aged <1 year, who are not eligible for the vaccine, in 2001. The average mortality reduction was 92% for all

groups but for those aged ≥50 years, for whom death certificate data was too unreliable to estimate.

- *School outbreaks.* Of five school outbreaks occurring in 2003 and 2004 in 3 states (Arkansas, Michigan, California), four had similar features. Data were presented on one outbreak in Michigan, as were the lessons learned. Outbreaks continue even among highly vaccinated school children and children without disease history, and while mild, the breakthrough cases were infectious. The outbreaks lasted for an average of ~2 months and attack rates of those vaccinated ranged between 7%-17%. *VE* was estimated in two outbreaks between 83%-85%; 70-90% in the California outbreak was among unvaccinated 6-grade students, and in 20 of 23 outbreaks and other studies, the VE against severe disease was >90%. *Potential risk factors* included age at and time since vaccination, the presence of asthma and/or use of steroids, eczema, and a failure of the cold chain. Some investigations suggested age at-, and time since, vaccination as risk factors for vaccine failure, but those data have been inconsistent.

So, even within reach of the 2010 goal of 85% national vaccination coverage among 19-35 month old children and a 90% reduction in disease, the U.S. would still have 400,000 cases of varicella annually. Elimination of varicella is now the goal toward which CDC is moving. That cannot happen with one dose, which does not provide enough protection for herd immunity. But the same strategies in place now, coupled with a routine two-dose schedule and more state mandates for school entry and middle school vaccination, could accomplish elimination. The expected 2005 licensure of a combination measles-mumps-rubella-varicella (MMRV) vaccine will help provide the second dose of varicella vaccine. An HZ vaccine trial has also completed enrollment, and data analysis is pending.

In *next steps,* the program will assess the acceptability of the current disease burden to parents and providers and continue related work with public health and private partners. A study is planned of the effectiveness of a second dose in school outbreak settings, as is a complete CE analysis of the 2-dose program using a mathematical model in development. Data review also will continue to determine a possible change in vaccination policy.

Data Summary: Two-Dose Varicella Vaccination

Presenter: Dr. Barbara Watson, Philadelphia Division of Disease Control

Overview: Review of published studies of healthy children provided with one- versus two doses of varicella vaccine (Ngai, Watson, Nader, Kuter) and of a booster dose (Watson, *JID* 1995). Four published studies of vaccinated children with underlying conditions (Levin, *J Pediatr*, 2001; Gershon, *Inf Dis Clin N America*, 1996; Webb, *Arch Dis Child*, 2000; and Furth, *J Pediatr*, 2003) were not presented due to lack of time. The committee was asked to judge if these data were sufficient for the safety, immunogenicity, and efficacy of the second dose; the merit of extrapolating the clinical trials' results to public health field effectiveness; and to address what remaining gaps in the knowledge.

Ngai (PIDJ, 1996). This study enrolled 2196 children aged 12 months-12 years (mean age 4 years) at 18 sites from December 1991 to January 1993. The children were randomized to receive 1 or 2 doses, 3 months apart, from 5 vaccine lots (2900-9000 PFU/dose). Serology was done before vaccination, 6 weeks after each injection, and 52 weeks after first injection. *Safety*

results: No difference was found for fevers or rashes between the first and second doses.

Watson and Arvin (CID, 1995) Cellular mediated immunity (CMI) was assessed in a subset at Children's Hospital of Philadelphia (Watson study) and at Stanford (Arvin study). The cohort was followed for 42 days after each injection for safety; development of and exposure to varicella and zoster. The mean GMT rose from 12 at six weeks after the first dose to 141.5 after two doses. Almost all the subjects (99.5%) stayed above the 5 gpELISA level after two doses, rising from 87.2% who did so after dose one. This is an important humoral response factor in terms of breakthroughs during continuing school outbreaks. Merck data also indicated more breakthrough occurring at <5 gpELISA units.

Nader (JID, 1995) studied VZV T-cell proliferation after 1- versus 2 doses of varicella vaccine and demonstrated huge increases after 2 doses. The study groups were administered different pfu units (3300 versus 9000) of vaccine, which showed SI stimulation of 22. at one dose and 36.3 with two. The latter level stayed up after one year (22.2), compared to the one-dose group, and was higher in subject children than adults 10.13. But there was no difference in the CMI response with the increased number of pfu's, which may be significant regarding the MMRV vaccine. Also interesting was that the baseline CMI response of initially seropositive and CMI-positive individuals increased (anamnestic) at 2-12 weeks, becoming equal to those given 2 doses. But at one year, it measured at 12.0 (±3.12), not differing greatly from the baseline SI measurement of 7.9 (±2.18).

Kuter (PIDJ, 2004) conducted a 10-year follow-up study of the persistence of varicella antibody (measured by gpELISA) after 1- versus 2 doses. While the GMTs were more than tenfold higher at dose 2 (142.6) than dose 1 (12.5), the difference faded greatly by nine years later (57.8 versus 61.0). But importantly, the number of breakthroughs or modified varicella cases after vaccine differed greatly over time between the two dose groups, particularly from 7 years out. From years 7-10, where the 1-dose group continued to have cases, the 2-dose group had none. The same difference was seen, but even more acutely, in terms of disease severity as measured by number of lesions. The 10-year VE for the 1-dose group (94.4%) was not so different from the 98.3% VE of the 2-dose group (although Dr. Watson noted that VE of ~70-80% is seen in the field), but the breakthrough rate at 10 years out for the 1-dose group was almost threefold higher (8 cases) than that of the 2-dose group (3).

Watson (JID, 1995). Dr. Watson's study of the safety of a second vaccine dose 6 years after primary vaccination followed 419 children with a mean age of 9 years (57% males). They had been given an initial dose of VZV vaccine in 1987-89, when they were aged 1 through 17 years. Safety monitoring done after the second dose of ~3000 pfu of varicella vaccine included blood samples take at 0, 7-10 days (to measure anamnestic boost), as well as 6 weeks in a subset, and 3 months after vaccination. The humoral antibody response was measured at Merck by gpELISA, and CMI was evaluated as in the previous studies. *Results:* There were no serious adverse events; symptoms of pain, redness and swelling were mild and disappeared at <48 hours. A few (1%) developed varicella-like rashes (mean of 6 lesions) within the 6 week observation phase, but other reports (URI, cough, etc.) were the same as their non-vaccinated siblings. An anamnestic boost demonstrated both humoral and CMI response. The latter continued up to three months but was not followed out long-term.

Summary. The data on 2 doses of varicella vaccine administered to healthy children indicate

that:

1. The second dose was generally well-tolerated except for injection site reactions at <3 days. The adverse events of the second dose were significantly less than those of the first dose.
2. The proportion of children with ≥5 gpELISA and GMT was higher at 6 weeks after the second dose compared to those at the first dose.
3. The CMI response was higher at 6 weeks and 52 weeks for the 2-dose group compared to the 1-dose group, and remained high for 10 years.
4. The GMT declined in year 2 after 2 doses, but the proportion of children with ≥5 gpELISA remained high for 10 years. In contrast to 6 weeks post vaccination response, humoral immunity indicators over time were similar between 1- and 2 doses.
5. Vaccinated subjects developed varicella, although the cases were mild.
6. Annual and cumulative attack rates were higher among the 1-dose group.
7. VE was ~4 percentage points higher in the 2-dose group, but there was no significant VE difference after household exposure between the 1- and 2-dose groups. Still, the difference in breakthrough cases bears scrutiny.

Correlates of Protection and MMRV Vaccine

Presenter: Dr. Barbara Kuter, Merck, Inc.

Overview: The Merck 1998-2003 Phase III clinical trials immunogenicity and safety results for ProQuad®, which added varicella vaccine to the MMR combination. Clinical program design and objectives; use of gpELISA as a correlate of protection for varicella.

The huge safety database (>446 million doses) compiled since MMR vaccine's 1978 licensure by Merck contributed to the development of ProQuad®, but determining the minimum required varicella dose for adequate immunogenicity was a primary goal, followed by production consistency and co-administration with other routine childhood vaccines.

Five clinical trials were conducted from 1998-2003: 1) A proof-of-concept study (009) coupled a ~4.8 log dose of varicella virus to the MMR antigens to assess adequate immunogenicity; 2) a dose-ranging study (011) followed for the varicella component, then 3) a consistency-lot trial (012) of >2900 children with another ~1000 divided into three consistency lots; 4) a concomitant-use study (013) of ProQuad® with DTaP and the Hib/hep B vaccines was followed by 5) the last trial (014), in which children aged 4-6 years received ProQuad® rather than the routine MMR vaccine.

In all, these safety trials involved 5833 children who received ProQuad,® 2038 controls who received MMR and Varivax,® and another 205 who received MMR only. ProQuad's® varicella component is about a log higher than the monovalent varicella vaccine.

The gpELISA test has been shown to be a more sensitive assessment of vaccine response than typical commercial antibody assays. The literature shows it correlating well with both neutralizing antibody (96-97%) and CMI (95%). With FDA agreement, Merck used a 5-unit gpELISA level as the correlate of protection for varicella. The antibody responses were examined for breakthrough rates, number of lesions, and vaccine efficacy (comparing antibody titers >5 and <5). Those with titers >5 had about 3.5-fold fewer breakthroughs than those with titers <5, and the same lesser ratio in number of lesions. VE was clearly superior (95%) with the gpELISA >5, versus 84% at <5. This was demonstrated on a charted life table estimating the 7-

year cumulative varicella event rates by 6-week antibody titer, after one dose of Varivax® was administered. (Li et al, *PIDJ* 2002; 21: 337-42). It showed the inverse relationship of the higher titers to the rates of breakthrough and lesion number.

Immunogenicity
Protocol 012. A single dose was administered to 12- to 23-month-old children, the focus population of most of the studies. ProQuad® was given to 2915 subjects and MMR and Varivax® to 1012. ProQuad's® responses were equivalent for seroconversion and GMTs for all four antigens (in fact, slightly higher for measles). ProQuad's® seroconversion rate of 94% was only 1% lower than Varivax®' and their GMTs were the same (18).

Protocol 013 assessed concomitant use with DTaP and Hib/Hep B (ComVax®) in the concomitant group at age 12 months, along with Tripedia®, a DTaP vaccine. The nonconcomitant group received ProQuad® at 12 months and Comvax® and Tripedia® at 13-1/2 months or six weeks later. ProQuad® met the non-inferiority hypothesis for all antigens except for pertussis. This was found to be more of a study design problem (the 6–week age difference in the DTaP injection). Further exploratory analysis showed the pertussis FHA immune responses to be comparable in children ≥13.5 months

Protocols 009 and 011. When ProQuad® was used as second dose at age 12 and 15 months, it produced a doubled GMT for measles, a significant increase for mumps and rubella, and a *forty*-fold GMT increase for varicella. The same rise in titers was seen when ProQuad® was given as a second dose to 4-6 year-old children who had received MMR and Varivax® at 12-months of age, except the varicella rise was 14-fold (26 to 322).

Safety, single ProQuad® dose. Parent-developed report cards were kept on adverse events six weeks after vaccination: injection site redness, a measles- or varicella-like rash, and fever ≥102º. The rates of injection site adverse responses were lower for the ProQuad® group (N=4497) than those who received MMR and VariVax® (N=2038); the varicella-like rash rate was virtually identical. The time of and average duration of fevers and varicella-like rash were similar between the groups, but the measles rash rate was significantly higher for the ProQuad® group (3.2% versus 2.2%). ProQuad's® fever rate was also higher, but the fevers were well tolerated and the rates of febrile seizures for both groups were minimal.

Safety, second ProQuad® dose. Among children aged 12 and 15 months, the second ProQuad® dose was well tolerated and the rates of adverse events were lower. Among the 4-6 year-old children who were vaccinated with MMR and VARIVAX® earlier, the ProQuad® was well tolerated and the rates of adverse events were comparable to MMR administered alone and co-administered with Varivax.®

Conclusions from the ProQuad® trials were:
- ❖ A single dose is comparable to the co-administration of MMR and Varivax® at separate sites.
- ❖ It can be administered concomitantly with Hib and hepatitis B vaccine, and with DTaP vaccine at age ≥13 months.
- ❖ It can be used as a second dose for children in place of MMR, either at three months after the dose one or at the 4 year-old visit.
- ❖ It is generally well-tolerated at either 1- or 2 doses. Its slightly higher rates of fever and

measles-like rash are transient and very mild, and injection-site reactions are few.

- ❖ It is very well-tolerated at age 4-6 years in place of a second MMR dose or MMR and Varivax®.

Cost effectiveness analysis of a 2-dose varicella vaccination program

Presenter: Dr. Fangjung Zhou, NIP

Overview: Economic evaluation of the U.S. universal varicella vaccination program

The three main studies that evaluated the economic aspects of universal varicella vaccination were published before the program began. All three calculated a societal benefit-cost ratio (BCR), which is defined as the program benefit (costs averted by the program) divided by the program costs. Preblud et al (1985) and Huse et al (1984) used a static model approach and found a BCR, respectively, of 6.9 and 2.4. Lieu et al (1994) used a dynamic approach and determined a societal BCR of 5.4.

NIP conducted a study to evaluate the economic impact of the universal 1-dose and a projected 2-dose varicella vaccination program in the U.S., from both a payer- and societal perspective. The ~4 million children of the 2003 birth cohort were used in decision tree and treatment algorithm analyses. If the BCR was found to be >1.0, the program's net present value (program benefits minus program costs), cost-effectiveness ratio (cost per health outcome, such as cost per year of life saved), and net savings ratios were calculated.

NIP gathered pertinent information from the literature, CDC data and the MarketScan® database on medical costs, in the following areas: demographics, vaccination (vaccine, administration, parents' time lost, adverse events), varicella incidence and the proportion of breakthrough cases, direct medical and non-medical varicella costs, costs of work loss due to varicella (parents' time lost, patients' time lost) and hospital infection-control costs. Prevaccination era (1990-94) data came from the NHIS and postvaccination (2002) data came from CDC's Varicella Active Surveillance Project data. The latter was adjusted for non- or under-reporting. A chart of these data showed incidence declines by orders of magnitude per 1000 population for all age groups. For example, incidence for children aged 1-4 years dropped from 98.4 per 1000 to 6.2 after one dose. Rash and the need for additional outpatient visits due to adverse events from vaccination were few and mild for both the one dose group (2% and 1%, respectively) and the dose group (15 and 0.5%).

The assumptions of the analysis of a one-dose campaign were based on the 2002 data: 89% of cases prevented by one dose, 7% of cases from those unvaccinated, and 4% in vaccinees (the latter cases were much milder). Assumptions for a 2-dose campaign were based on the projected data of coverage and VE: 89% second dose coverage among those already vaccinated once, 8% of cases still occurring, and 3% prevented by the second dose (29% of the residual).

The analysis was done in three segments, comparing no vaccination program with, first, a one-dose program and then a two-dose program, and then finally comparing the one- and two-dose programs to each other. The 2003 dollar value and a 3% discount rate were used.

One dose program analysis, preliminary results

Item	Direct costs (million)	Indirect costs (million)	Total costs (million)
Without vaccination	$293	$1,077	$1,370
With 1-dose vaccination	$28	$110	$138
Costs averted	$265	$967	$1,231
Program costs	$241	$33	$274
Net Present Value (net saving)	$24		**$958**
Benefit-cost Ratio	**1.10**		**4.49**

CE analysis conclusion: From a societal point of view, the one-dose program is cost-saving in terms of prevented case (3.6 million), deaths (66 prevented) and years of life saved (4,312 years).

Two-dose program analysis preliminary results

Item	Direct costs (million)	Indirect costs (million)	Total costs (million)
Without vaccination	$293	$1,077	$1,370
With 2-dose vaccination	$20	$78	$98
Costs averted	$273	$999	$1,272
Program costs	$451	$34	$485
Net Present Value (net saving)			$787
Benefit-cost Ratio	**0.61**		**2.62**

CE analysis conclusion: From a societal point of view, the two-dose program is cost-saving in terms of prevented cases (3.7 million prevented), deaths (69 prevented) and years of life saved (4,445 years).

Comparison of both programs; preliminary incremental results

Item	Direct costs (million)	Indirect costs (million)	Total costs (million)
With 1-dose vaccination	$28	$110	$138
With 2-dose vaccination	$20	$78	$98
Costs averted	$8	$32	$40
Program costs	$210	$1	$211

Item	Direct costs (million)	Indirect costs (million)	Total costs (million)
Net Present Value (net saving)	-	-	-
Benefit-cost Ratio	**0.04**		**0.19**

CE analysis conclusion: Compared with the 1-dose varicella vaccination program, the 2-dose program prevents ~130 thousand additional cases, 2 additional deaths, and adds 133 years of life. In terms of direct cost, the second-dose varicella vaccination program spends about $1,316 to prevent one varicella case; $78 million to prevent one varicella-related death; $1.3 million to save one life year; and $4.5 million to save one discounted year of life.

Univariate sensitivity analyses of varicella incidence, program costs and discount rates

	Payers (Direct) Benefit Cost Ratios	Societal (Direct + Indirect) Benefit Cost Ratios	Direct costs per discounted year of life saved*
Base Case (29% prevented)	0.04	0.19	$4,473,057
50% prevented	0.07	0.33	$2,214,670
90% prevented	0.12	0.60	$782,165
MMRV vaccine	0.05	0.26	$3,150,550

Assuming an equal price for MMRV vaccine and MMR plus varicella vaccine, the BCR rose. In all the sensitivity analyses, the direct BCRs were at- or slightly above 1.0, while the societal BCR benefit-cost ratios were much higher (ranging from 3.73 to 6.0). The results were very stable.

Sensitivity analysis with second dose preventing >29% of residual cases

	Payers (Direct) Benefit Cost Ratios	Societal (Direct + Indirect) Benefit Cost Ratios	Direct costs per discounted year of life saved*
Base Case (29% prevented)	0.04	0.19	$4,473,057
50% prevented	0.07	0.33	$2,214,670
90% prevented	0.12	0.60	$782,165
MMRV vaccine	0.05	0.26	$3,150,550

Study limitations. Due to insufficient data, the costs associated with herpes zoster were not factored in this analysis, neither for vaccinees from the varicella vaccine strain or wild-type varicella nor for relatively naïve persons who developed varicella (postulate only). Some studies suggest that zoster in vaccinees will decline; others disagree; the former would raise the BCR while the latter would reduce it. Also not included was the cost of pain and suffering, which would raise the BCR, nor outbreak management costs. The latter would reduce the BCR for the one-dose program, but raise it for the two-dose program.

Conclusions. The one-dose varicella vaccination program was about break-even from the payers' perspective and cost beneficial (cost saving) from the societal perspective. Compared to no varicella vaccination program, a two-dose program would be cost beneficial (cost saving) from a societal perspective, but compared to the one-dose program, the two-dose program may not be cost effective.

Discussion included:

- *What causes such a significant boosting increase when the vaccine is readministered? This differs from the live measles, mumps or rubella vaccines.* Dr. Watson reported a kinetic study of CMI which showed ~40% of T-cells being activated at two weeks, but twice the antibody response at 4 weeks, when virtually all T-cells respond. For that reason, the T-cells are already ahead at the second dose, producing a tremendous anamnestic response. Dr. Florian Schodel of Merck speculated that this differs from MMR because the neutralizing immunity to a first varicella dose, which would prevent take, is less absolute than for the other live viruses, so ProQuad's® additional viral antigen stimulates that. But the same effect comes from the monovalent vaccine's low-dose antigen. The data shared by Drs. Watson and Kuter on the second dose with the monovalent seemed to indicate that the key is the antigen non-neutralization by antibodies and therefore its availability for the immune system, unlike the case for measles, mumps and rubella.
- Dr. Ann Gershon, of Columbia University, who long has studied varicella vaccine, strongly recommended the use of a second dose, even though the CE data are not as strong as might be wished. She appreciated CDC's plan to assess if dose 2 would control outbreaks as an important first step to determining any protective efficacy from that second dose. Even if not cost effective, she advocated use of the MMRV to provide the varicella component. Any progress toward preventing the disease helps to avoid parental doubts about vaccination in general, particularly when their children fall ill even after receiving vaccine.
- Regarding zoster, Dr. Gershon reported that in their studies of leukemic children, those children who developed a rash (from either vaccine or wild type virus) were ten times more likely to develop zoster than the children who did not. This has also been reported in Japan. There is increasing evidence that VZV reaches sensory neurons through its presence on the skin. This exposure risk is far greater to patients with vesicular lesions than from exposure in a viremic phase. It is logical that keeping virus off the skin by a second dose should reduce zoster in future. However, this can only be proven in a person who died with latent virus, by a postmortem assessment for latent infection in dorsal root, cranial and enteric ganglia.
- Dr. Schodel confirmed the possibility that the varicella vaccine virus is causing a local immune suppression and an increase in measles virus replication that is demonstrated by the higher rates of measles-like rash. It is a local rather than systemic reaction, since the timing of the fevers is the same as that for measles. Merck does not think that this is a nonspecific VZV suppression, because there is no such effect for the rubella or mumps vaccines administered locally at the same time. The current hypothesis is that the varicella and measles virus are coinfecting the same or proximate areas of the body and engaging in a specific interaction, but how that works is as yet unknown.
- Dr. Cody Meisner, Vice Chair of the AAP's Committee on Infectious Disease, expressed the COID's concern that the current one-dose vaccination strategy may not offer full protection for all children, based on the 20-30% breakthrough varicella rate. They shared Dr. Gershon's concern about the implications to zoster later in life. And, if zoster is less severe in those vaccinated than among those who have wild-type disease, they wondered if breakthrough

disease may be followed by more severe zoster. Finally, if it is the need for a second dose rather than vaccine failure causing outbreaks among highly vaccinated children, not giving it could cause an unwarranted loss of confidence in the vaccine by healthcare providers or parents. That would be unfortunate, in view of the demonstrated disease reduction accomplished by the vaccine. The COID would strongly support consideration and evaluation of a second dose of the varicella vaccine. Issues that would need to be worked out include whether a monovalent or combination vaccine should be used and the timing of the dose. Great care would be needed to avoid any negative impact on the very successful vaccination timing of the measles vaccine.

- Dr. Phil LaRusso, of Columbia University, also supported the second dose to further reduce varicella and, over the long term (although perhaps not the short term), zoster. He suggested the use of an experimental model to analyze ProQuad's® increase in measles titer, which he suspected related to varicella component's prompt increase in measles antigen presentation to the immune system. There is no evidence that measles virus was recovered from the cited rashes or from the oral pharynx of ProQuad® recipients.
- Dr. Abramson called for study of the continued breakthrough disease, although at a lower rate, even after a second dose. He also anticipated the release of an NIH study soon on the effect of varicella vaccine among adults as it relates to zoster. Zoster in adults, particularly >50 years, differs greatly from that in children; it is a very painful disease.
- In view of the cost of study to establish the effectiveness of a second dose, Dr. Lieu requested more research on its duration of immunity, which also pertains to the timing of a second dose (i.e., 3 months, 5 or 15 years of age, or extended out to early adulthood, an even more difficult time to reach the cohort in need). This will be answered over time, as seen in the data presented of the 5-fold increase in titer over 7-8 years, but dynamic modeling might provide more insight to this question.
- Dr. Poland cited zoster's high burden of disease as the primary outcome of concern and called for its inclusion in the modeling. Dr. Seward reported that this is planned. The challenge will be in predicting for those who are unvaccinated. Dr. Rafael Harpaz, of the NIP, reported that there are few good data on zoster, but the risk is very reduced early after vaccination for children who had breakthrough disease, and for immunocompromised children. But there are no data about the longer term, nor are there about zoster risk in persons who received the vaccine strain or those who received two doses versus one. There could conceivably be an increased risk of vaccine-strain zoster in children who receive two doses.
- Dr. Gershon raised two questions regarding zoster, which should be separated. One is the issue of latent varicella (probably wild type) in those with breakthrough disease, who may not develop zoster for many years. The two-dose schedule might prevent that latency and therefore, later, prevent zoster. The other question, being studied by Dr. Levin, explores vaccination of those already with latent wild-type virus infection, and whether boosting immunity prevents or modifies zoster in them. Some data suggest that immunity to VZV, even with circulation of wild-type virus, wanes in a few vaccinated children. The ongoing Yale-Columbia case-control study has already shown a significant loss of immunity, especially in year one post-vaccination. Other researchers have expressed concern that the gpELISA test might, in fact, be overly sensitive and therefore produce a higher seroconversion rate than is protective. For those reasons, she again supported the second vaccine dose, as done for measles in MMR, to catch-up those individuals who had no take from the first vaccination.
- Dr. Gershon also speculated on the VZV immunity boost with MMRV's dose two. The

immune response to rubella and mumps, which do not cause severe infections in immunocompromised hosts, is clearly different than that to VZV and measles, which do. The immune boost with dose 2 may be partly due to the immune response to VZV, which was suppressed in dose one by the greater measles multiplication, since measles is immunosuppressive. Whatever the reason, it needs to be discovered.

- Dr. Ivan Chan, of Merck, cited the more than three-fold reduction in breakthrough disease with two doses, despite the VE difference of only ~4%. If the reduced breakthrough disease is factored, the VE would rise from ~80% to ~95% with two doses. He also commented that the baseline assumption of a 90% coverage for one dose and a 29% reduction of residual disease after two doses may be low assumptions. Dr. Watson's data indicate a residual protection of ~75%. Dr. Seward appreciated those comments and reported that work in progress. She also confirmed that the Phase 4 data analysis will be done with Dr. Steven Black and will involve examination of the influence on antibody persistence or breakthrough rates by the timing of- or age-at the first dose. The current hypothesis is that the second dose will provide more benefit than changing the age of vaccination.
- Dr. Jeff Silber, of Merck, reported their conduct of two analyses. One was of the 6-week antibody titers, stratified by the age of the children in the 6 different pre- and post-licensure studies. The ages ranged from 12 months to 3-4 years. The 12-14 month-olds (the majority group of the cohorts) had antibody titers at least as high as those in children vaccinated at a later age, regardless of any level (or none) of lingering maternal antibody. And, when long-term VE and long-term immunogenicity were broken out by age, the 12-14 month-olds' was no less than children vaccinated at a later age. Additional, parent-reported follow-up data from Kaiser on 7500 children vaccinated in their second year of life was delineated by month. While overall the breakthrough rates looked higher, it became apparent that the 12-14 month-old vaccinees had rates no higher than children vaccinated in their second year. Their antibody titers ten years out were similar to those vaccinated later in life.
- The fact that the data are affected by environmental boosting was raised by Dr. Levin. But Dr. Silber noted that the early data of the 10-year studies would include the years when there was still circulating virus. Susceptible children then could have had more breakthrough disease, unless they had some level of immune response that was sufficiently boosted after vaccination to prevent clinical disease.
- Dr. Chevelle, of Merck, reported that they will have more data from abroad on concomitant use of ProQuad's® use with vaccines holding the same antigens as U.S. vaccines. Those data indicate that the nonresponsiveness of the pertussis antigen may be attributable to study design. The pertussis antigens in particular seem to have an age-dependent response rate relevant to the 12-15 months age group. Dr. Kuter confirmed that a comparison of 12 month-old versus 13½ month-old children showed different levels of antibody rises.
- Dr. Kuter reported Philadelphia's experience of an "ongoing outbreak" due to breakthrough disease in those vaccinated. The parents, knowing the child was vaccinated, suspected something else such as flea bites, and send the child to school to spread the disease. She strongly supported a second dose recommendation. Dr. Birkhead agreed, particularly if the second dose would help prevent disease clusters from occurring. Ms. Stinchfield added her support from the perspective of hospital nurseries' decisions about letting siblings visiting newborns.

ACIP Statement on Sub-prioritization of Influenza Vaccine

Presenter: Dr. Ban Allos, Vanderbilt School of Medicine

A statement was generated on the sub-prioritization of influenza vaccine during this shortage, to validate that done by local groups when necessary, and to help avoid any impression by the healthy general public that only high priority and high-risk groups need the vaccine. The statement was as follows:

> "The public health goal for the prevention and control of influenza in the U.S. is to encourage and recommend influenza immunization for all eligible persons. However, due to the unanticipated significant shortage of TIV this year, on October 6th, 2004, the ACIP recommended that persons in eight high risk groups preferentially receive TIV and that all others either receive LAIV as eligible or forego immunization this season. The ACIP recognizes that at local levels public health authorities may face shortages of inactivated vaccine and choose to sub-prioritize among the ACIP recommended high priority groups."

Discussion included:

- Edits: Sentence 1: replace "goal" with "objective"; delete "eligible" to just say "to all persons"
- Add another sentence at the end saying the use of LAIV is encouraged in persons for whom TIV is not indicated.
- Delete the specific reference to vaccine to say that those "…in the eight high priority (not "risk") groups should preferentially receive the inactivated influenza vaccine and all others should forego it." This was preferred by NIP to avoid confusion over the two different types of vaccine.
- The problem with not stating the vaccines (as in the proposed statement) was the risk that, if the live attenuated vaccine FluMist® is again left over and destroyed, there may be only one company producing influenza vaccine next year. The use of LAIV should be specified to ensure that no one thinks that access to that is restricted.
- Dr. Levin suggested ending the statement after citing the eight groups to preferentially receive TIV, at "TIV." However, that did not account for healthcare workers and left the door open for a surplus of LAIV after the season.
- Sentence 3 was left as it was. Another was added to indicate that "LAIV is recommended for healthy adults between 5 and 49, including healthcare workers and direct contacts." The problem there was that it seemed to prioritize LAIV to that group over TIV.
- The order of sentences 3 and 4 were reversed.

Dr. Levin asked for the sense of the committee. All but for Dr. Treanor, who had a conflict with MedImmune, voted in support of the amended statement, which was finalized as follows:

"The public health goal for the prevention and control of influenza in the U.S. is to encourage and recommend influenza immunization for all eligible persons. However, due to the unanticipated significant shortage of TIV this year, on October 6th, 2004, the ACIP recommended that persons in eight high priority groups preferentially receive TIV. Intranasally administered, live, attenuated influenza vaccine, if available, should be encouraged for healthy persons who are aged 5–49 years and are not pregnant, including health-care workers (except those who care for severely immunocompromised patients in special care units) and persons caring for children aged <6 months. The LAIV is recommended for healthy adults between 5 and 49, including healthcare workers and direct contacts. The ACIP recognizes that at local levels public health authorities may face shortages of inactivated vaccine and choose to sub-prioritize among the ACIP recommended high priority groups."

Workgroup Report on Revisions to the 2002 General Recommendations
Presenter: Dr. Andrew Kroger, NIP

The ACIP's document of General Recommendations On Immunization has been revised by the General Recommendations Workgroup six times since 1976. As its name signifies, the General Recommendations document is not vaccine-specific. The Workgroup is reviewing it again and expects to release it in 2006 in coordination with the COID's Red Book publication. They have met by teleconference and set up their timeline of work. Ascertainment of what revisions need to be made will come from the Workgroup members' review and from input received from providers. Aside from minor edits, the major changes will concern the following new categories:

- **Timing and Spacing of Immunobiologics**
- **Contraindications and Precautions**
- **Vaccine Administration**
  - Recommended routes of injection (strengthened regarding routes of injection and needle length).
  - Preventing adverse reactions after vaccination (added language on screening).
- **Storage and Handling of Immunobiologics**
  - Special Situations
  - Altered immunocompetence (e.g., TB screening and skin test reactivity, latex allergy). This is also included under "Special Situations" regarding the restoration of immune memory.
  - Parameters for the use of new immunosuppressive medications (e.g., time before administering a live vaccine after medication such as immune mediators, colony stimulating factors, interferons, immunomodulators (Levamisole or BCG), and isoantibodies which break down into soluble cytokine antagonists or therapeutic monoclonal antibodies.
    - **Ex-post-facto policies following receipt of live vaccine in individuals receiving these medications**
- **Bone marrow and solid organ transplants**
  - Scope of the Issue (currently in the stand-alone 1993 document revision, which may also have to be amended).
  - Vaccination records (references to the applicable laws, situations the patient's vaccination status is unknown, international adoptions).
  - Reporting adverse events after vaccination (screening information, etc.)
  - Vaccination programs (principally information about strategies to increase immunization rates)
  - Vaccine information sources
- **Combination vaccine issues**:
  - Combination vaccine components not licensed for all doses in a series. Current ACIP language could suggest off-label usage, since it states that combinations should be used if the components of the combination are indicated and none of the components are contraindicated.
  - Potentially generalized language about vaccine components administered in combination vaccine (as done for hepatitis B).

Minor changes anticipated include address of:

- Spacing of "recovery" vaccine (after an invalid dose), both live and inactivated. Currently, there is a minor interval from the previous invalid dose, and the language is specific enough to apply to both live and inactivated vaccines. Clarification will be provided of the many ways that vaccine doses can be invalidated (e.g., too short of a minimum interval, wrong route of administration, partial doses, expired vaccines, etc.)
- Table 1, which lists the routinely recommended vaccines and recommended and minimum ages and intervals of administration, may be separated out into two separate tables. In general, the document may have more tables.
- Addition of new, now routinely-recommended vaccines (e.g., influenza) to tables where they should be listed.

Next steps toward completing the document by October 2005 for *MMWR* publication will be to continue literature searches; consult with subject matter experts, liaisons, and consultants, meet by teleconference and provide a draft by the February 10-11, 2005 meeting. The input of the general committee will be welcomed.

Revisions for Influenza to the Harmonized Childhood Immunization Schedule
Presenter: Dr. Louisa Chapman, NIP
VOTE

In 2003, two harmonized childhood schedules were published (January and April) to include the influenza vaccination recommendation change (from "consider" to "recommended") for children aged 6-23 months. The April schedule covered the period of July through December. There have been no policy changes since then, nor changes to the interim recommendations because of flu vaccine. However, other issues may call for another childhood schedule to be published in 2005.

The current changes to the 2003-04 schedule:
- Changed the date to 2005 on pages 1 and 2 (from April-December 2004), and to make it effective as of April 1, 2004.
- Updated the references in Footnote 7 to show the April *MMWR* as no longer in press.
- Updated the statement on influenza.

The catch-up schedule changed only the dates.

Discussion included the statement that the schedule's format will be improved for 2006 by a Workgroup chaired by Dr. Julie Morita. Dr. Schaffner asked that Workgroup to communicate with the Adult Immunization Workgroup to harmonize the two schedules.

Vote
There was no conflict of interest involved in the vote to accept the schedules. Dr. Treanor **moved to approve the harmonized immunization schedules as presented** and Ms. Stinchfield seconded the motion. **The vote was unanimously in favor** to approve the schedules. Two members were absent: Dr. Poland and Mr. Salamone.

Report of the Evidence-Based Workgroup
Presenter: Dr. Louisa Chapman, NIP

The practice of medicine and public health has always blended art and science, but science has dominated over the last century. Given that, the basis of recommendations on proven science has become increasingly important. However, the extent to which to which recommendations *including the ACIP's* are based on science is not always transparent to the reader.

A background on the "evidence-based medicine" movement was provided. This emphasizes systematic and analytic review of the evidence and the use of report formats that make the evidence-basis of the recommendations transparent. Dr. Archie Cochrane described this approach in the 1972 document, *Effectiveness and Efficiency.* It was formalized in 1992 as "Evidence Based Medicine" by a group at McMaster University, which the next year established the Cochrane Collaboration. The latter is an international coalition which develops and disseminates evidence bases on interventions. CDC established the Task Force for the Guide to Community Preventive Services (the "Community Guide") to document the evidence base for public health, and in ~1994 the Health Care Infection Control Practices Advisory Committee (HICPAC) adopted the evidence based format for its recommendations as well.

Clearly, adult immunization recommendations have not translated into clinical practice as effectively as those for childhood. When CDC explored a collaborative arrangement with the American College of Physicians to more effectively disseminate the adult vaccination recommendations, they responded with regret that their endorsement must be based on clear evidence.

So, in 2003, the ACIP formed the Evidence-Based Recommendations Workgroup, which has examined many potential models. The impediments to their use included that many were developed for existing models developed mostly to guide physicians' diagnosis and treatment of individual patients, not populations. The Community Guide staff and the Task Force have done pioneering work in this regard, including in the area of immunizations, but that was not a perfect fit either. And, beyond the science, public policy decisions that impact vaccination involve values, feasibility, political and other considerations.

This presentation was just to advise the committee that it would be hearing a good deal of this at future meetings. Before the February 2005 meeting, the members will receive written information for their review before the meeting's discussions with the Workgroup Chairs, Robin Womeodu and Dan Fishbein. They hope in February to gain the committee's endorsement to launch a pilot method to apply the evidence bases to new or revised ACIP recommendations. Then, they hope in 2006 to offer an improved version based on the pilot's lessons learned, for ACIP approval.

Presentation of a Proposed Methodology for Evidence-Based ACIP Recommendations
Presenter: Dr. Dan Fishbein, NIP

Overview: Presentation of an analytic framework methodology with which to review evidence in a systematic manner; transparent to all, complete, consistent with other guidelines as well as consistent over time and between vaccines, and compatible with other guidelines. Description of the recommendation process development for individual and public health outcomes and for economic analysis

The *analytic framework* of the proposed methodology consists of three steps: individual health

outcomes, public health outcomes, and economic analysis. The analysis weights each step for the magnitude of the effect and study quality (e.g., as done by the USPSTF, 1 to 5 scale, strongest to weakest) and.

1. *Individual health outcomes* measured directly by vaccine effectiveness to reduce health outcomes or indirectly, by demonstrated safety and an intermediate outcome (surrogate for the health outcome).
2. *Public health outcomes*, measured in two ways: positive and negative public health outcomes ("externalities"). The latter are the vaccine effects extending beyond the individual person. Positive ones would include herd immunity, disease eradication, transmission interruption, etc. Negative ones could be transmission of live attenuated vaccine strains; the possible substitution effect in which the use of the vaccine would negate another necessary health service; bombarding the public and clinicians with too many recommendations; or taking more of the clinicians' time to interpret them.
3. *Economic analyses* support both the individual and the public health outcomes, to demonstrate the vaccine's effect on the individual and the public health level.

Overall recommendations could be provided in letter grades: A, B, C, D, and I. An I would represent insufficient evidence to issue any opinion. An A would be a recommendation; B would be considered an option; C would be no recommendation; and D would recommend against or not recommend (i.e., a contraindication).

Discussion included:

- The B category could be subdivided (e.g., B-1 and B-2) to indicate either an encouragement for the intervention or its consideration as an option.
- While the letter grades do not allow for differentiation (e.g., for a case where the study evidence may not be strong but the unpublished or anecdotal evidence is very strong), the weighting scheme factors that in. That was not presented at this meeting but was in the meeting handout.
- The difference between the I and C categories were clarified, such that "I" is the absence of evidence, but "C" would be a case for which there is evidence, but the ACIP would not wish to comment on it.
- Under individual health-outcomes, Dr. Lieu suggested either quantifying or explicitly stating that the harms of the vaccine were considered, in addition to stating that the vaccination is safe.
- Dr. Langley advised making the "D" category more explicit to reflect that there is a harm potentially associated with the intervention. "Not recommended" could be interpreted as the decision to not make a statement versus recommending against it. The term "recommendation against" will be discussed in the next Workgroup telephone call.

Update: DoD/CDC Smallpox Vaccine Cardiac Adverse Events Monitoring

First, Col. Grabenstein provided an update on the DoD's anthrax vaccination program. DoD is abiding by a ruling delivered on the previous day which enjoined the DoD from continuing its anthrax vaccinations. The ruling was based on a procedural issue relevant to FDA actions (the absence of a 90-day comment period), not on the FDA's findings for the vaccine's safety and effectiveness. Counsel for DoD, DHHS, and the Department of Justice stated that the anthrax vaccination program meets all legal requirements, and the vaccine continues to be licensed by the FDA.

DHHS/CDC
Co-Presenters: Dr. Gina Mootrey, DHHS/CDC/NIP; Col. John Grabenstein, DoD

Overview: Background of the DoDand DHHS Smallpox Vaccination Programs and summary of the monitoring done for adverse cardiac events.

The national smallpox vaccination program was announced in December 2002. DoD began vaccinations that month and DHHS began in January 2003. In February, 2003, the first myocarditis case was reported by the military to the Vaccine Adverse Events Reporting System (VAERS). By March, more ischemic cardiac events (ICE) were reported, as were three cardiac deaths, two in the DHHS program and one in the DoD program.

On March 28, the ACIP recommended vaccination deferral for persons with known cardiac disease, a history of stroke or TIA, OR three or more risk factors for ischemic cardiac disease (e.g., hypertension, hypercholesterolemia, diabetes, family history of heart disease, or currently smoking tobacco). Both programs adopted that deferral policy.

As of June 30, 2004, the DHHS program had vaccinated 39,566 persons; DoD had vaccinated 628,414. Their goal was to vaccinate >660,000 by October 15, 2004. The composition of the two programs' cohorts is almost opposite. The DHHS program (screening and vaccinating the public) involves an older cohort (median age 48 years) that is primarily female (63%), while the DoD military cohort is younger (median age 26) and primarily male (88%). Not surprisingly, 75% of the DHHS cohort consists of revaccinees and nearly the same amount (71%) of the DoD cohort are primary vaccinees. Data were presented, as follow:

Preventable Adverse Events

	DHHS n = 39,566 as of 30 Jun 04	**DoD n = 628,414 as of 30 Jun 04**
Eczema vaccinatum	0	0
Progressive vaccinia	0	0
Fetal vaccinia	0	0
Contact Transfer – Nosocomial	0	0
Contact Transfer – <u>Not</u> Nosocomial	0	46 secondary; 2 tertiary *
* 7.6/100K vaccinees; 10.4/100K primary vaccinees – given enhanced scrutiny, comparable to historic rates despite non-immune contact population		
Inadvertent inoculation – Non-ocular	21	57
Inadvertent inoculation – Ocular	3	14

The 48 contact cases in the DoD program were principally household contacts with intimate adult partners. DoD changed their educational materials to warn vaccinees' against relaxing their safety guard at home. The two tertiary cases have been published in the *MMWR*; the risk is principally among primary vaccinees. Anticipated, not-preventable adverse vaccination events

occurred, all mild and almost all treated as outpatients. However, what was not anticipated were the ischemic cardiac adverse events.

Not-Preventable Adverse Vaccination Events

	DHHS n = 39,566 as of 30 June 04	**DoD n = 628,414 as of 30 June 04**
Generalized vaccinia (All mild, no sequelae)	2 suspected; 1 confirmed	40 suspect or probable; 0 confirmed
Post-vaccination encephalitis (Both atypical)	1	1 – recovered, serving in Korea
Stevens-Johnson Syndrome (erythema multiforme major)	0	1

Ischemic Cardiac Adverse Events

	DHHS n = 39,566 as of 30 June 04	**DoD n = 628,414 as of 30 June 04**
Ischemic Cardiac Events (ICE) within 6 weeks after vaccination	**10** 2 - # fatal	**16** (+ 6 admittance diagnoses of ICE changed to carditis) 3 - # fatal
Dilated Cardiomyopathy (DCM)	**3**	**4**
Myo-pericarditis	**21** -16 suspect - 5 probable - 0 confirmed	**79** - 6 suspect - 69 probable - 4 confirmed

Technically, the DoD program had 22 cases according to admission diagnoses, but with cardiology consults, six were changed to myocarditis. Two of these were fatal in the DHHS program and three were fatal in DoD's program.

Ischemic Events. A slide charting the ischemic cardiac events according to the time since vaccination showed no case clustering by time for acute MIs or angina. Generally, the ICEs occurred within a mean of 4.5 days after vaccination, but the civilian cohort showed a wide range from 0-28 days. The events occurred mostly in the men in both cohorts, and they were generally older than that of the overall vaccinated population. If the deferral criteria had been effective civilian population, Dr. Mootrey estimated that seven of the ten ICEs could have been prevented.

Status: All of those with ICEs or angina recovered in the DHHS cohort; all are back at work and most are again exercising. Two of the DHHS MI cases died; the other four are back at work but are not yet able to exercise fully. However, although the observed number of MI cases exceeded what was expected, it was still within the predicted 95 CI, and the number of angina cases was less than expected in the three weeks after vaccination.

Dilated cardiomyopathy cases. Another slide of the cases of dilated cardiomyopathy by week of diagnosis (December 2002-June 2004) again showed no clustering. Three civilians, all revaccinees in their mid-fifties (two female, one male) were diagnosed with dilated

cardiomyopathy. They are all back to work, but their exercise capacity remains decreased. Of DoD's four cases, all were male and slightly older (mid-30s to mid-40s) than their cohort's overall age. Three of the four were revaccinees. One is back at work; the others are on limited duty or permanent disability.

Myo-pericarditis among Smallpox Vaccine Recipients also was charted by day of onset for the same period. Unlike the previous adverse event categories, these showed a very clear temporal clustering pattern, particularly in the week two post-vaccination (days 7-14). The characteristics of the cases were as follow:

Characteristics	**DHHS (n=21)**	**DoD (n=79)**
Differences		
Male	7 / 21 (33%) (37% overall)	77 / 79 (97%) (88% overall)
Primary Vaccinee	3 / 21 (14%) (24% overall)	76 / 79 (96%) (71% overall)
Mean Age	47.4 years (47+/-10 overall)	26.3 years (29 +/-9 overall)
Similarities		
Vaccination to symptom onset, **days** Mean ± SD, median (range)	9.5 ± 7.78 11 (2 to 42)	10.2 ± 3.9 10 (1 to 25)
Vaccination to initial evaluation, **days** Mean ± SD, median (range)	14 ± 11.31 13 (2 to 94)	10.5 ± 4.4 10 (1 to 29)

So, there were no significant differences between the DoD and DHHS cases in terms of clinical presentation, time to symptom onset, or time to evaluation. The differences lied in:

- Suspect-to-probable-to-confirmed ratios: DHHS had more of the suspect cases.
- Proportion of primary vaccinees: DHHS had more revaccinees.
- Proportion of cases who were male: DoD had more male cases.
- Age distribution: DHHS cases were older.
- Case ascertainment was the major difference. DoD's was streamlined through its integrated health system, while CDC had to work with state health departments to obtain patient records and follow-up information.
- DoD determined a relative risk of 7.5 for its primary vaccinees from the 16.11 cases/100,000 vaccinees observed, well above the expected rate of 2.16/100,000. They documented close temporal clustering, wide geographic and cross-seasonal distribution (not due to other circulated viruses), focused among primary vaccinees. The rate for revaccinees (2.1/100,000) was not statistically different from what was expected.

Rate/extent of recovery, myo-pericarditis cases. DoD's follow up of 64 of 67 cases (96%) at a mean of 32 weeks after diagnosis, showed all with objective normalization of ECG, echocardiography, laboratory testing, graded exercise (treadmill) testing, and functional status; 8 of the 64 (12.5%) reported an atypical, non-limiting, persistent chest discomfort. In the DHHS cohort, follow-up of the 21 (100%) cases at a mean of 40.2 weeks after diagnosis showed objective normalization for all, for ECG, echocardiography, laboratory testing, and functional status. None reported any atypical, non-limiting, persistent chest discomfort. The resolution or normalization of these cases was charted.

There were some limitations to this analysis: 1) the DHHS clinical evaluations were not consistent and some medical records were incomplete; 2) DoD and DHHS imprecision in the retrospective collection of subjective symptoms; and 3) DoD's clinical evaluations and follow-up of myopericarditis was based on a common algorithm that was implemented at multiple sites, while the DHHS program could not be so.

Conclusions by the two programs, based on these data, were that:

- ❖ A causal association exists between smallpox vaccination and myopericarditis, but a high degree of clinical recovery in those individuals has been seen to date.
- ❖ Biological mechanisms could plausibly support an association between smallpox vaccination and ischemic cardiac events. The cardiac data do not support but also do not refute a causal association.
- ❖ Data are insufficient to move away from neutrality regarding a causal association between smallpox vaccine and dilated cardiomyopathy. Biological mechanisms that support the hypothesis could exist, possibly, through intervening myocarditis. However, this is still an unknown, and further evaluation is needed.

Next steps include plans to publish a peer-reviewed report of the findings from the entire program (December 2002-June 2404) including additional follow-up on cardiac cases and pregnancies. Once that is done, the ACIP work will be concluded and the joint Workgroup (ACIP and the Armed Forces Epidemiological Board [AFEB]) will disband (or perhaps, just "hibernate"). The AFEB's subcommittee will continue to annually review the accumulating DoD smallpox vaccination data and copy the report of their findings to the CDC and ACIP. If any unexpected events occur, the AFEB would rejoin with ACIP for joint review of the data.

Discussion included report that four of the DoD cases were biopsy-positive for carditis, but the PCR and viral cultures were negative. Why that occurred remains unknown. But, since there is no evidence of an infectious etiology, Col. Grabenstein tended to think the mechanism was inflammatory. In a prospective trial, DoD will study antibodies, perhaps including cross-reactive antibodies to cardiac muscle.

Myocarditis Associated with Acambis Smallpox Vaccines

Presenter: Dr. Niranjan Kanesa-Thason, Acambis Vaccine

Overview: Characteristics of the ACAM2000® smallpox vaccine, its clinical trials; ascertainment of cardiac adverse events; myocarditis incidence in ACAM2000® Phase 3 trials, myocarditis case reviews; case-control study; proposed revised case definitions for ACIP consideration; preliminary results of Acambis' unaudited clinical data.

The smallpox vaccine, ACAM2000®, was derived from the original Dryvax® (New York City Board of Health) strain. It is a plaque-purified, clonal vaccinia virus that is grown in Vero cells. It has no bovine serum or other protein. It is a purified virus formulated in a buffer that is then taken from the cell supinatants to formulation in a buffer with human serum albumin. It is less neurovirulent in animal models (mice, monkeys), in which it showed typical dermovirulence, immunogenicity and protective activity.

In the 709 participants of the Phase 1 and 2 trials, ~28% received at- or near the intended dose.

The most commonly reported adverse events were injection site pruritis, erythema or pain. There was only one vaccine-related cardiac serious adverse event, late in Phase 2, a case of probable myocarditis in a vaccinia-naïve subject.

Phase 3 involved two randomized, double-blind trials using Dryvax®-controls in vaccinia-naïve and previously vaccinated subjects. Each trial had a 3:1 randomization, with 2040 receiving ACAM2000 and 680 receiving Dryvax.® The co-primary non-inferiority efficacy endpoints were safety, cutaneous "takes" and immunogenicity. One trial also tested the clinical consistency of three lots among naïve subjects. Exclusion criteria rejected subjects at risk for cardiac adverse events. The overall analytic framework for the trials and that for cardiac assessments were shown.

Cardiac assessments focused on the clustering seen in the DoD and civilian cohorts around days 7-10. Right after vaccination, a physical exam was given, with specific questions asked about cardiac symptoms; on day 10, post-vaccination record ECGs and cardiac troponin tests were done. Re-interviews about symptoms, another exam and ECG were done on Day 21. The subjects were examined again on day 30 and later re-interviewed by telephone about cardiac symptoms. Those reporting these (e.g., dyspnea, chest pain, palpitations, reduced tolerance to exercise) and had an abnormal ECG or troponin, were recalled to the clinic for a repeated interview, examination, ECG and troponin, as well as a CK-MB fraction test.

Suspect myopericarditis was defined as a case with an abnormal ECG or cardiac function study, with- or without symptoms or elevated cardiac enzymes. These were referred to a cardiologist for further evaluation and a cardiac function study (echocardiogram, cardiac MRI, or radionuclide) as well as serology and virus isolation. Probable myocarditis was defined as cases meeting the definition for probable myocarditis plus cardiac enzyme elevation, with- or without symptoms. Details of the cases seen for each of these categories were outlined.

A *case control* study was done based on the selected age, gender, and site-matched controls of the eight cases seen, blinded to their treatment. The ages of the 59 controls was not significantly different, nor were gender distribution or race/ethnicity background. Not surprisingly, the cases reported a similar increased frequency of symptoms (e.g., elevated temperature, chills, malaise, fatigue) as well as chest pain, dyspnea, palpitations, and reduced tolerance to exercise. There was no difference seen in injection site adverse events (pain, swelling, redness/erythema, itchiness) or lymph node tenderness. All the cases and most of the controls had major cutaneous reactions which were not significantly different, but the cases' lesion measurements were less than those of the controls.

Conclusions The serious cardiac adverse events occurring in the vaccinia-naive subjects were restricted to clinical or subclinical myocarditis. Probable myocarditis occurred only in Caucasian subjects. Subclinical myocarditis presentations occurred in three of the eight subjects, all ACAM2000 vaccinees. The DoD cohort's 7:1 male-to-female distribution of cases was not significantly different from this cohorts' overall gender distribution. The preliminary observations of the case-control analysis also indicate comparable clinical responses in both the cases and the controls, except for two factors: more cardiac symptoms and less prominent cutaneous responses than the controls.

Ongoing Evaluations of myocarditis cases included continued cardiology follow-up of all

subjects until 12 months after vaccination. All appear to have had clinical resolution with no persistence of cardiac symptoms, and none have been hospitalized. Three- and six-month follow-ups have been done without incident. A centralized review of cardiac function studies (e.g. ECHOs, MRI, radionuclide scan) is being done, and they hope to do this for any follow-up ECGs or follow-up studies as well. A retrospective review of a randomly selected sample of normal ECGs of 289 subjects is also being done.

Following the review of these data by their expert cardiology panel, the original case definitions were revised. The added symptoms are italicized.

- Suspected myocarditis is now defined as the presence of symptoms (chest pain/discomfort, dyspnea, palpitations, exertional dyspnea, *syncope/near syncope, PND, orthopnea*) **AND** ECG abnormalities (ST-T changes, AV block, IVCD, long QTc, arrhythmia) **OR** evidence of abnormal LV function (focal or diffuse) by appropriate imaging study (e.g. ECHO, MRI) **AND** no evidence of other probable cause for the symptoms and findings.
- *Probable myocarditis* meets the definition of suspected myocarditis **AND one or more of the following:** ECG evidence of treatment-emergent ST-wave elevations of ≥2 mm and/or T-wave inversion on 2 or more contiguous leads with no other probable cause; troponin-I above the upper limit of normal (ref lab), evidence, as determined by the central core lab, of abnormal LV function (focal or diffuse), by echocardiogram or other appropriate imaging study, abnormal cardiac radionuclide imaging consistent with myocardial inflammation **AND n**o evidence of other probable cause for symptoms and findings.

Discussion included:

- *What was the frequency of elevated triponins on Day 10 in the two groups?* The level of 1.4 is considered by labs as suggestive of acute myocardial inflammation, but Dr. Kanesa-Thasan did not have the frequency at this meeting. While most patients identified at that level met the myocarditis case definition, there were also one or two subjects with completely silent elevations. This may relate to the patients' high level of activity, but the data are too preliminary to say.
- Potential cofactors to the cardiomyopathy seen in the data to date include drinking alcohol, high levels of activity (e.g., one was an outside garden worker), smoking, and morbid obesity. The screening only documented the absence of three or more of certain risk factors listed in CDC's recommendations. Record review will be needed to see which were recorded.
- Future plans could include, after the audit/review of these data, re-doing the entire analysis again, and perhaps resubmitting it to the expert cardiology panel. A consultation will be done with one of those panel members about other immune mechanisms, about looking whether specific antimyosin or anticardiomyosin antibodies might have rise over the post-vaccination period during these studies.
- The future of ACAM200® is being discussed with the FDA. Actually, the Phase 1 and 2 studies data suggested that more myocarditis was expected to be found. This may be a foreseeable event, related to the biology of vaccinia viruses.
- Dr. Plotkin found these studies to be extremely important. The pathogenic factors in these studies must be found to determine if they may apply to the use of attenuated vaccinia for other purposes (e.g., HIV and malaria vaccines). Dr. Kanesa-Thason agreed. These well-screened patients had no prior vaccinia exposure, but still mounted a fairly prominent response at- or around the time they developed antibodies. How this fits into the disease's natural history is as yet unknown.

Final Report of the ACIP-AFEB Smallpox Vaccine Safety Workgroup
Presenter: Dr. John Neff, Workgroup Chair

Dr. Neff expressed his appreciation to the whole Workgroup and for the "remarkable collaboration" of the study partners. Under his leadership and that of his Co-chair, Dr. Guthrie Birkhead, the Workgroup was charged to evaluate the smallpox vaccine's safety data and the DHHS and DoD anthrax vaccine safety monitoring and treatment systems. They were also to monitor the safety data on the use of vaccinia immune globulin (VIG) and cidofovir for any civilian under the IND protocol of the DHHS program. The Workgroup membership was multi-representative, including experts in public health, internal medicine and infectious disease epidemiology, as well as smallpox and the vaccinia virus. The Workgroup members met weekly to begin with, held one face-to-face meeting to determine the trigger points for action, and then met weekly or monthly until finishing their work.

As already presented, the Workgroup found:

- No cases of progressive vaccinia, eczema vaccinatum, or nosocomial spread.
- Only two cases of possible post vaccinial encephalitis, one recovered and one improved but not back to baseline. However, the latter is a possible but uncertain case. These two cases do not meet even the predicted rate for this population.
- One case of biopsy-confirmed erythema multiforme major (Stevens-Johnson Syndrome).
- One case of confirmed generalized vaccinia and 42 suspect- or probable cases.
- 48 cases of contact vaccinia, none in the work place.
- 17 inoculated ocular infections, with no corneal involvement.
- VIG was released 5 times but administered only in 3 cases: 1) released and administered once to prevent vaccinia dissemination when a recent vaccinee suffered 45% surface burn; 2) released 3 times but administered only twice to treat ocular non-corneal inoculations; and 3) released once but not administered to a person with decompensated myocarditis.
- There were no cases of fetal vaccinia.
- Ten persons with undiagnosed HIV infection were inadvertently vaccinated. They had a mean CD4 count of 483 cells/mm^3 and a mean log10 plasma HIV-1 RNA load of 4.13 copies/cm^3. Three were primary vaccinees and 7 were re-vaccinees and all had normal robust take without complication.
- Smallpox vaccine well tolerated. There was one lupus-like syndrome reported that favored a causal relationship to the immunization experience, but since that individual in the DoD cohort had received several immunizations simultaneously, the evidence was not definitive.
- There were five ischemic deaths for which a causal relationship could neither be included nor excluded and four deaths where the casual relationship was definitely rejected.
- Cardiac findings included 79 DoD cases of myocarditis, 21 DHHS cases, and 8 Acambis vaccine trial cases.
    - Ischemic cardiac events were seen in 26 cases, with no elevation in risk among either the DoD or the DHHS vaccinees. If only the probable DHHS cases are counted, this cohort's rate is similar to that of the DoD (1:8000).
- Dilated cardiomyopathy findings: 4 DoD cases and 3 DHHS cases; none with previous myocarditis. One was successfully transplanted and one awaits transplant; the others are stable or recovering. There are no data to determine if the rate of this condition is above what would be expected in a similar population.

The Workgroup's conclusions were:

- The anticipated serious, preventable adverse events as well as nosocomial spread were reduced through excellent education, screening, and attention to vaccination site management. Contact transfer of vaccinia occurred primarily in the home setting from intimate contact. Analysis is needed as to whether that can be further reduced. It is expected that most cases reported in the past as generalized vaccinia were likely hypersensitivity reactions.
- Disseminated generalized vaccinia was extremely rare and was not observed.
- Screening and education reduced, but did not eliminate, inadvertent exposure of pregnant women. Nonetheless, fetal vaccinia was a rare event.
- Myopericarditis is causally associated with smallpox vaccination, and the Acambis data indicate that it may be directly related to the vaccinia virus. To date, all the observed cases have recovered completely.
- The observed rate in the DoD cohort was ~1 case per 8000 vaccinees and 1/2000 vaccinees in the DHHS cohort. All the cases in both groups were retrospectively-determined symptomatic cases. The Acambis prospective study's rate seemed to be closer to 1:145 vaccinees, including clinical and subclinical cases. Data on ischemic cardiac events are inadequate to definitely reject or accept a causal relationship. The biological mechanisms that could support a causal relationship could be hypothesized. The Workgroup definitely recommended that persons with ≥3 cardiac risk factors continue to be excluded from pre-event vaccination.
- Further study of dilated cardiomyopathy cases is warranted, as the biological mechanism supports the hypothesis of an association to intervening myocarditis. The data remain insufficient to move away from neutrality to favor or reject a causal association.

Discussion included

- In view of the relatively rare cutaneous complications, Dr. Nancy Bennet asked if the eczema vaccination exclusion was still felt necessary, and Dr. Neff said yes.
- In the one case of generalized vaccinia, the biopsied lesions were PCR-positive, but it is never clear whether such a PCR-positive really represents the kind of dissemination that the name implies. The dermatologist on the Joint Safety Workgroup thought them to look more like hypersensitivity reactions.

Dr. Traenor **moved to disband the ACIP-AFEB Smallpox Vaccine Safety Workgroup** and the motion was seconded by Ms. Stinchfield. With the lack of a quorum, Dr. Levin deputized Drs. Evans and Baylor to vote on the motion. Upon a vote, all were in favor, none were opposed, and none abstained. **The motion passed unanimously.**

Public Comment

Public comment was solicited, to no response. With Dr. Levin's thanks, the meeting adjourned at 4:15 p.m.

Certification.

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
Ban Mishu Allos, MD
Guthrie S. Birkhead, MD, MPH
Judith R. Campbell, MD
Reginald Finger, MD, MPH
Janet R. Gilsdorf, MD
Myron J. Levin, MD, Chair
Tracy Lieu, MD
Edgar K. Marcuse, MD, MPH
Julia Moria, MD
Gregory A. Poland, MD
John B. Salamone
Patsy Stinchfield, NP
John J. Treanor, MD
Robin J. Womeodu, MD
Richard Zimmerman, MD

Members absent were: Mr. John B. Salamone

Ex-Officio Members

Centers for Disease Control and Prevention
Stephen L. Cochi, MD, MPH
Julie Gerberding, MD, MPH
Stephen C. Hadler, MD, Acting Executive Secretary
Alison Mawle, MD
Gina Mootrey, DO, MPH
Charles Vitek, MD

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

Liaison Representatives

William Alexander, MD, American Association of Health Plans (AAHP)
Carol J. Baker, MD, and Margaret Rennels, MD, American Academy of Pediatrics (AAP), Committee on Infectious Diseases (COID)
Damian A. Braga and Peter Paradiso, PhD, Pharmaceutical Research and Manufacturers of America (PHARMA)
Dennis A. Brooks, MD, MPH, National Medical Association (NMA)
Richard Clover, MD, and Jonathan Temte, MD, American Academy of Family Practitioners (AAFP)
James Randolph Farris, MD, Centers for Medicare and Medicaid Services (CMS)
Stephan L. Foster, PharmD, American Pharmacists Association (ApharmA)
Stanley Gall, MD, American College of Obstetrics and Gynecology (ACOG)
Steve Gordon, MD, Hospital Infections Control and Prevention Advisory Committee (HICPAC)

Charles Helms, MD, National Vaccine Advisory Committee (NVAC)
Jody H. Hershey, MD, MPH, and Nancy Bennett, MD, MS, National Association of County and City Health Officers (NACCHO)
Samuel Katz, MD, Infectious Disease Society of America (IDSA)
Joanne Langley, MD, National Advisory Committee on Immunization, Ontario, Canada
Clement Lewin, PhD, MBA, Biotechnology Industry Organization (BIO)
W. Paul McKinney, MD, Association of Teachers of Preventive Medicine (ATPM)
Amy B. Middleman, MD, MPH, Society for Adolescent Medicine (SAM)
David A. Neumann, PhD, National Coalition for Adult Immunization (NCAI)
Kathleen M. Neuzil, MD, MPH, American College of Physicians (ACP)
Romeo S. Rodriguez, MD, National Immunization Council and Child Health Program, Mexico
Robert Scalettar, MD, MPH, American Association of Health Plans (AAHP)
William Schaffner, MD, Infectious Diseases Society of America (IDSA)
Litjen Tan, PhD, American Medical Association (AMA)
James C. Turner, MD, American College Health Association (ACHA)

Liaisons absent: David M. Salisbury, MD, London Department of Health

Agency Staff

Agency for Toxic Substances and Disease Registry: Preethi Rao

Department of Health and Human Services (DHHS)

Centers for Disease Control and Prevention (CDC):

No C/I/O identified: D. Doyle, Allison Rue, John Anderton, Judd Fletch, Bonnie Nebeit, Abby Shefer, Shannon Stokley, SuraSak Young Pairoj, Erin Burns, Miriam Sabin, Bonnie Zell, Deborah Levy, Bridget Lyons, Lisa Jacques, Richard Dixon, Raine Alexander,

Office of the Director: Kevin Malone, Office of General Counsel

Epidemiology Program Office (EPO): Rosaline Dhara

Management Analysis and Services Office (MASO): Douan Kirivong

National Center for HIV, STD and TB Prevention: Bernard Branson

National Center for Infectious Diseases (NCID):

John Barson
Niransjan Bhat
Oleg Bilukha
Roz Dewart
Keiji Fukuda
Marika Iwane
Martin Meltzer
Ida Onorato

National Immunization Program (NIP):
James P. Alexander
Bill Atkinson
Karen Broder
Susan Chu
Jeff Chen
Amanda Cohn
Margaret Coleman
M. Cortese
Kathy Garrett, Nerck Vaccine
Jane Gidudu
Holly Groom
Renina Haber
Scott Harper
Andrew Kroger
Laurie A. Johnson
Jessica Leung
Megan Lindley
Tasneem Malik
Mike McNeil
Christine Mijalski
Elaine Miller
Rick Nelson
Ismael Ortega-Sanchez
Suzanne Pickering
Bette Pollard
Lance Rodewald
Nancy Rosenberg
Tammy Santibanez
Jeanne Santoli
Kari Sapsis
Jim Singleton
Tejpratap Tiwari
Donna Weaver
Eddie Wilder
Carla Winston

Office of Terrorism Preparedness and Response: Sue Gorman

National Institute for Allergies and Infectious Diseases (NIAID): David L. Klein

National Vaccine Program Office (NVPO): Ben Schwartz

Department of Defense (DOD): John D. Grabenstein

Members of the public or presenters to the committee in attendance were:
Vincent Ahonkhen, GlaxoSmithKline (GSK)
Steve Allred, getaflushot.com
Allyn Bandell, MedImmune
Howard Bedecker, California Immunization Program
Joan Benson, Merck & Co., Inc.
Patti Boyle, Aventis Pasteur
Margaret Burgess, NCIPS, Australia
Brian Cox, Henry Schein, Inc.
Lisa Danzig, MD, Chiron
Michael Decker, AventisPasteur
Shelley Deeks, Public Health Agency of Canada
Kenneth Dennison
Alen Rex Ellington
Dorelle Humphrey Franklin, Georgia Division of Public Health
Robert Frencle, Herbor/UCLA Medicxal Center
Len Friedland, GSK
Diane Gaffoglio, CCR, CVR-CN
Ronan Gannon, GSK
Greg Gilmot, Aventis Pasteur
Jill Hackell, Wyeth
Neal Halsey, Johns Hopkins University, Baltimore, MD

Claire Hannan, Association of State and Territorial Health Officers (ASTHO)
Carrie Harper
Kim Hazelwood, Georgia Department of Public Health
Joy Hill, (CDC) Tennessee Immunization Program
Philip Hosbach, Aventis Pasteur
Barbara Howe, GSK
Dominic Iacuzio, Roche Labs, Inc.
Melanie Jackson, Georgia Chapter, AAP
Varsha K. Jain, GSIK
David R. Johnson, Aventis Pasteur
Barbara Kuter, Merck
Philip LaRossa, Columbia University
Geoff McKinley, Baxter
Marie-Michele Leger, AAPA
John Modlin, Vermont Department of Health
Julie Morita, Chicago Department of Public Health
Marie Murray, Recorder, Atlanta, GA
Martin Myers, National Network for Immunization Information, Galveston, TX
Karen Nielsen, GSK
Walter Orenstein, Emory University Vaccine Center
Peter Patriarca, MedImmune Vaccines
Diane C. Peterson, Immunization Action Coalition
Stanley Plotkin, MD, Aventis Pasteur, Doylestown, PA
Geoff Porgess, Alliance Bernstein, NYC,NY
David Rein, RTI International
Loleta Robinson, MedImmune
Jane Quinn, GSK
James Ransom, National Association of City and County Health Officers (NACCHO)
Judith Shindman, Aventis Pasteur Ltd.
Jeff Silber, Merck
Dr. Alan J. Sievert, AAP, East Metro Health District, Lawrenceville, GA
Bonnie Thomas, Colorado Wellness Connection
Ted Tsai, Wyeth
Jean Walters, Merck
Joel Ward, UCLA
Martin Wasserman, GSK
Barbara Watson, MD, Division of Disease Control, Philadelphia, PA
Deborah Wexler, Immunization Action Coalition, St. Paul, MN
Celia Woodhill, California Department of Health Services
John Zahradnik, Aventis Pasteur