CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL IMMUNIZATION PROGRAM

RECORD OF THE MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

October 26-27, 2005

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

Acronyms Used In This Report

AAFP	American Academy of Family Practitioners
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
AMA	American Medical Association
APERT	Acellular Pertussis Efficacy Randomized Trial
CDC	Centers for Disease Control and Prevention
CE	Cost Effectiveness
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment Network
CMI	Cell-Mediated Immunity
CNS	Central Nervous System
COID	Committee on Infectious Disease (AAP)
COPD	Chronic Obstructive Pulmonary Disease
DALYS	Dollars-Per-Life-Year Saved
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus, Acellular Pertussis (vaccine)
DTP	Diphtheria, Tetanus, Pertussis
ED	Emergency Department
ELISA	Enzyme-Linked Immunosorbent Assay
ELS	Extensive Limb Swelling
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GI	Gastrointestinal
GMC	Granulocyte Macrophage Colony
GMT	Geometric Mean Titer
gp	Glycoprotein
GSK	GlaxoSmithKline
HAV	Hepatitis A Virus
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus (Vaccine)
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HPV	Human Papillomavirus
HZ	Herpes Zoster
HZO	Ophthalmic Herpes Zoster
IAC	Immunization Action Coalition
Ig	Immune Globulin (IgA, class A; IgG, class G)
ISO	Immunization Safety Office
ID	Intradermal
IDU	Intravenous Drug User
IM	Intramuscular
IND	Investigational New Drug
IOM	Institute of Medicine

LAIV	Live Attenuated Influenza Vaccine
LAIVC	Live Attenuated Influenza Vaccine - Cold (adapted)
MBPHL/MBL	Massachusetts Biologics Public Health Laboratory
MCV	Meningococcal Conjugate Vaccine
MITT	Modified Intention To Treat
MMRV	Measles, Mumps, Rubella, Varicella
MMWR	Morbidity and Mortality Weekly Report
MPSV	Meningococcal Polysaccharide Vaccine
MSM	Men Who Have Sex With Men
NCHS	National Center for Health Statistics
NCHSTP	National Center for HIV, STD and TB Prevention
NCID	National Center for Infectious Disease
NHIS	National Health Interview Survey
NI	Neuraminidase Inhibitor
NIP	National Immunization Program
NNDSS	National Notifiable Disease Surveillance System
NVPO	National Vaccine Program Office
OPV	Oral Poliovirus Vaccine
PEP	Post-Exposure Prophylaxis
PHN	Postherpetic Neuralgia
PRV	Pentavalent Bovine-Human Rotavirus Vaccine
QALYS	Quality-Adjusted Life-Year Saved
REST	Rotavirus Efficacy and Safety Trial
RTI	Research Triangle Institute
STD	Sexually Transmitted Disease
TIV	Trivalent Influenza Vaccine
USPSTF	U.S. Preventive Services Task Force
VAERS	Vaccine Adverse Event Reporting System
VaIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
VAPP	Vaccine Associated Paralytic Polio
VE	Vaccine Efficacy
VFC	Vaccines for Children (Program)
VSD	Vaccine Safety Datalink
VTEU	Vaccine Treatment Evaluation Unit
VZIG	Varicella Zoster Immune Globulin
VZV	Varicella Zoster Virus
WHO	World Health Organization

Table of Contents

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

MINUTES OF THE MEETING
OCTOBER 26-27, 2005

OCTOBER 26, 2005

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 26-27, 2005. The meeting agenda was posted on CDC's Website. The meeting was convened at 8:38 a.m. by ACIP Chairman Dr. Jon Abramson, who welcomed all in attendance (see Attachment #1).

OPENING COMMENTS

ACIP Executive Secretary Dr. Larry Pickering made several announcements:

- He welcomed three distinguished visitors from China: Dr. Cui Gang, Director, Ministry of Health, Epidemiology Division; Dr. Liang Xiaogeng, Director, National Immunization Program of China; and Dr. Xu Aiqiang, Deputy Director, Shangdon Provincial Center for Disease Control.
- Members newly appointed were Mr. Robert Beck, ACIP consumer representative, Dr. Harry Hull, Minnesota State Epidemiologist, and Dr. Dale Morse, New York State Department of Health (not present at this meeting).
- New liaisons were: Dr. Keith Powell, American Academy of Pediatrics, and Dr. Patricia Whitley-Williams, National Medical Association
- This was the last meeting for Dr. Richard Clover, who was thanked for his many years of service to the committee. During the meeting, Dr. Abramson also thanked Ms. Dee Gardner for her excellent work in coordinating the ACIP meetings.
- The ACIP home page is http://www.cdc.gov/nip/acip and the e-mail address is mailto:acip@cdc.gov
- The 2006 ACIP meeting dates are February 21-22, June 26-27, and October 24-25.
- ACIP Protocol: A quorum of ACIP members must be maintained to conduct committee business. In the absence of a quorum (eight members) qualified to vote, the ACIP charter allows the Executive Secretary to temporarily designate *ex officio* members as voting members. If voting, the *ex officio* members are asked to disclose any potential conflicts of interest. 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 can be 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 who serve on a Data Safety Monitoring Board (DSMB). Those members may provide information to the committee and discuss other vaccines produced by the same company, but they may not participate in discussion on the vaccine involving their conflict, nor in any related votes.
- 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 and time permits.

The members and liaisons then introduced themselves (see Attachment #1). Those reporting potential conflicts of interest were Mr. Beck (awaiting a decision from the Office of General Counsel about stock), Dr. Gilsdorf (IND safety monitor for an NIH vaccine trial, but not compensated), and Dr. John Treanor (clinical trials for laboratory studies underway or pending grant support, for: Alphavax, Protein Sciences, Merck, PowderMed, EpImmune, and ID Biomedical (which is being purchased by GlaxoSmithKline, or GSK). Dr. Tracy Lieu had no conflicts but reported receiving research support from the CDC.

AGENDA ITEMS

HEPATITIS

Hepatitis B Vaccine Recommendations for Adults

Presenter: Dr. Eric Mast, NCID

Overview: Background/rationale for adult hepatitis B virus (HBV) vaccination strategies; proposed adult hepatitis B vaccine recommendations

Background. ACIP has recommended vaccination for adults at risk for HBV infection since 1982, but implementation has been poor. Many health care settings do not vaccinate high risk adults and vaccine coverage among high risk adults is low. Clearly, new implementation strategies are needed.

The process to develop new recommendations began in October of 2004, with an overview presented to the ACIP. Draft recommendations were posted for public comment on the Division of Viral Hepatitis (DVH) web site from January 28-March 4, 2005. The childhood statement was approved at the June 2005 ACIP meeting. Input has been received since the distributed of the February 2005 draft recommendations, from the ACIP and its Hepatitis Vaccine Working Group, from the public and from CDC staff. An external consultation was also held in May to discuss implementation barriers in the public and private sectors and the strategies or experiences that could address them.

In response to this input, expanded implementation recommendations were developed. These provide guidance on setting-specific strategies to reach adults, including specific recommendations to address barriers. They also have guidance on vaccination in primary care settings, including option for age-based vaccination in situations where risk assessment is not feasible.

Information is also provided in the statement about hepatitis B surface antigen (HBsAg) testing as a component of hepatitis B vaccination services. Racial-ethnic disparities in disease burden are discussed, as is the rationale for identification and management of HBsAg-positive persons. A separate section provides the recommendations for hepatitis B serologic testing in routine immunization activities.

A Working Group was formed to prepare proposed ACIP adult hepatitis B vaccine recommendations. The Working Group will draft recommendations, propose funding (a draft

proposal is in CDC review), prepare program guidance, plan health education and communication strategies, and identify the data needed to evaluate implementation.

Data from 1990-2004 were charted on 1) U.S. cases of acute hepatitis B incidence by age group and race/ethnicity to age 20 years, and 2) 2002 vaccine coverage for all age groups, and reported acute hepatitis B incidence in 2004 by age and sex. Reported risk characteristics among U.S. adults with acute hepatitis B (2001-2003) included high risk behavior heterosexuals (>1 sex partner in prior 6 months, sexual contact with HBsAg-positive person) (39%), men who have sex with men (MSM ─ 25%), injection drug users (IDU ─ 14%), and other exposures (household contact, institutionalization, hemodialysis, blood transfusion, occupational exposure) (7%). About 15% had no identified risk.

In primary care and specialty medical settings, the data indicate that risk-targeted vaccination is the most efficient delivery method because only ~15-20% of all adults report risk factors for infection that would make them a candidate for vaccination. Risk identification has also been recommended by the AAFP, AMA, USPSTF. In addition to hepatitis B vaccination, many persons at risk for HBV infection have other prevention needs (e.g., screening for HIV and STDs, or drug abuse treatment).

Of those who had acute hepatitis B from 2001-2004, 61% had prior opportunities for vaccination (in detention, or at STD or substance abuse clinics). Demonstration projects in high-risk settings have established the needed program components to successfully implement adult hepatitis B vaccination. They have also demonstrated the feasibility of delivery in STD, HIV/AIDS and hepatitis prevention services, achieving a 75%-85% first-dose acceptance rate. Funding for vaccine and administration was identified as the primary barrier to implementation in these settings.

The barriers to hepatitis B vaccination in primary care and specialty medical settings were identified and addressed in the implementation recommendations:

- *The lack of an adult vaccination infrastructure*, with delivery mechanisms not yet well-established. Implementation: The public health and medical communities should educate providers about methods to implement and support hepatitis B vaccination services**.**
- *Lack of tracking systems.* Implementation: Health departments were encouraged to implement adult immunization registries.
- *Lack of time and low priority for this vaccination* is cited by providers, as well as limitations in providers' ability to ascertain patient high risk behaviors. Implementation: Providers should be knowledgeable about hepatitis B and the need for vaccination. To educate them, the public health/medical communities should define the vaccination's benefits. Implementation: use questionnaires or interviews by office staff to identify eligible persons and simplify the risk assessment, emphasizing risks for sexual transmission and percutaneous or mucosal blood exposures. If risk ascertainment is a barrier, alternative vaccination strategies can be used (e.g., targeting age groups at highest risk).
- *Lack of awareness of the part of patients that they may need the vaccine, and fear of the stigma that comes from acknowledging risk behaviors.* Implementation: Health departments and CBOs should increase awareness of the benefits of hepB vaccination, particularly among risk populations; providers should help patients assess their need for vaccination; acknowledgement of specific risk factor is not a requirement for vaccination.

- Unclear fiscal/reimbursement assurances, perhaps most important. There are little data on reimbursement mechanisms and many patients have no vaccination insurance coverage.

The proposed recommendations were as follow:

- Hepatitis B vaccination is recommended for all unvaccinated adults at risk for HBV infection and all adults seeking protection from HBV infection. Acknowledgement of a specific risk factor is not a requirement for vaccination.
- Unvaccinated adults at risk for HBV infection are those at risk for sexual transmission (sexual partners of HBsAg-positive persons, sexually-active persons not in a long term, mutually monogamous relationship (e.g., >1 partner in the prior 6 months), persons evaluated/treated for STDs (including HIV), men who have sex with men, those at risk for transmission by percutaneous or mucosal exposure to blood, and others (e.g., international travelers and persons with chronic liver disease)."

Implementation recommendations were structured to take into account setting-specific vaccination strategies, to achieve high coverage among the persons for whom it is recommended.

- *Hepatitis B vaccination is recommended for all adults in*: STD and HIV treatment facilities, HIV testing facilities, drug abuse treatment and prevention facilities, correctional facilities, health care settings serving MSM, chronic hemodialysis facilities and end-stage renal disease programs, and institutions and nonresidential daycare facilities for developmentally disabled persons. *Implementation*: Assume all unvaccinated adults are at risk; implement standing orders to administer hepatitis B vaccine to unvaccinated adults as part of routine services; provide hepatitis B vaccine as a component of STD, HIV/AIDS, and other viral hepatitis prevention services; and when feasible, provide Hepatitis B in outreach settings.
- In primary-care and specialty medical settings hepatitis B vaccination is recommended for: all unvaccinated adults at risk for HBV infection and all adults seeking protection from HBV infection. Acknowledgment of a specific risk factor is not a requirement for vaccination. Implementation: Providers should help patients assess their need for vaccination by obtaining their risk history and emphasizing sexual transmission and percutaneous or mucosal exposure to blood. If ascertainment of HBV infection risk is a barrier, providers are encouraged to use other vaccination strategies, such as offering hepatitis B to all unvaccinated adults in the age groups of highest infection risk (i.e.., <45 years).

HBsAg screening as a component of immunization services can identify of HBsAg positive persons and allow the prevention of transmission to others by vaccinating at-risk contacts. This also could reduce the risk of chronic liver disease in infected persons by providing medical management and antiviral therapy. The management of HBsAg-positive persons can enhance vaccination strategies to eliminate HBV transmission. HBsAg testing for chronic infection should be undertaken for:

- All persons born in countries with HBsAg prevalence >2% (e.g., countries of Asia and Africa with high prevalence, Pacific Islands).
- Other persons who should be tested for HBsAg in the context of immunization services include pregnant women, persons testing positive for anti-HBc before vaccination, and non-responders to vaccination.

- Those who are determined to be HBsAg-positive should receive appropriate medical management and their susceptible household, sexual, or needle-sharing contacts should be identified and vaccinated.
- Those who are tested as HBsAg-negative require no further management unless hepatitis B vaccine is recommended.

Summary:

- Adult hepatitis B rates have declined by >70% since 1990. This decline is expected to continue with aging of vaccinated cohorts of infants, children and adolescents
- Elimination of HBV transmission can be accelerated by increasing vaccination coverage among at-risk adults, since ~85% of cases occur among persons with risk characteristics
- The recommendations provide setting-specific implementation strategies to achieve high vaccination coverage among at risk adults and recommendations to overcome barriers to vaccination.

Hepatitis B Working Group Discussions

Presenter: Dr. Tracy Lieu, Chair

There was some controversy among Working Group members about making the adult recommendations age-based and universal. Most did not support the potential addition of universal vaccination of those aged 19-25 years, although a few did or were undecided. A permissive universal vaccination "where feasible" had little support. However, all the Working Group members supported risk-targeted vaccination.

Risk-targeted strategy. The *advantages* of a risk-targeted strategy were that it: 1)targets those persons who comprise >90% of those contracting hepatitis B, including ~40% of cases with no identified risk factor; 2) is consistent with existing recommendations for assessment of patient drug and sex behavior; 3) it reaches adults at risk in all age groups, 4) venues exist for program implementation, and 5) it is demonstrably feasible and cost-effective.

- The disadvantages were that: 1) providers often do not inquire about behavioral risk factors, and 2) this approach does not reach all adults with no identified risk factors.

Universal vaccination. The potential addition of universal vaccination of 19- to 25-year-olds would essentially be a catch up strategy, since many of these would have been vaccinated against hepatitis B in the childhood schedule. The advantages of adding universal vaccination of 19- to 25-year-olds were that: 1) this could potentially reach more young adults, including those with no identified risk factor, 2) it could simplify vaccination decision making, 3) remove the stigma of having to disclose risk factors, and 4) spur the needed development of an infrastructure for adult vaccination.

However, the rationale against adding universal vaccination of 19- to 25-year-olds was that: 1) this would likely prevent few additional cases beyond risk-targeted vaccination; 2) >90% of those contracting hepatitis B could be identified by a risk-targeted strategy; 3) the highest-risk persons may not seek primary care in these or any setting; 4) there was no evidence of feasibility to implement; 5) this approach would cost substantially more than risk-targeted vaccination; and 6) it may divert resources from risk-targeted efforts. This argument was found to be more compelling, particularly the last.

Three options were offered, with the first recommended by the Working Group:

A. Risk-targeted strategy alone (recommended by Working Group).
B. Risk-targeted strategy plus universal vaccination of 19-25 year-olds.
C. Risk targeted strategy plus universal vaccination of 19-25 year-olds "when feasible."

Discussion included:

- Option A was supported by Drs. Morita and Gilsdorf as a better use of public health resources. They felt it premature to define the risk-based strategy as unsuccessful, as it has only been implemented for a few years. A universal recommendation would likely have less impact than a targeted one, and could divert limited resources from the highest risk groups.
- Option B was supported by Dr. Allos, since >50% of those with hepatitis B did not have the risk factor of more than one sexual partner in the last six months, and physicians most often screen MSM and IDUs. She also hoped for age-based recommendations to raise the flat reduction rates of the last six years. Option C was supported by Dr. Marcuse in order to convey clearly that universal hepatitis B vaccination of adults is desirable, although the ACIP should clarify its recommendation to "where feasible" as due to resource issues. Drs. Temte and Middleman agreed, since practices are already overloaded, addressing at least three problems per patient, and the clinics catering to the highest risk groups are chaotic and under funded. The risk-based strategy has not worked in the past among adolescents, who are fertile and also at highest risk (and uncomfortable disclosing it). Dr. Middleman suggested consideration of using an immunization platform for those aged 14-21, building on growing influenza vaccination interest and the imminent Tdap vaccine release. Dr. Tan expressed the AMA's support of that, but if not done, they would support universal vaccination.

Identified challenges to the ultimate eradication of hepatitis B included:

- The need for additional strategies to achieve administration of the second and third doses for a full vaccination series. Providers are currently advised to track doses and use reminder systems to accomplish that. Immunization registries will also help.
- One unaddressed failure of the risk-based strategy is the lack of funding to implement adult vaccination, something NIP has struggled to fund for >20 years. CDC leadership has highly prioritized and planned an initiative to target risk groups, but has no funding as yet to do so. CDC and other immunization partners need to state this as a problem.

Challenges to a universal recommendation were listed:

- It may not be feasible to know who has been vaccinated if an age-based system is used. Most parents do not know their children's vaccination schedule and many cannot produce records. Without the latter, vaccination of the entire cohort may be required.
- Physicians' safety net is already stretched thin. Being deprived of some "wiggle room" would leave them open to liability risk.
- A universal HBV vaccination may divert health departments' limited vaccine supplies from the targeted groups.

Models. The ACHA has successfully produced a 65%-66% uptake among college graduates. College health services should be added to the list of facilities proving vaccination services to all adults. Correctional facilities' inmates are vaccinated in six or seven states, with an 80%-85% acceptance and high third dose coverage.

Dr. Deborah Wexler, of the Immunization Action Coalition (IAC) expressed their opinion that this recommendation is too complicated. She recommended a review of its feasibility by family physicians, health departments, internists and obstetricians. Risk-based vaccination historically has been difficult to implement. The IAC suggested, at a minimum, a catch-up program so that 18-25 year-olds would automatically be screened upon visiting their physician. The recommendation also did not address the disproportionately high rate of hepatitis B in African-Americans.

Dr. Tan noted the ACIP recommendations' weight with providers and insurance carriers. If ACIP offers encouragement rather than a recommendation of the vaccination, it likely will not be covered or well implemented.

PUBLIC COMMENT

Dr. Joel Engardio, of Stanford University's Asian Liver Center, spoke as a patient advocate. There is chronic infection in older Americans, but his late partner, Dr. Mark Lin, was diagnosed with terminal liver cancer caused by chronic hepatitis B at only age 30. He was a non-drinker and did not use drugs. He was Asian-American; his mother was born in China. Hepatitis is the "silent killer of Asian-Americans" and one in ten are unaware of their chronic hepatitis B infection. Even Dr. Lin did not know the risk. Particularly in areas like San Francisco with large Asian populations, education about this epidemic is needed. The vaccine is simple to use, effective and available, and vaccination should be promoted.

Dr. Samuel So, of the USC Cancer Center, thought this issue important enough that he canceled his clinic hours to attend this meeting. The greatest health disparity between Americans and Asians is the prevalence of hepatitis B. Most physicians do not know about Asians' 25% chance of dying from the sequelae of chronic hepatitis B infection. A vaccine has been available for the last 20 years that could prevent 80% of liver cancer in Asians, but their five-year survival rate is <10%. Testing to identify those chronically infected is also important because new antivirals can reduce the risk of liver cirrhosis and cancer. The ACIP recommendations have a great impact on choices made by physicians and health care plans. Dr. So urged ACIP to name Asian-Americans as a high risk group and to recommend HBsAg testing of children and adults, appropriate treatment of those testing positive, and testing/vaccination of all their family members and partners. He additionally requested a section to address the need to educate health care providers about the importance of addressing this disease among Asian-Americans.

Ms. Marie Bresnahan is the vice president of programs for the American Liver Foundation and a member of the National Viral Hepatitis Roundtable, which comprises >100 member organizations. Viral hepatitis patients have joined the Roundtable and have written a national strategy to eliminate hepatitis B. Because current strategies do not identify or reach those at risk and needing vaccination, the NVHR hoped the ACIP recommendations would be expanded. The ALF is also developing their policy statement. They asked to be involved in the process.

The ***proposed recommendation*** was risk targeted vaccination with an implementation recommendation to offer vaccination to all adults in selected settings, including STD clinics, drug-abuse treatment facilities, HIV-testing sites, and correctional facilities. Primary care and specialty medical care settings should offer hepatitis B vaccine to adults in high-risk groups. If risk ascertainment is a barrier in primary care and specialty medical settings, alternative

vaccination strategies can be used (e.g., targeting age groups at highest risk). More discussion of screening for HBsAg surface antigen status and the related criteria was requested. With new treatments, the benefits of screening are becoming more clear and further guidance will be needed.

Dr. Abramson conducted a straw poll of the committee members on the three options: Option A: Beck, Campbell, Finger, Gilsdorf, Hall, Lieu, Morita, Abramson
Option B: Allos
Option C: Marcuse, Womeodu

Dr. Lieu **moved to adopt Option A** as the ACIP's recommendation. Dr. Marcuse seconded the motion.

Vote:
In favor: Beck, Campbell, Finger, Gilsdorf, Hill, Lieu, Marcuse, Morita, Abramson
Opposed: Allos, Womeodu
Abstained: None (Dr. Treanor had a conflict but was not present to vote)

The vote passed.

VARICELLA

Varicella Zoster Immune Globulin (VZIG)

Introduction
Dr. Judith Campbell, Working Group Chair

The ACIP issued recommendations for the use of varicella zoster immune globulin (VZIG) in 1984, and revised them in 1996 and 1999. VZIG is used for post-exposure prophylaxis (PEP) among those with no evidence of immunity, those for whom exposure is likely to result in infection, and those at high risk of severe varicella disease. The latter group includes immunocompromised individuals (children, adolescents and adults), perinatally exposed neonates and exposed premature infants, pregnant women, health-care workers and individually exposed adolescents and adults. Vaccination offers the best protection to high-risk groups, directly or indirectly (e.g., household contacts of neonates and immune-compromised individuals) and is recommended for primary protection.

Over the last ten years, the need for VZIG has decreased and its sole producer, the Massachusetts Biological Laboratory (MBL), decided in 2004 to stop manufacturing the product. In response, the Working Group held conference calls to discuss the key issues relevant to varicella post-exposure prophylaxis, with the participation of a representative of the FDA's blood products advisory committee. The manufacturer estimated the supply to be available through April 2006, but may be exhausted at an earlier date.

FDA Update on VZIG Status/New Product
Presenter: Dr. Dorothy Scott, FDA

Overview: FDA update on VZIG status and possible licensure of new product.

VZIG is an intramuscular plasma preparation containing high anti-VZV antibody titers. It should be administered within 96 hours of exposure to persons at high risk for severe varicella and complications. The supply is now expected to last only until January 2006. Annually, an equivalent of about 10,000 125-unit vials (625-unit vials are also available) are administered to approximately 2000-10,000 patients (the dose is weight dependent).

FDA's Blood Products Advisory Committee has publicly encouraged the development of an investigational new drug (IND) application for VZIG, and has communicated with CDC about various options. The Committee, which last met in July 2005, is working to define a feasible path to the licensure of a new VZIG preparation. This includes defining the necessary lab and clinical efficacy data. Target populations and surrogate markers with which to assess efficacy and support licensure have been discussed.

Also discussed were the considerations for clinical trials and the current knowledge relative to the use of IGIV or acyclovir rather than VZIG. These cannot be studied quickly, as vaccination has left few remaining susceptible persons. Other challenges included the variety of clinical situations that will further reduce the number of subjects in each category.

For surrogate markers, the committee indicated pharmacokinetic equivalence in normal subjects compared to the licensed VZIG product, coupled with laboratory-demonstrated equivalence or superiority to the (old) licensed product. Then, a Phase IV trial will be needed to further study the product among those with an indication for use.

Committee conclusions. The committee had some uncertainty that IGIV could substitute for VZIG, for several reasons: an unknown variability of varicella antibody titer between IGIV lots, the potential of lessened titers among the donor vaccinees replacing naturally-infected donors, and whether the latter affects antibody quality or affinity. The committee also decided that there was insufficient evidence to recommend the use of acyclovir as a VZIG substitute.

CDC assessed the anti-varicella-zoster virus (VZV) antibody titers in the IGIV products licensed for general use. These are normally used to replace immune globulin in patients with primary immune deficiency or with thrombocytopenia. Other off-label uses are also known.

FDA sent blinded samples of seven licensed IGIV products, and the MBL sent VZIG, to CDC. The gpELISA analysis showed the titers in VZIG to be highest of all, but a number of IGIV lots also had fairly comparable levels. This suggests that current immune globulins have anti-varicella titers following natural infection or vaccination, but the titers are unpredictable even within one product type.

The FDA's ongoing monitoring of the VZIG supply indicates that there are no remaining 125-unit vials, and a current use of ~200, 625-unit vials per month. With FDA encouragement, the one distributor (FFF Enterprises) is shipping only on an as-needed basis. FFF also tracks the supply to allow stock transfers as needed.

FDA awaits IND applications and will review them under the financially-attractive orphan drug classification, which allows cost recovery requests. Treatment protocols with the new product also will be considered for patients in need.

FDA is communicating the licensed uses of VZIG, how to obtain VZIG from FFF, and the anticipated shortage (http://www.fda.gov/cber/infosheets/mphvzig092005.htm). They are also urging clinicians and pharmacists to order VZIG only for identified patients in need. Shipment within 24 hours in the continental U.S. can be arranged and hospital-to-hospital product transfer is possible.

At least one company has expressed interest in manufacturing a VZIG product. FDA will make an IND available as soon as possible, but that is not likely by January 2006.

Varicella Zoster Virus and PEP Options
Presenter: Philip LaRussa, MD, Columbia University

> Overview: High risk groups, correlates of protection, options for post-exposure prophylaxis, alternatives to VZIG.

Varicella's pathogenesis involves two viremic phases that can be targeted for prophylactic interventions: a small primary viremia within a day or two following exposure and the larger, secondary viremia, at 10-12 days following exposure (1-2 days before the rash). The disease is highly contagious to naïve populations. Some groups are at higher risk for serious disease:

- immunocompromised persons (however, in late-1980s Feldman et al showed a 50% decrease in pneumonitis in children with cancer (attack rate of 5%) among those who received VZIG).
- neonates whose mothers developed chickenpox within 5 days preceding delivery
- pregnant women
- adults in general.

Correlates of protection - Literature review.

- Ross (*NEJM*, 1962) demonstrated that the more immune serum globulin (ISG) administered, the higher the geometric mean titer (GMT) and the more effective the varicella prevention.
- Gershon (*J Clinical Microbiology*, 1978) examined immunocompromised children given ISG or zoster immune globulin (ZIG) and supported Ross' findings, finding with higher GMTs a likely seroconversion at 48 hours post-exposure. Disease occurred among ~30% of patients and was mild. Of three subjects who did not seroconvert, two developed severe disease.
- Orenstein (*J Pediatrics*, 1981) showed that high-risk patients who received ZIG and had a four-fold titer rise at 48 hours had a lower disease risk than those without such a titer rise. Again, recipients of higher-titered ZIG had a more consistent four-fold rise than those receiving the lower titer. The latter also had more complications.
- Zaia (*JID*, 1983) showed VZIG equivalence to ZIG in preventing varicella among immunosuppressed children, both dropping the attack rate to ~15%-18%. But VZIG seemed to better prevent sub-clinical infection and again, preparations with high titers were more effective than those with lower titers. Antibody titers 48 h post -VZIG/ZIG did not correlate with infection rate or severity of disease.

*As far as markers for correlates of protection, v*accine studies or skin test measurements of CMI response have clearly demonstrated varicella susceptibility among persons with FAMA titers <2. For vaccinated children, a gpELISA titer ≥5 units at six weeks after immunization correlated

highly with protection (95.5%, versus 83% at <5 units). The challenge was in distinguishing the antibody effects from those of the vaccine-induced CMI. Gershon's small study of vaccinated leukemic children who were later exposed to varicella at home, and who had an antibody *plus* CMI response, showed that none developed the disease. All the children with neither antibody nor CMI response developed varicella, and those with one or the other had variable rates of disease.

Options for post-exposure prophylaxis (PEP) for persons at high risk for severe varicella disease, other than VZIG (if produced again), were outlined with their advantages and disadvantages.

Intravenous gamma globulin (Immune globulin intravenous, IGIV): *Advantages:* There are some data to support the use of IGIV. It produces good anti-varicella titers, although more is needed to be comparable to VZIG in effectiveness; supply is normally good. Because it produces a peak serum level faster than VZIG does, the window for prophylactic use may be extended beyond that of VZIG. The *disadvantages* include IGIV's greater cost (~$ 240 per 10 kg child) than VZIG (~$125); unclear volume to be used in neonates; possible variation in efficacy, since these preparations are not titered for anti-VZV antibodies; and the possibility, with rising numbers of vaccinated individuals, that higher doses will be needed.

Studies of IGIV use as prophylaxis against varicella are few.

- Paryani et al (*J Pediatr*, 1984) compared VZV IgG antibody titers in oncology patients who received VZIG (4 ml/Kg) versus IGIV (6 ml/Kg) four- or six weeks apart, respectively. Titers measured 3-4 weeks after VZIG or IGIV administration were equivalent but the peak was achieved within 24 h after IGIV and 7 days after VZIG
- Shu-Huey et al (*Pediatr Hematol and Oncology*, 1992) showed no varicella disease among five susceptible children with leukemia given IGIV after exposure.
- Kavaliotis et al (*Med and Pediatr Oncol*, 1998) also showed no varicella among the 11 children with cancer given VZIG within three days of a hospital exposure. Three of the 30 who received IGIV were infected, and three of the 38 who received both were infected. While IGIV was not 100% effective and infection rates varied, disease severity was certainly alleviated.
- Ferdman et al (*PID*, 2000) reported three patients who developed varicella despite IGIV therapy. The disease was mild, but they concluded that IGIV-treated individuals with profound T-cell deficiency or dysfunction may not respond as well and VZIG prophylaxis should be considered.

Vaccine used as prophylaxis has the *advantages* of being highly efficacious if given to healthy children within 36 hours of exposure, and of being a one-time, easy administration. The *disadvantages* include its inappropriateness for use among immunocompromised patients, pregnant women, or newborns, lack of certainty that one dose is efficacious as post exposure prophylaxis in adults, and difficulty of administering two doses in a prophylactic setting.

Antivirals for use as prophylaxis include acyclovir, famciclovir, and valacyclovir. Some data support their use. *Advantages:* They can be effective after the VZIG window and therefore can be given later in the incubation period. *Disadvantages* include limited data on their use among immunocompromised patients and their status as Class B drugs for use in pregnancy. Animal trials showed the drugs to be safe. Data are very limited on antiviral use as prophylaxis in newborns. Most of the data are with Acyclovir, where there is concern about absorption when

administered orally. The absence of a liquid formulation for the other two drugs limits their use among very young children and infants. In addition, antivirals require compliance with multi-day regimens and that may influence the efficacy. Suga et al (*Arch Disease Child,* 1993) studied infection in children given acyclovir for seven days in a dose of 40 mg/Kg. The infection rates, compared between prophylaxis begun at 3-, 6-, and 10-days post-exposure, versus none, were comparable. However, when administered at the end of the incubation period, at onset of the large, secondary viremia, acyclovir was very effective and disease was much milder. Acyclovir inhibits viral replication, and the antibody titers in children receiving acyclovir were somewhat lower than in children not receiving it. There have been no follow-up studies to see if that affects later exposures.

Options. Most of the immunocompromised patients seen now will probably have been vaccinated as healthy hosts. If they are not immune, IGIV or an antiviral can be used. In those for whom a vaccine is not appropriate (neonates, pregnant women, children aged <1 year), IGIV or an antiviral can be used. Vaccine may be used for PEP among non-pregnant healthy adolescents and adults.

In summary, a substitute product is still needed. IGIV is probably equivalent or superior to VZIG at an appropriate dose, but will have to be re-evaluated periodically. Whether the window for IGIV use matches that for VZIG also needs to be determined. Antivirals could be useful, especially when the window for administration of IGIV is missed. More studies are needed to test antivirals in populations other than healthy children. Vaccine is currently of limited utility as a substitute for VZIG.

Issues Related to PEP with VZIG or IGIV Use
Presenter: Dr. Mona Marin, NIP

> Overview: Content of the proposed statement on PEP against severe varicella during a VZIG shortage.

The Working Group reviewed the literature on alternative methods for post-exposure prophylaxis of persons at high risk for severe varicella. The current scientific data is not strong enough to fully support one or another alternative method – there are limitations due to the studies' small numbers and design (lack of a control group), difficulty in ascertainment of exposure, and limited data among immunocompromised persons or clinical data showing efficacy. Although limited, there is stronger scientific evidence supporting IGIV use as PEP against severe varicella when VZIG is not available. However, some experts indicated that based on limited clinical experience, acyclovir could be considered, especially for cases occurring ≥96 hours after exposure, when it is too late to administer IGIV. A footnote states this as a consideration with or without use of other methods. There are no data to support its use among immunocompromised persons.

Based on the literature and expert opinion, the Working Group identified VZIG as the preferred method for PEP for patients at high risk for severe varicella and complications. If VZIG is not available, IGIV can be used for:

- Immunocompromised patients without evidence of varicella immunity.
- Neonates whose mothers develop varicella symptoms from five days prior to two days after delivery.

- Premature infants exposed during the neonatal period whose mothers are not immune to varicella.
- All premature infants of <28 weeks gestation or weighing ≤1000 grams at birth, regardless of maternal varicella history.
- Pregnant women: IGIV administration or close monitoring for signs and symptoms of varicella is recommended, along with acyclovir treatment if illness develops.

Exposed patients already receiving IGIV therapy at ≥ 400 mg/Kg at regular intervals with the last dose within three weeks after exposure, may not need a new IGIV dose.

Any patient receiving IGIV for varicella prevention should subsequently receive varicella vaccine, if not contraindicated, but not before eight months after the IGIV administration. Vaccination is not necessary if varicella develops after IGIV.

Acyclovir used as PEP should be administered late in the incubation period (from day 7 to day 10 after exposure) and given for seven consecutive days. Children's dose should be 40-80 mg/kg per day; adults should receive 80 mg five times a day. Varicella vaccine should be administered at a later date unless contraindicated and the patient does not develop varicella.

Patient management after PEP. Any patient receiving IGIV or acyclovir should be monitored closely for varicella for 28 days after exposure. Antiviral therapy should begin at the earliest signs or symptoms. Physicians should judge the route and duration of administration, based on specific host factors, extent of infection, and initial response to therapy.

Discussion included:

- Dr. Marcuse suggested checking the recommended interval between receiving IGIV and MMR, thinking it was 11 rather than 8 months.
- Other countries also have IGIV products, which would require FDA approval to be administered in the U.S.

Dr. Myers questioned the wisdom of waiting to administer acyclovir until the mother is symptomatic, since the fetus may be affected by the mother's viremia. The Working Group discussed this extensively. The Working Group physicians were uncomfortable recommending acyclovir in the first or second trimester of pregnancy. Since there are no efficacy or safety data to support that, the decision favored monitoring the mother. They agreed that physicians could have IGIV as an option, but acknowledged concerns about the necessary high doses. Dr. Campbell reassured all that Dr. Stan Gall, of ACOG, had participated in the discussion and in preparation of the documentation. Dr. Jim Cherry, of UCLA, urged that the importance be stressed of diagnosing the index case. There is anecdotal evidence of VZIG being administered after exposure to rashes that were not varicella. Dr. Abramson agreed.

Dr. Campbell **moved to accept the recommendation that IGIV be the primary PEP method against varicella in a situation of VZIG shortage**. Dr. Marcuse seconded the motion.

Vote

In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Treanor, Womeodu, Abramson

Opposed: None

Abstained: None

The vote passed.

HEPATITIS A

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

> Overview: Review of hepatitis A epidemiology; progress of past and current recommendations' implementation; proposed language on: 1) routine vaccination of 1 year old children nationwide; 2) maintaining vaccination of 2-18 year old children in areas with existing programs; and 3) consideration of vaccination of 2-18 year old children in areas without existing programs.

ACIP recommendations for hepatitis A vaccination of children have been implemented incrementally, beginning in 1996 with vaccination of children living in so-called "high rate" communities. In 1999, the ACIP took another incremental step by recommending routine vaccination of children living in states and communities with hepatitis A incidence rates that were consistently higher than the national average during a defined baseline period in the pre-vaccine era. The ACIP indicated that the final step in the incremental strategy was routine vaccination of all children nationwide, and that implementation of this policy would be facilitated by the availability of hepatitis A vaccines for use in children aged <2 years. Routine vaccination of children nationwide would allow consideration of elimination of indigenous hepatitis A virus (HAV) transmission.

The 17 states in which, according to the 1999 ACIP recommendations, routine hepatitis A vaccination of children was recommended or should be considered include ~33% of the U.S. population, but ~66% of the reported hepatitis A cases during the pre-vaccine era baseline period.

The 1999 recommendations included permissive language with respect to implementation strategies. They suggested determining the age groups to be vaccinated based on community disease patterns and proposed a number of possible vaccination strategies (e.g., one or more single-age cohorts, in selected settings such as day care, or children in a wide age range when they presented for medical care). As a result, approaches and implementation have varied considerably among the states in the five years since the recommendations were made.

Current vaccination coverage.

- National Immunization Survey, 2003 and 2004: One-dose coverage among children aged 24-35 months averaged 51%-54% in the 11 states where vaccination was recommended (range 6%-74%), 25%-27% in the 6 states where it was to be considered (range 1%-35%), and 1%-2% in the other states.
- Preliminary results of a CDC-RTI telephone survey (with provider verification of immunization record) in Arizona and Oregon indicate ~70% coverage among 2½-5 year-old children in those states, declining to ~25-30% among older children.
- Although information on trends in vaccination coverage is limited, available data suggest that coverage appears to be rising slowly, if at all, in recent years. Implementation has been accomplished primarily using voluntary strategies, and few states have mandates. There has been little change in states' vaccination policies in recent years.

Remarkable changes in hepatitis A epidemiology have been observed since implementation of the 1999 recommendations. Overall incidence has declined, with sharper declines in the areas in which vaccination was recommended. In 2004, the incidence rate was 1.9 per 100,000 ─ the lowest rate in the approximately 40 years that these data have been collected. Declines occurred in all age groups, but were greater among children. In the pre-vaccine era, rates among children were consistently higher than those of adults, but since 2001, rates among children have been lower than among adults. Differences in hepatitis A incidence among racial/ethnic groups also have narrowed or been eliminated. In the pre-vaccine era, hepatitis A incidence among American Indians and Alaska Natives was approximately10 times higher than among whites, but currently is among the lowest of any racial/ethnic group. Rate differences between Hispanics and non-Hispanics have also narrowed, although rates remain higher among Hispanics.

In examining recent trends in hepatitis A incidence by age group, it can be seen that the rates among children aged 2-9 years living in areas where vaccination is recommended steadily declined to 2003 and then plateaued in 2004. Among children living in areas where vaccination is not recommended, there was a slight increase in incidence in 2004 compared to 2003, and this group had the highest age- and region-specific rate in 2004. A similar pattern was observed for those aged 10-18 years, with plateauing of rates in both vaccinating and non-vaccinating regions. Incidence rates among adults continued to decline in both regions, and most of the overall decline in incidence between 2003 and 2004 was attributable to declines among adults.

The distribution of cases by age group and region during the pre-vaccine era and in 2004 was compared. The overall proportion of cases among children fell from approximately 36% to 27%. Whereas in the pre-vaccine era approximately two thirds of all cases were reported from states in which vaccination was then recommended, in 2004 cases from these vaccinating states accounted for about one third of cases and ~66% of cases in 2004 occurred in areas not using vaccine.

In vaccinating states, the incidence among Hispanic children has dramatically declined, to 2.9/100,000, but this rate remains somewhat higher than among non-Hispanic (0.5/ 100,000) children. In the non-vaccinating states, the difference in the incidence rate between Hispanic (7.1/100,000) and non-Hispanic (1.0 /100,000) children remains large. The 2004 rate among Hispanic children in non-vaccinating states was the highest age-specific rate in either vaccinating or non-vaccinating states.

In summary, the overall hepatitis A incidence rate has continued to fall in recent years, primarily because of continuing declines among adults; rates among children appear to have plateaued. Despite this progress, about 5,000 to 7,000 cases are reported each year, and an estimated 20,000-30,000 symptomatic cases occur. Rates are similar across regions, and are highest among Hispanic children in non-vaccinating states. Most cases are reported from states without routine vaccination recommendations.

Although difficult to predict with any certainty, if the current ACIP recommendations were to be maintained unchanged, theoretical models of incidence dynamics when a new vaccine is introduced predict an initial nadir followed by a rebound to a new steady state, which will be lower than before vaccine introduction but higher than the nadir. A model of expected incidence predicts 5000-11,000 cases per year over the next ten years without immunization in the non-

vaccinating states.

Nationwide vaccination of children with hepatitis A vaccine will move this childhood vaccination into the mainstream, improving its sustainability and increasing the probability of achieving high coverage. It is consistent with the incremental strategy. The availability of two vaccines for use from 12 months of age will allow the incorporation of hepatitis A vaccine into the routine childhood vaccination schedule. Nationwide routine vaccination of children is likely to result in lower rates over time, to further narrow demographic disparities, and allow eventual consideration of elimination of indigenous transmission. The economic analyses of this strategy are favorable.

Working Group Discussions/Economic Analyses
Presenter: Dr. Tracy Lieu, Working Group Chair

In early September, a poll of ACIP members revealed general support for universal hepatitis A vaccination, although a few members were undecided. The ACIP hepatitis vaccines Working Group also supported universal vaccination. Several key questions arose from the working group deliberations as well in discussions with other ACIP members:

Why is universal vaccination needed now? The 1999 ACIP recommendations for "high-incidence" states were an interim step; ACIP's intent has always been to eventually implement nationwide hepatitis A vaccination. Hepatitis A vaccines are now available for use in one-year-olds, improving the feasibility of this strategy, as initially envisaged by the ACIP. Finally, the current policy of vaccination in "high-incidence" states is not sustainable.

Why is the status quo not sustainable? The policy of selective vaccination is not sustainable because states that used to be "high-incidence" now have lower incidence than the "low-incidence" states where vaccination is not recommended. Hence the rationale for continued vaccination in these areas doesn't make sense to people, and anecdotal evidence suggests that states may lose support for continued vaccination. Even if selective vaccination were sustainable, its impact probably would not be sustained, as shown by plateaued disease rates among children and the persistence of disparities. Without universal vaccination, models predict that hepatitis A incidence probably would rise again.

Cost-benefit of universal vaccination. Predictions of the CDC-RTI economic model were summarized.

Health Benefit (annual, with vaccination at age 1 year):

- Retaining the status quo is predicted to prevent 81,000 cases, or 41% of potential cases, versus the 199,000 cases with no vaccination. Eleven lives and 1,100 quality-adjusted life-years (QALYs) would be saved. Expanding the policy to nationwide vaccination would prevent 180,000 (or 90%) hepatitis A cases, saving 32 lives and 2,300 QALYs.
- The incremental difference in health benefits is 99,000 (49%) hepatitis A cases prevented, 21 lives saved, and 1,200 QALYs saved.

Costs (annual, with vaccination at age 1 year):

- Vaccine doses and administration would be $48/child in either the status quo or nationwide strategy. The $22 million direct vaccination costs for the status quo would rise to $134 million with nationwide vaccination, an incremental cost of $112 million.

Vaccination in the status quo scenario saves $18 million. The net societal cost of vaccination nationwide is $45 million.

Cost-effectiveness

- The status quo is cost saving with respect to QALYs and dollars-per-life-year saved . With nationwide vaccination, the cost per QALY would be $25,000 and per life year saved, $180,000. The "incremental" benefit, the difference between the status quo and nationwide vaccination, was estimated to be $60,000 per QALY and $430,000, per life year saved.
- A comparison was made of the economics of nationwide hepatitis A vaccination compared to other recently-recommended vaccination policies -- adolescent pertussis vaccination and meningococcal vaccination. Implementation of the respective vaccination policies would prevent an estimated 180,000 hepatitis A disease cases, 31,000 pertussis disease cases and 270 cases of meningococcal disease, respectively. The hepatitis A program saved slightly more QALYs than the other two vaccination policies. Its direct vaccination cost ($134 million) rested between pertussis and meningococcal vaccination, and its net societal cost of $45 million was closer to that of pertussis ($33 million) than to meningococcus ($159 million). The cost per QALY saved of universal hepatitis A vaccination of one year olds of $25,000 was similar to the estimate for pertussis vaccination of adolescents ($20,000) and less than that for meningococcal vaccination ($138,000).
- In summary, universal hepatitis A vaccination of one year old children would more than double the benefit compared with the status quo. And, while it would increase the direct cost of vaccination (six fold), the CE is very reasonable compared to other vaccines.

For these reasons, the Working Group reached consensus to support this recommendation. However, they also agreed that the added vaccine financing of this and other new vaccine recommendations needs to be addressed in the larger context of ACIP.

Proposed Recommendation Wording

- *Routine vaccination of young children*: All children should receive hepatitis A vaccine at 1 year of age (i.e., 12-23 months). Vaccination should be completed according to the licensed schedules and integrated into the routine childhood vaccination schedule. Children who are not vaccinated by 2 years of age can be vaccinated at subsequent visits.
- *Older children and adolescents in areas with existing programs (catch-up vaccination):* States, counties, and communities with existing hepatitis A vaccination programs for children aged 2-18 years are encouraged to maintain these programs. In these areas, new efforts focused on routine vaccination of 1 year old children should enhance, not replace, ongoing programs directed at a broader population of children.
- *Older children and adolescents in areas without existing programs:* In areas without existing hepatitis A vaccination programs, catch-up vaccination of unvaccinated children aged 2-18 years can be considered. Such programs might especially be warranted in the context of rising incidence or ongoing outbreaks among children or adolescents.

Discussion:

- Preschool children were not included in this recommendation to avoid having to vaccinate all four cohorts to preschool age, particularly since not all the vaccines were licensed for one year of age. The adult disease rates might invite an adult vaccination

platform; the Working Group did not wish to address the existing adult recommendations at this time.

- Despite better hygiene, etc., CDC does not expect the hepatitis A disease cycles to change. They are currently in a downward cycle that will not continue, but when they rise again, they are unlikely to go to pre-vaccine levels.
- There is indirect evidence that many adult cases stem from children. There were "huge" rate declines among adults in the states that vaccinated children. A published CDC model of vaccination impact through 2001 estimated that about a third of the program's impact might be attributable to herd immunity.
- The disease analysis did not assume lifelong immunity to hepatitis A. Dr. Armstrong explained that the economic analysis assumed a 93% one-dose immunization coverage at age one year, and ~85% for two doses. Belgian data on declining antibody levels among vaccinated individuals were incorporated in a model to estimate the duration of immunity. The current data support immunity to 12 years post-vaccination, and long term protection of at least 20 years is expected based on modeling studies.
- Dr. Diane Peterson, of the Immunization Action Coalition, suggested that the recommendation advise vaccination for "all children aged 12-35 months with catch-up vaccination all throughout the pre-school years." She also advised adding children aged ≥5 years with risk factors for vaccination to the routine schedule. Dr. Baker expressed AAP's strong support for clarification that primary immunization occurs from 12-25 months and all else is catch-up.
- With the impending release of MMRV, zoster, rotavirus, and HPV vaccines, Dr. Katz urged prioritization that is related to the overall costs, to avoid disruption of the VFC entitlement program. Dr. Abramson reported very different feelings about prioritization among ACIP members, but all agree that if the financial problems are not solved, nothing will come of the recommendations.
- Dr. Cochi stated that it is not the ACIP's primary responsibility to solve the financing problem, but only to examine the cost benefit and other considerations. However, an ACIP recommendation is an important stimulus to attention to this crisis. Dr. Plotkin firmly stated that ACIP's role is to recommend on public health, and its recommendations should be based only on that. Dr. Orenstein added that Congress' intent, in establishing the VFC program in 1993, was to keep other groups from recommending on these issues because the cost issues might bias them. Dr. Hull agreed, noting that congressional seats change and congress' attention is only caught for short periods of time. Recommendations to Congress should be based only on what is necessary for public health.
- Dr. Tim Townsend, of Johns Hopkins, had examined this question from different aspects: stopping vaccination, which endangers the public health, or continuing the status quo, in which states with rising rates will have to be funded. Since funds from other states cannot be diverted for that, the only obvious answer is universal recommendation.

Dr. Lieu **moved to support the hepatitis A recommendation with the friendly amendments to clarify it.** Dr. Campbell seconded the motion.

Vote

In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Womeodu, Abramson

Opposed: None

Abstained: Treanor (conflict).

The vote passed.

VFC Resolution Vote
Presenter: Dr. Greg Wallace

ACIP approval of a VFC resolution establishes the vaccine's eligibility to be administered for free to children in the VFC program. VFC eligibility is conferred to those aged ≤ 18 years and eligible for Medicaid, those without health insurance, Native Americans or Alaska Natives, or those underinsured for vaccines who are vaccinated in a federally qualified health center or a rural health clinic.

This VFC resolution for hepatitis A was to revise the previous resolution to incorporate this new universal vaccine recommendation, and to extend that recommendation down to age one year. It specifies all persons aged 1-18 years as eligible through the VFC program. Of the vaccines, Twinrix® is licensed only for those aged ≥18 years and is given in three doses at intervals of 0, 1, and 6 months. The Havrix® and Vaqta® schedules have a two dose series, with the second dose at 6-12 or 6-18 months, respectively, after the first. An asterisk addresses the catch-up as discussed, and enhancing existing programs to reach one-year-olds, but not replacing existing programs. Finally, the text on high-risk groups was deleted, since this is now a universal recommendation.

Dr. Lieu **moved to approve the VFC resolution** and Dr. Morita seconded the motion.

Vote
In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Womeodu, Abramson
Opposed: None
Abstained: Treanor (conflict).

The vote passed.

PERTUSSIS

ACIP Pertussis Vaccine (Tdap) Working Group
Presenter: Dr. Morita, for Dr. Dale Morse, Pertussis Working Group Chair

> Overview: Working Group activities, June 2005 adolescent recommendation, proposed recommendation for adult Tdap vaccination

Since June of 2004, the multi-representational Pertussis Working Group held more than 30 meetings and teleconferences and was invited to participate in an international pertussis panel. The Working Group presented information to the ACIP in February and June 2005. At the June ACIP meeting, the ACIP recommended a single dose of Tdap routinely at age 11-12 years, and for all adolescents aged 11-18 years if they have not received Td. The ACIP recommended that adolescents who received Td but not Tdap receive a single dose of Tdap for pertussis protection, taking into account the interval from the last dose of tetanus and diphtheria toxoid-containing

vaccine.

In this meeting, the ACIP will be asked to consider recommendations for one of the two U.S. Tdap products licensed for single-dose use among adults through age 64 years. The primary objective for a Tdap program for adults is to protect vaccinated adults from pertussis. Secondary objectives include vaccinating adults to: decrease exposures of persons at increased risk of severe pertussis and its complications (e.g., infants aged <6 months), to reduce the costs and disruption of pertussis outbreaks in institutional settings, and to reduce the overall reservoir of *Bordetella pertussis*.

Several assumptions underlie presentations today. Tdap is licensed for use as a single dose among adults less than 65 years of age. Immunity to pertussis wanes at 5-10 years after either vaccine or infection. Booster doses will be required about every ten years to maintain protection. Uptake of decennial Td booster by adults is suboptimal and will require education to improve protection against pertussis via Tdap (1999 NHIS found ~55-67% Td vaccinated adults). Tdap price is ~$20 more than Td. No acellular pertussis vaccine without tetanus and diphtheria toxoids is available; this decreases flexibility for adding protecting against pertussis.

The Working Group reached strong consensus in support of replacing Tdap for Td in adults, proposing:

- A general recommendation for adult Tdap to replace one dose of decennial Td. This proposal was based on recognition that most susceptible adults are not in an identified risk group, yet still have substantial morbidity with pertussis.
- A targeted recommendation for adults who have or will have contact with infants aged <6 months.
- Consideration for administering Tdap at shortened intervals after Td in situations when the perceived risk of pertussis or the benefits of vaccine are high.

A discussion of Tdap for health-care workers and adults aged >65 years will be deferred to a subsequent ACIP meeting.

Efficacy/Safety of Tdap Use among Adults
Presenter: Dr. Karen Broder, NIP

> Overview: Review of immunogenicity and safety data from U.S. Tdap (ADACEL™) pre-licensure trials in adults and a Canadian post-licensure safety study of intervals <5 years between Td and Tdap.

Two Tdap (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccines, Adsorbed) vaccines were FDA-licensed in 2005 for use among adolescents and adults. GlaxoSmithKline Biologicals', BOOSTRIX® is indicated for use among adolescents aged 10-18 years, and sanofi pasteur's ADACEL™ is indicated for adolescents and adults aged 11-64 years. Tdap is indicated as a single-dose booster to prevent tetanus, diphtheria, and pertussis; neither Tdap vaccine is licensed for use in more than one dose.

sanofi pasteur's Tdap for use among adults aged 18-64 years contains lower levels of diphtheria toxoid and inactivated pertussis toxin than sanofi pasteur's DAPTACEL® (DTaP) product, formulated for use in infants and children. The Tdap and Td vaccines manufactured by sanofi

pasteur have the same quantities of tetanus and diphtheria toxoids.

Efficacy. Tdap licensure was based on comparative immunogenicity and safety studies, and the protective efficacy of the antigens in Tdap was inferred from the immunogenicity data. The seroprotective and booster response rates in adults one month after Tdap vaccination were non-inferior to Td, the standard of care. In contrast to tetanus and diphtheria, there are no well acceptable serological correlates of protection against pertussis. The geometric mean antibody concentrations (GMCs) for pertussis antigens in adults vaccinated with one dose of $Tdap_{sp}$ were non-inferior to the GMCs in Swedish infants vaccinated with 3 doses of DAPTACEL® DTaP. In the Sweden I vaccine efficacy (VE) trial, the VE of 3 doses of DAPTACEL® against WHO-defined pertussis was 85% (80%-89%). Booster responses to pertussis antigens in adults vaccinated with $Tdap_{sp}$ were acceptable based on pre-defined criteria

*Safety. A*dverse reaction rates were compared between Tdap and Td recipients. Rates of pain, erythema and swelling were similar in the two groups demonstrating non-inferiority. No case of whole-arm swelling was reported. Adults reported pain at a lower rate than adolescents studied in a separate Tdap study. Rates of fever and other systemic reactions were comparable after Tdap and Td, as were rates of serious adverse events assessed at six-months after the adult primary safety study. After four U.S. ADACEL® pre-licensure safety studies (N=6000 subjects), two serious adverse events in adults were assessed by the study investigators as possibly related to Tdap. Both occurred in women and both resolved without sequelae.

Canadian trials. A Canadian study examined short interval between tetanus and diphtheria toxoid-containing vaccinations for rates of local and systemic adverse reactions, including Arthus. Use of tetanus and diphtheria toxoid-containing vaccines at short, frequent intervals historically was associated with unacceptable rates of local and systemic adverse vaccination reactions, including Arthus. The ACIP currently routinely recommends Td boosters in adults every 10 years. Td is recommended at a 5 year interval after the last Td in wound management.

A decennial Td booster schedule provides adequate protection against tetanus and diphtheria. Administration of Tdap at intervals shorter than 5 years after Td to protect against pertussis might be desirable. Halperin et al (*PIDJ*, in press, 2006) studied Tdap at intervals <5 years after Td or the last childhood DTP/DTaP in Canada using ADACEL™ (same vaccine licensed in the United States) . Outcomes among ~6000 Prince Edward Island children and adolescents aged 7-19 years were assessed. Rates of selected adverse events after Tdap were compared between subjects vaccinated at 2-9 years since the last tetanus- and diphtheria-containing vaccine versus a reference cohort who received a tetanus and diphtheria-toxoid containing vaccine ≥10 years earlier. The 2-year interval cohort included 464 subjects who were vaccinated with tetanus and diphtheria toxoid-containing vaccine18-30 months before Tdap.

Results: No vaccine-related serious adverse event or Arthus was reported. Rates of pain and fever were comparable in all cohorts. Higher rates of "any erythema" and swelling, but not "severe erythema" and swelling were found in the 4-7 year interval cohorts, but were not observed in other cohorts, including the two-year interval cohort. The 4-7-year interval cohorts received one or two doses of acellular DTaP vaccine during childhood, whereas the other cohorts received only whole-cell DTP vaccine during childhood. This finding suggested that rates of reactions after Tdap might be higher among subjects who receive acellular DTaP compared with subjects who receive only whole-cell DTP vaccine.

No safety study of short intervals among adults was done. In the ADACEL pre-licensure trials, rates of local and systemic reactions following administration of Tdap in adults were lower than or comparable to rates in adolescents. The safety of using intervals as short as approximately 2 years between Td and Tdap in adults can be inferred from data in the Canadian study of children and adolescents

In summary, a single dose of Tdap ADACEL® is safe and immunogenic in adults aged 19 to 64 years. Repeat doses of Tdap have not been studied. The safety of intervals as short as approximately two years between Td or childhood DTP/DTaP and Tdap is supported by a Canadian post-licensure study.

Post-licensure Safety of Tdap and Td in Adults
Presenter: Dr. John Iskander, Immunization Safety Office (ISO)

> Overview: Early post-marketing VAERS Tdap safety data and other post-licensure safety data; neurological adverse events possibly (but rarely) associated with tetanus- or pertussis-containing vaccines.

VAERS is a national passive surveillance system for licensed vaccines; its data must be carefully interpreted as the system is limited by underreporting and reporting of unconfirmed diagnoses. To date, VAERS has received 39 reports for licensed Tdap products. Most events occurred in adolescents who received Tdap alone or in combination with meningococcal conjugate vaccine. Most of the symptoms reported were local and mild systemic reactions. Adverse events reported included:

- One sudden cardiac death from cardiac arrhythmia, two weeks after vaccination.
- Five reports of seizure occurring after vaccination with Tdap; all recovered.
- No Tdap reports of Guillain-Barré Syndrome, brachial neuritis, transverse myelitis, or Bell's Palsy.
- Two cases of seizure judged to be vaccine-related in persons with numerous other possible causes of seizure in their medical histories, or with concurrent illness.
- One pregnancy exposure. Pregnancy is not a contraindication in the preliminary ACIP recommendations for Tdap in adolescents.
- Vaccine administration errors; none resulted in significant adverse reactions. Tdap and a pediatric DTaP formulations are similarly packaged.
- Two reports of injection-site reactions fit a general description of extensive limb swelling (ELS); both patients recovered. ELS was previously documented following DTaP, MCV4, and several other pediatric and adult vaccines.
- Serious Td-related local reactions appear to be rare; some literature suggests that the local reaction profile for Tdap could resemble that of Td.

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Neurologic events. Two 1994 IOM reports found a rare causal relationship between tetanus toxoid containing vaccines and Guillain-Barré Syndrome and brachial neuritis, both based on uncontrolled data. Post-licensure Tdap data from both VAERS and published sources support a similar safety profile to that of Td. While rare serious neurological adverse events warrant continued surveillance, none has been associated with Tdap in post-licensure safety reports. The current recommendations were outlined for the administration or deferral of pertussis vaccines in children with seizure disorders or certain other neurological conditions. (source: ACIP recommendations published in MMWR in 1997, 2002)

Pertussis in Adults
Presenter: Dr. Margaret Cortese, NIP

Overview: Clinical pertussis disease data supporting the case for prevention.

The licensure and uptake of pertussis vaccine were associated with reduction in reported U.S. cases by 99%, from ~270,000 cases and >10,000 deaths in the mid-1930s to ~< 2000 cases in 1976. However, pertussis remains endemic in the US, and reported cases peak every 3-4 years. Reported annual number of cases rose to almost 26,000 in 2004, and 28% of the reported cases were in adults. The clinical spectrum of pertussis in adults ranges widely from mild cough illness (which is contagious), to classic pertussis. Asymptomatic infection also occurs. The clinical outcome of pertussis is determined in part by the degree of immunity. Immunity depends on the time since the last exposure to vaccine or to *B. pertussis*. Vaccination before exposure is the best prevention; the effectiveness of post-exposure antibiotic prophylaxis is limited as a public-health response.

Morbidity. These data are charted from 1996-2004 U.S. passive surveillance reports of pertussis among adults aged 19-64 years (the adult age group for whom Tdap is currently licensed), and aged ≥ 65 years. Also charted are Massachusetts surveillance reports of pertussis among adults aged ≥18 years. The clinical features of the U.S. and Massachusetts groups are very similar. Adult pertussis illness features were:

- Paroxysmal cough: 77% of adults, 40-50% with vomiting (less in older adults).
- Coughing spells causing urinary incontinence: 28%, Massachusetts; 33%, Quebec, among women aged ≥50 years.
- Cough syncope (unconsciousness): 6%,Massachusetts, 3%, Quebec; 0%, Sweden, Australia.
- Rib fractures: 4%, Massachusetts; 4%, Quebec, all among women; 1%, Sweden. It is possible that persons with severe cardiac or pulmonary disease, or the very elderly, could suffer greater adverse outcomes from severe coughing spells.
- Other features: difficulty breathing, sleeping: 86%; weight loss: 33%; seizures: 1%; X-ray-confirmed pneumonia: 2-5%, possibly higher in older adults; hospitalization: 2-3% (10% in older adults).
- Cough in pertussis is prolonged: commonly three weeks, median in adults 2-3 months, range 2 weeks to 8 months. Patients usually cough (and spread infection) for weeks before they're diagnosed; 50% of Massachusetts adults had been coughing for ≥1 month before diagnosis, at which point treatment does not lessen symptoms.
- Number of visits for medical care visits was 0-12, with a median of two visit in a Massachusetts study; from Massachusetts surveillance data, 33% patients required ≥3 medical visits. Extensive testing may be undertaken by providers if pertussis is not

suspected.

- Work lost, mean of 10 days, in 61% of cases among employed Massachusetts adults; range was1 to 180 days; data from foreign studies are similar.
- Other rare complications (anecdotally reported) include pneumo-thorax, pneumo-mediastinum, carotid dissection, herniated lumbar disc, inguinal hernia, pertussis encephalopathy.

Mortality. Deaths among adults from pertussis are rare, although likely underreported. Five were reported since 1997; each occurred in an adult with significant underlying medical condition. One reported outbreak in the Netherlands among elderly women in a religious institution occurred in 1992. The attack rate was 53%; 3 deaths were reported from acute intracranial hemorrhage during pertussis cough illnesses of >100 days.

The burden of pertussis in US adults is clearly underestimated by passive surveillance data, in part because of the limited availability of accurate diagnostics, limited physician awareness of pertussis in adults, and the difficulty in clinically distinguishing non-classic pertussis from other respiratory illnesses in adults.

U.S. Data. Prospective studies are needed to estimate the true burden of pertussis in adults; these are challenging because of the limitations of laboratory test confirmation and by ascertaining the target population for surveillance. However, some studies provide useful information. Pertussis incidence studies by Strebel (1995-1996), Ward (1997-2001), Nennig (1994-1995) and Mink (1986-1989) are outlined here. Diagnoses were made using from culture, PCR and/or anti-pertussis toxin serology results (and other serological assays in one study). For comparison, the 2004 pertussis cases reported to the NNDSS among adults in this age group was approximately 6,700, or 4 per 100,000, demonstrating the great underestimation of passive surveillance.

The Strebel et al study reported an incidence of 361 per 100,000 person-years, and Ward et al study estimated 370/100,000 person-years. These extrapolate to annual case estimates of 600,000 and 615,000 (applying the study incidence rates to the 2000 U.S. census population for persons aged 20-64 years), respectively. Nennig et al found an incidence of 176/100,000 person-years, or 300,000 cases per year (by extrapolation). Mink et al focused on college students and estimated incidence at 35 and 69 per 100,000 (depending on the laboratory diagnostic criteria used) for annual adult case estimates of 58,000 and 115,000, if these rates were applied to the adult age group. The studies' range of results is due in part to the age group studied, the type of confirmatory laboratory tests used, the source of the study population (e.g., HMO outpatient visit, prospective vaccine trial, etc).

These studies, and 3 other US studies estimate the proportion of cough illness in adults attributable to pertussis. The studies differ somewhat in methodology. Using the most stringent laboratory requirements, 1%-12% of all cough illness was laboratory confirmed as pertussis. The three other studies produced similar ranges, from 1%-16%. Higher proportions of pertussis among cough illness were obtained with less pertussis-specific serologic assays (up to 17-26%).

An analysis of NHANES III 1991-1994 data by Baughman et al determined the proportion of the population with elevated IgG anti-pertussis toxin, to estimate the prevalence of recent pertussis infection in US adolescents and adults. Their estimate among U.S. adults aged 20-49 years was 2,700 per 100,000 population; these estimates support the concept that pertussis is endemic

among U.S. adults. In a 2004 statewide outbreak of pertussis in Wisconsin, active early case detection, treatment and prophylaxis identified 5070 PCR-confirmed cases, including 111 hospitalized cases, half among infants aged <6 months, at highest risk of severe disease. Of the 1660 cases in adults aged 20-64 years (again, passive surveillance data, incidence of 50/100,000), 53 had pneumonia, 25 were hospitalized, and one elderly man with COPD died.

Adults as source of pertussis for young infants will now be reviewed. Charted data from 1984-2004 show the highest incidence of pertussis (≥200/100,000) is among the youngest infants (aged 0-2 months), who are at highest risk for severe disease, and have the highest mortality rates of older infants and young children. Most of the deaths occurred before the infant could have received the second or third protective dose of pertussis-containing vaccine. During 2000-2004, more infants died of pertussis than in all of the 1990s; of these, 92% were aged <6 months. Again, these data are under-reports. Vitek et al (*Pediatr Infect Disease J* 2003,22:828-34) determined ~65% case report to CDC completeness of *diagnosed* cases from 1990-1999. Studies abroad also indicate pertussis deaths in infants are under-reported.

Bisgard et al (*Pediatr Infect Disease J* 2004,23:985-989) reported interviews of parents of infants with pertussis to determine the source of pertussis, defined as persons with acute cough illness in contact with the infant 7-20 days before the infant's cough onset. If more than one source was identified, the one spending the "most time" with the infant was considered to be the source. Of 494 infants aged < 4 months with pertussis (1999-2002), the source relationship was unknown for 57%, but was a mother, father, or grandparent for 24%. The age of source case was unknown in 64% cases; 20% of the infants were reported infected by an adult aged ≥20 years.

Economics and Cost Effectiveness of Adult Pertussis Vaccination
Presenter: Dr. Grace Lee, Harvard Medical School/Harvard Pilgrim Health Care

Overview: Analysis to explore the cost effectiveness (or cost saving) of adult prevention strategies at varying incidence rates and severity of disease.

Background. Prior economic analyses of adult vaccination strategies disagreed as to the cost effectiveness (CE) of this intervention. In 2004, Purdy et al analyzed the approach of one-dose vaccination against pertussis of all adults aged ≥20 years and found it to be cost saving, while Dr. Lee and her team's 2005 analysis of adult vaccination with decennial boosters found it not to be cost-effective. Aside from study design, a major reason for different conclusions could be the use of different incidence figures (Purdy's of 159-548/100,000, Lee's of 11/100,000). In addition, neither study adjusted for disease severity with increased incidence, which may favor more cost effectiveness or savings.

The Lee study analyzed the CE of one dose of vaccine for adults aged 20-64 years, and the impact of incidence and disease severity on CE. The decision tree moves from vaccination or not vaccinated, to no pertussis or pertussis; and if the latter, severity of disease and adverse events (or not) from local reactions to anaphylaxis.

Lee study assumptions estimated:

- Disease severity for a range of incidence rates, 10/100,000 to 500/100,000. For the former, 67% cases were assumed to have severe cough, 30% cases moderate cough, none with mild cough, and 3% with pneumonia. For the high (500) incidence, 38% cases were

assumed to have mild cough, 21% moderate cough, 40% severe cough, and 1% with pneumonia.

- Vaccine coverage: 57%-66% (using NHIS data) with a VE of 87%.
- Incremental vaccine events (Tdap versus Td):
  - 1) 2% local reactions, 1% systemic reactions, 0.0001% anaphylaxis, and no adverse events due to vaccination, and
  - 2) waning immunity over time, dropping VE from 87% to ~20% at ten years and zero at 15 years.
- Medical costs averaged ~$338 per case and non-medical costs for severe cough illness of ~$460 (most from work lost).
- Incremental vaccine cost (Tdap and Td cost difference) of ~$20.
- No vaccination costs (Tdap simply replacing Td).

The QALY analysis estimated the benefit from prevented morbidity as well as mortality. The same metric was used to measure both disease and vaccine outcomes as well as vaccine and non-vaccine interventions (e.g., vaccination benefits versus risk of adverse events). Also considered was the impact of a pertussis vaccination program on other interventions in a setting of limited resources.

To assign values for different pertussis-associated health states (varied widely between studies), a time trade-off method was used (i.e., willingness to sacrifice time from life's end to avoid an 8-week severe cough). The results were charted on a scale ranging from 0 (equal to death) to 1 (equal to perfect health). Infant respiratory and neurological outcomes were the least acceptable, with a value of 0.5. Local or systemic reactions due to vaccination were the most acceptable (~0.9), and moderate or severe cough illness was in between at ~0.8. Vaccine adverse events were preferred to adult pertussis, and adult pertussis was preferred to infant pertussis. Quality-adjusted life-years saved (QALYs) were calculated by multiplying these health state values times the duration of the health state.

The *outcome measures* were: prevented pertussis cases, QALYs saved, and total programmatic costs. The *CE measures* were the dollar per case prevented and cost per QALY saved, and $50,000-$100,000/QALY was the CE benchmark. Results were:

- *Very low incidence* of 10/100,000, ~164,000 cases over a ten-year period, 72,000 cases preventable with a vaccination program: *Not CE* (in fact, negative QALYs), because minor vaccine events are not necessarily offset by the gain in quality of life achieved by preventing pertussis when disease incidences is very low.
- Disease incidence of 500/100,000, 8 million cases of pertussis, 3.5 million cases (104,000 QALYs saved) preventable with adult vaccination: *CE*. The quality of life gained from prevented pertussis outweigh potential vaccine adverse events.
- *Disease incidence,* with fixed vaccination program costs of $2.1 billion, at 10/100,000 incidence ($100 million saved): *Net cost* remains $2 billion; at 500/100,000 incidence ($1.6 billion saved), net cost is ~$500 million.
- *Disease incidence levels and CE ratios.* Costs vary according to disease incidence, ranging from $25,000 per case prevented with low-incidence (10/100,000) to $100/case at 500/100,000 incidence. The cost per QALY saved ranged from dominated (at low incidence) to $4,000 (at 500/100,000). The CE threshold for an adult vaccination program begins at incidence rates of ~100/100,000. As incidence rises, the cost per QALY drops.

- *Severity of illness at high-incidence*. When no change in the distribution of disease severity was assumed, the overall CE of adult pertussis vaccination changed little.
- *Impact of herd immunity* on vaccine CE was analyzed in three scenarios: no herd immunity; herd immunity from one vaccination to 57%-66% of adults preventing an additional 5% of infant cases and 15% of adult cases; and herd immunity from one vaccination preventing an additional 10% of cases in infants and 30% in adults. Not surprisingly, the inclusion of herd immunity improved the CE of a vaccination program. The program is very CE at high-incidence rates, but CE could be improved further by herd immunity in low-incidence settings.

Study limitations were the assumption that incidence rates average out over time (pertussis is an endemic disease with epidemic cycles every few years) and the unknown degree of herd immunity provided by an adult pertussis vaccination program, which depend on vaccine uptake and contact patterns in the population.

Physician Perspectives on Tdap Administration to Adults
Presenter: Dr. Katrina Kretsinger, NIP

Overview: Results of a survey of family practitioners, internists and obstetricians about adult Tdap vaccination

Data were collected on the current vaccination practices reported by primary-care adult physicians and by obstetricians, as well as factors affecting their likelihood to recommend and administer Tdap if ACIP recommends Tdap for the general adult population and for adults in close contact with infants <6 months of age. A national cross-sectional sample of internists, family physicians and obstetricians (400 each) was requested from the AMA master data file. Two questionnaires, one for internists and family physicians and one for obstetricians, and accompanying fact sheets on pertussis and Tdap were sent in a single mailing. The response rate was 46% by internists, 52% by family physicians and 54% by obstetricians. Results were:

- *Among family practitioners and internists who reported seeing adults for primary care:*
  - *Td booster practices:* 63% routinely assess Td at health-maintenance visits, 68% administer Td for routine health maintenance, and 93% administer Td for wound management as indicated.
  - *Major barriers* to routine Td vaccination: knowing who needs a Td booster (51%), too busy (42%), patient reluctance (42%). Reimbursement and vaccine supply issues were also raised.
  - *Disease severity justification:* 50% of primary-care physicians agreed that adult pertussis was serious enough to warrant vaccinating adults, 13% disagreed; 73% agreed that infant pertussis was serious enough to warrant vaccination of adult contacts of infants ≤6 months of age.
  - *Anticipated response to ACIP recommendation of one Tdap dose to replace Td.* 71% would stock Tdap; 81% would recommend it to their patients.
  - *Vaccine cost:* >80% reported $20 increased incremental cost of Tdap over Td would constitute a slight or strong barrier to stocking Tdap; ~75% found the increase in cost a slight or strong barrier to recommending it to their patients.
  - *Responsibility for promoting and administering Tdap to adults* rests with primary-care providers: ~89% would promote it and 95% would administer it; the responsibility should be shared among pediatricians, obstetricians and

other public-health providers.

- *Among obstetricians who reported providing obstetrical care:*
  - 61% reported routinely administering influenza vaccine during pregnancy and 87% reported routinely administering MMR to a rubella non-immune woman immediately after delivery during the postpartum hospital stay.
  - If recommended by ACIP/ACOG, 78% would recommend Tdap for women immediately after delivery during the postpartum hospital stay; 69% would recommend Tdap for pregnant women.
  - Likely *barriers* to Tdap vaccination included not knowing the date of the last booster vaccination (74%) and patient reluctance (4%); 14% cited cost or reimbursement concerns.
  - OBs believed that adult primary-care providers should be responsible for promoting (72%) and administering (62%) Tdap to adults likely to come into contact with infants ≤6 months of age; the role of promoting vaccination should be shared.

Discussion included

- Only a few of the cough studies looked for pathogens other than pertussis (e.g., mycoplasma), due to the difficulty of diagnosing the etiology of cough illness.
- Dr. Treanor recalled the APERT studies' determination of influenza as a significant cause of prolonged cough illness. That suggests the wisdom of recommending routine influenza vaccination as well.
- The administration of tetanus toxoid during pregnancy is a standard of care. The high percentage of respondents willing to administer Tdap during pregnancy and post-partum was a surprise to NIP, which expected a more cautious response.
- Dr. James Cherry reported that their study of college students found few cases of *Mycoplasma pneumoniae*, and only a few other co-infections or cross-reacting antibody. A study of military personnel in Korea showed some mycoplasma and *Chlamydia pneumoniae* but no adenovirus. Most studies of prolonged paroxysmal cough find pertussis as the primary cause.
- Dr. Martin Myers asked about data on co-administration of Tdap with MMR in children, and with influenza and pneumococcal polysaccharide vaccines in adults. Dr. Broder reported that the one concomitant administration trial done with trivalent influenza vaccine compared immune responses of the simultaneous group to those of the sequential group (influenza first, followed later by Tdap). Immunogenicity and safety responses were non-inferior except for pertactin (lower in simultaneous group), as they also were when hepatitis was simultaneously administered to adolescents.

Working Group Recommendations on ACIP Decision for Tdap Use Among Adults

Presenter: Dr. Kretsinger

Overview: Information on and rationale for the proposed recommendations on Tdap use among adults, for ACIP decision.

The FDA licensed Tdap vaccine for use among persons 11-64 years of age, and ACIP recommended its use among adolescents 11-18 years of age. There is no ACIP guidance on Tdap use among the other age groups for which it is licensed. The Pertussis Working Group's discussions involved several general principles and assumptions: 1) maintaining the ACIP

standard of care for tetanus and diphtheria (decennial boosters or five years after the last Td shot in the event of a tetanus-prone wound); 2) future expected licensure of Tdap boosters (this first proposed recommendation assumed a 10-year duration of immunity); and 3) recommendations for adults aged 19-64 years, not previously addressed. Issues to be addressed later relate to Tdap use during pregnancy and among health-care workers.

The proposed recommendations were based on two objectives: 1) protection of the vaccinated adult from pertussis morbidity, and 2) decreased transmission of pertussis to infants aged <6 months. The recommendations were weighed by the science or evidence, the existing standard of care and programmatic considerations. They were formatted in three sections:

Routine Tdap vaccination. To protect the vaccinated adult from pertussis, tetanus and diphtheria, the Working Group proposes that a single dose of Tdap should replace one dose of Td for adults aged 19-64 years, if ≥10 years have elapsed since the last Td and Tdap was not previously administered. This proposed recommendation is justified by safety and efficacy data of the vaccine, and substantial morbidity of pertussis among adults. The standard of care for tetanus and diphtheria protection of adults will be maintained with this recommendation, and it parallels the June ACIP recommended substitution of one Tdap for one Td dose among adolescents. Programmatically, Tdap can be given within the existing immunization infrastructure, replacing one Td vaccination in the routine schedule, is easy to understand and implement, applies to the general adult population and therefore to all risk groups, and physician acceptance is likely with an ACIP recommendation.

Intervals. The Working Group proposed that Tdap be given at intervals shorter than 5-10 years to protect against pertussis, when adults are not otherwise due for tetanus and diphtheria boosting. A minimum interval should not be specified. The safety of a two-year interval is described in Special Situations and the text allows for shorter intervals. The option of an "accelerated" schedule allows flexibility for catch-up vaccination with Tdap, which may be particularly helpful when the Td vaccination history is unreliable.

Vaccination of adults in close contact with infants aged <6 months is proposed by the Working Group to reduce transmission of pertussis from adults to infants. This group includes women in the preconception and postpartum periods who have not received Tdap, with an encouragement for all women of childbearing age to receive Tdap. Adults are known to be a source of infant pertussis, and mothers in particular are a common source of the infant's pertussis, when a source is identified. Infants < 6 months of age with pertussis have severe pertussis and are at high risk for death; infants complete the routine 3 dose series of DTaP at 6 months of age. Because infants aged <2 months are at the highest risk of death and complications from pertussis, their close contacts should receive Tdap before or as soon as possible after the birth of the infant.

Four complementary programmatic strategies are outlined, targeting: 1) any adult contact, 2) women in preconception, planning a pregnancy, 3) postpartum women, and 4) women of childbearing age in general. Existing program models exist, such as those for MMR and influenza. Targeting women of childbearing age would protect against pertussis in unintended pregnancies (estimated at 50% of pregnancies) and would protect against peri-partum transmission at delivery. A postpartum strategy is likely to be accepted by providers, as was MMR administration in that period.

Core recommendation. The core elements of the routine recommendation include:

1. Tdap vaccination instead of Td for the next regularly scheduled booster - recommended
2. Tdap may be administered after Td at a shorter interval to provide pertussis protection; the safety of intervals shorter than 2 years has been demonstrated and may be used – this would be a permissive recommendation;
3. Tdap is recommended for adults in close contact with infants < 6 months of age, and for women at preconception and post-partum, if not already vaccinated with Tdap; Tdap is encouraged for women of childbearing age at an implied shorter interval.

Contraindications and precautions. The Working Group retained the wording of the previous ACIP adolescent Tdap recommendation as follows:
Contraindications are unchanged and include a history of serious allergic reactions (anaphylaxis) and a history of encephalopathy within 7 days of receipt of a pertussis vaccine

Precautions and Reasons to Defer Tdap: The following are unchanged: Guillain-Barré Syndrome, moderate or severe acute illness or history of an Arthus hypersensitivity reaction following a prior dose of tetanus toxoid and/or diphtheria toxoid-containing vaccine. *Changes* were made to drop the term "progressive neurological conditions" in the adult patient population, since that could be applied to patients with dementia, Parkinson's disease, and other progressive conditions that are not precautions to Tdap, and replace with "unstable neurological condition (e.g., cerebrovascular event, acute encephalopathic condition, etc.)"

Conditions Not Contraindications or Precautions to Tdap Use: No change was made to these conditions from the adolescent statement. The reader is referred to the adolescent statement for changes from the pediatric contraindications. The standard wound management algorithm was retained, substituting Tdap for Td. Recommendations for non-simultaneous administration of Tdap was unchanged from the provisional adolescent recommendations.

- *Special situations.* The Working Group proposed the following: recommend Tdap during pertussis outbreaks or other settings of increased exposure, given the safety data. Health departments and physicians are allowed discretion on use of Tdap in such settings. Although not specifically indicated, health care settings could be inferred.
- *Prior pertussis*. In situations in which the patient had pertussis, Tdap should be administered if otherwise indicated for incomplete or unclear primary vaccination history. Tdap should be one of the three-dose primary series.
- *Sequencing. A* preference for simultaneous vaccination was proposed, with vaccines administered in any sequence when simultaneous vaccination is not feasible.
- *Adults ≥ 65 years of age.* There are no pre-licensure safety or immunogenicity data available; Tdap showed tetanus and diphtheria protection that was non-inferior compared with Td. The working group proposed that older adults not be included in the general recommendations; it be stated that there is no known risk to administration of Tdap in older adults.

Discussion:

- It can be clarified that the data support a vaccination interval of two years and, in certain circumstances, shorter than that. The U.S. Td post-licensure data suggest no excess serious local reactions among adults vaccinated at "short" intervals. While not

impossible, it is highly unlikely that many people would be hyper-immunized from annual boosters, as was seen in the 1950s and 1960s.

- Based on data indicating that infants have a higher rate of hospitalization to nine months, Dr. Neal Halsey suggested omitting the <6 month text and simply saying "infants."
- Dr. Middleman suggested dropping the text referencing the "next regularly scheduled booster," since use of a 2- or 5-year interval could lower incidence rates more quickly, and wondered whether the Working Group had considered a catch-up campaign.
- The Working Group considered giving pediatricians the option of immunizing mothers when they come in with their children, to use that infrastructure for pertussis as well as influenza. .
- Dr. Neuzil asked if the wording on infant contacts should include older adults, >64 years of age, who are not included in the routine recommendation (i.e., to include all ages). Dr. Kretsinger said that this situation was not specifically addressed, but the recommendation may be interpreted as permissive for Tdap among persons > 64 years.
- Dr. Michael Decker reported sanofi pasteur's intent to submit data to FDA on Tdap among adults ≥65 years of age to extend the license indication. Mr. Phil Hosbach assured that the vaccine supply should be sufficient. Although vaccine uptake is unpredictable, sanofi pasteur anticipated a recommendation for healthcare workers and key contacts.
- Dr. Nichol suggested consideration of alternative immunization settings for Tdap, as done for those offering pneumococcal vaccine.
- Dr. Sandra Hammer, of the state of California, commented that Tdap might take as long for the public to convert as it took to go from TT to Td. She urged the ACIP to do all in its power to encourage use of Tdap, particularly for wound management.

Public Comment

Ms. Pamela Durkin of Hatboro, Pennsylvania, spoke of her fourth son, Colin. He became ill with pertussis at age 5 weeks, and died four days after entering the hospital. She had followed the routine schedule for all her children, but did not know how contagious and dangerous pertussis could be. She recommended vaccination for all ages to control 'this real threat that affects real lives, with devastating consequences."

Proposed Recommendation

"The following sections present recommendations for the use of Tdap (ADACEL™, sanofi pasteur, Toronto, Ontario, Canada) for booster immunization against tetanus, diphtheria and pertussis among adults aged 19-64 years who have not received Tdap before. Tdap is licensed for use as a single dose.

"Adults should receive decennial Td boosters, beginning 10 years after Tdap, until guidance on subsequent Tdap doses is available (ACIP. MMWR 1991,40(RR-10):1-28). Recommendations for Tdap use among adolescents are described elsewhere (CDC, ACIP adolescent Tdap statement, 2006).

"Routine recommendations for adults: Adults who received their last dose of Td ≥ 10 years earlier should receive a single dose of Tdap to replace a single dose of Td, for booster immunization against tetanus, diphtheria and pertussis."

The ACIP accepted this text as presented.

"Shorter interval between Td and Tdap: Intervals shorter than 10 years since the last Td may be used to protect against pertussis. Particularly in settings that carry an increased risk of pertussis or its complications, the benefits of using a single dose of Tdap at shorter intervals to protect against pertussis generally outweigh the risk of local and systemic reactions after vaccination. The safety of intervals of approximately 2 years between Td and Tdap is supported by a Canadian study; shorter intervals may be used."

Discussion included:

- Dr. Middleman reiterated that recommending shorter intervals would be a stronger statement and more quickly affect the disease burden. Dr. Abramson rejoined that the statement gives the flexibility to do that, while clearly not advocating catch-up campaigns.
- Dr. Marcuse asked that wound management be specifically mentioned. Dr. Kretsinger pointed out that wound care is addressed in Section 3, Special Situations, but acknowledged the wish to move it up in the recommendation.

The recommendation continues:

"Prevention of pertussis exposure in infants aged < 6 months. Adults who have or who anticipate having close contact with an infant aged <6 months (e.g., parents, caregivers) should receive a single dose of Tdap to protect against pertussis if they have not received Tdap. Ideally, these adults should receive Tdap at least one month before beginning close contact with the infant.

"A 2-year interval between Td and Tdap is suggested to reduce the risk of local and systemic reactions after vaccination; shorter intervals may be used (See Shorter Interval, see Pregnancy Considerations)."

Discussion included:

- "Caregivers" is open to interpretation. If this term includes daycare providers, that should be explicitly stated.
- Dr. Baker supported post-pregnancy Tdap administration to take advantage of the existing infrastructure. And, with outbreaks already occurring in children's hospitals, she stressed the importance of exposure control. The AAP would not ask for a blanket recommendation on healthcare workers, but wished for specific attention for others such as daycare providers, as a large proportion of U.S. infants are in daycare full- or part-time. Dr. Murphy stated that healthcare workers will be addressed at a future date. Currently, the NIP is consulting with health care worker stakeholder organizations.
- Text changes suggested were: "… e.g., daycare or in-home care givers, etc.," "up to one year of age," and "adults of any age" (the latter to include grandparents), and "if or when licensed" referring to the vaccine.
- Dr. Pickering cautioned the committee about making a recommendation for adults older than 64 years of age when Tdap is unlicensed with few data in this age group. Dr. Baylor disagreed, citing FDA's encouragement that a recommendation be made by ACIP.

The recommendation continues:

"Women should receive a dose of Tdap as soon as feasible in the immediate post-partum period if they have not previously received Tdap.

"When possible, women should receive Tdap prior to conception. Since it is estimated that approximately half of all pregnancies in the United States are unplanned, any woman of childbearing age who might become pregnant is encouraged to receive a single dose of Tdap."

Discussion included advice that the text refer to "infants" in general (i.e., those aged <12 months), but with particular emphasis on those younger, such as the 0-2 month-olds with the highest mortality.

Contraindications. Recommended contraindications include:

- History of serious allergic reaction (i.e., anaphylaxis) to any component of the vaccine (Tdap)
- History of encephalopathy (e.g., coma, prolonged seizures) within 7 days of administration of a pertussis vaccine, that is not attributable to another identifiable cause. These individuals should receive Td instead of Tdap.

The ACIP accepted this text as presented..

Precautions. Proposed recommendations on precautions were as follow:

- Guillain-Barré Syndrome ≤6 weeks after a previous dose of a tetanus toxoid-containing vaccine.
- Moderate or severe acute illness with or without fever.
- Unstable neurological condition (e.g., cerebrovascular events, acute encephalopathic conditions).
- History of an Arthus hypersensitivity reaction following a prior dose of a tetanus toxoid and/or diphtheria toxoid-containing vaccine. A footnote advises consideration of "deferring Tdap or Td vaccination until 10 years after the last tetanus or diphtheria toxoid-containing vaccine."

The ACIP agreed to this text as presented.

*Other Conditions that are <u>Not</u> Contraindications or Precautions for Tdap***.**
The proposed recommendations included:

- Stable neurological disorder including well-controlled seizures, a history of seizure disorder that has resolved, and cerebral palsy.
- Brachial neuritis.
- Immunosuppression.
- Pregnancy (See Special Situations, Pregnancy).
- Breastfeeding.
- Intercurrent minor illness.
- Antibiotic use.
- History of extensive limb swelling (ELS) reactions following pediatric DTaP/DTP or Td that was not an Arthus reaction.
- "Certain systemic reactions following administration of pediatric DTP/DTaP are precautions for pediatric DTaP but not for Tdap (CDC ACIP adolescent Tdap statement, 2006)."

Discussion included Dr. Marcuse's suggestion that the last conditions be listed in the adult Tdap recommendations, rather than referencing the adolescent Tdap statement, for adult providers' quick referral.

Special Situations proposed recommendations included:

- *Outbreaks/increased exposure***:** Tdap at intervals shorter than 10 years may be considered; safety of intervals as short as approximately 2 years is supported. Further guidance on health-care workers will be considered by ACIP in the future.

The ACIP accepted this text as presented.

The recommendation continues:

- *Tetanus prophylaxis in wound management*: Tdap is preferred over Td if there was no prior Tdap administered and Tdap is available.
- *History of pertussis*: Tdap as otherwise indicated.
- *Adults with incomplete or unknown DTP/DTaP vaccination history:* Use a 3-dose primary series, and Tdap should replace <u>one</u> Td dose (Tdap is preferred for the first dose).

Proposed Special Situations, Non-simultaneous Vaccination with Tdap and Other Vaccines, including MCV4. The proposed recommendation was as follows:

> "ACIP states that inactivated vaccines may be administered at any time before or after a different inactivated or live vaccine, unless a contraindication exists (CDC, ACIP General recommendations 2002). Simultaneous administration of Tdap and MCV4 (which all contain diphtheria toxoid) during the same visit is preferred when both Tdap and MCV4 vaccines are indicated (CDC. 54, RR-7:2005, CDC. MMWR. 54.1-3. 2005). If simultaneous vaccination is not feasible (e.g., a vaccine is not available), MCV4 and Tdap can be administered in any sequence."

The ACIP accepted this text as presented which was identical to that of the adolescent recommendations:

Older Adults Aged <u>≥</u> 65 years. The proposed recommendation was as follows:

> "Tdap is not licensed for use among persons aged <u>≥</u> 65 years. There are no pre-licensure data on safety and immunogenicity in this population. There are no known risks to replacing Td with a single dose of Tdap among adults aged <u>≥</u> 65 years to provide protection against pertussis."

The ACIP accepted this text as presented.

Dr. Marcuse suggested, to general agreement, that the text on wound management, citing that the patient "can" receive, be changed to "should" receive to encourage rather than be permissive on the vaccine's use. Wound management would also be referenced at the beginning of the recommendation.

Dr. Finger **moved to accept the Tdap recommendations as amended**. Dr. Allos seconded the motion.

Vote

In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Treanor, Womeodu, Abramson
Opposed: None
Abstained: None

The vote passed.

Tdap Use in Pregnancy
Presenter: Dr. Trudy Murphy, NIP

Overview: There was divergence of opinion on the Working Group about the use of Tdap during pregnancy, to be discussed in greater depth at the February meeting. Language options as place holders until that later discussion were presented.

Option 1 Summary, Tdap during pregnancy to protect against tetanus

*"*Tdap is preferred to Td for protection against tetanus if ≥10 years since last tetanus toxoid-containing vaccine; Td is an acceptable alternative. Vaccination in the 2nd or 3rd trimester is preferred for both Tdap and Td. Providers are encouraged to report women vaccinated with Tdap during pregnancy to the sanofi pasteur registry."

Option 2 - Tdap during pregnancy for protection against tetanus and pertussis. There were no negative responses among the Working Group to the following language. Option 2 allows Tdap to be used at intervals <10 years after the last tetanus toxoid-containing vaccine, in settings with increased risk of maternal exposure to pertussis:

"For protection against tetanus, Tdap is preferred (Option 1). Tdap may be considered at intervals shorter than 10 years after the last tetanus toxoid containing vaccine in settings with increased risk of maternal exposure to pertussis."

Discussion:

- Dr. Keith Powell reported that the AAP's COID will issue a statement, either later this year or early next year, recommending Tdap for adolescents regardless of pregnancy status.
- While this text was not a recommendation, its wording on tetanus would be that of the adolescent recommendation (i.e., if tetanus protection is needed, Tdap can be given rather than Td). But if a tetanus booster is **not** needed (i.e., <10 years since last tetanus toxoid injection), Tdap may be considered for this shorter interval in settings of increased risk of maternal exposure to pertussis.
- Dr. Baker asked why pregnant teens were being addressed differently. Dr. Murphy explained that, since the pertinent data were not presented at the last meeting, the Working Group had planned to do present the information at this meeting. Approximately10% of U.S. births are to adolescent mothers. Data are insufficient to definitively resolve whether the vaccinated mother's high antibodies could interfere with the infant's immune response to the primary series of DTaP vaccine. The main problem is that pertussis, unlike other diseases, does not have a good correlate of protection; it is

not possible to know if antibody actively transported to the infant provides protection. These concerns will be discussed in February

- Dr. Wexler suggested, rather than "maternal exposure," saying "prenatal exposure," or, Dr. Baker suggested, "exposure to pertussis by pregnant women."

Dr. Morita **moved to accept Option 2 as a placeholder until the February meeting.** The motion was seconded by Mr. Beck

Vote
In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Treanor, Womeodu, Abramson
Opposed: None
Abstained: None

The vote passed.

Possible Association of MCV4 (Menactra®) with GBS
Presenter: Dr. John Iskander, on behalf of the Guillain-Barré Syndrome (GBS) Investigation Team (CDC, FDA, CISA Network)

Overview: VAERS reports of GBS after Menactra® vaccination; some key clinical and epidemiologic features; GBS incidence among 11-19 year-olds (internationally); planned controlled studies of the VAERS signal.

The quadrivalent meningococcal vaccine, Menactra,® was FDA-licensed in January 2005 for use in those aged 11-55 years. It is a polysaccharide-diphtheria toxoid conjugate vaccine comprising polysacharrides of meingococcal serogroups A, C, Y, and W-135. The ACIP in February recommended its routine use at the preadolescent visit and high school entry, among college freshmen living in dormitories, and for other high-risk groups (e.g., travelers, military recruits, immunodeficient individuals, and laboratory microbiologists).

Meningococcal disease occurs in a natural cycle, and 2005 is a trough year. The rate for 11-30 year-olds is ~0.5/100,000, and vaccination impact is not yet evident. By October 24, VAERS had recorded six cases of Guillain-Barré Syndrome (GBS) after Menactra® vaccination. These occurred in different states during June or July, and involved five different vaccine lots. Sanofi pasteur provided data on the 2.7 million Menactra® doses distributed through October 20, 2005. Because purchases have been restricted since late May, little vaccine is likely to have been stored. The four states reporting the first five GBS cases accounted for 24% percent of the doses distributed.

GBS is a serious neurologic disorder involving peripheral nerve demyelination. It begins with subacute but progressive, symmetrical weakness, along with areflexia. Sensory and/or cranial nerve abnormalities may emerge, and paralysis of respiratory muscles can ensue. About 5% of those afflicted die and ~20% of survivors may have prolonged disability. GBS can occur spontaneously or after antecedent events (e.g., infections or vaccinations), but up to 66% of cases in large case series studies identified no antecedent infection or other event. Of those that were found, *Campylobacter jejuni* infection preceded in 20%-40% of cases. GBS has also been linked to cytomegalovirus, Epstein-Barr virus and *Mycoplasma pneumoniae* infections.

Clinical and epidemiologic features. All the VAERS case report patients were 17-19 years old and all symptoms began 2-5 weeks after MCV4 vaccination. One patient had two prior episodes of post-vaccination (not meningococcal) GBS, and one had known acute illness (not gastrointestinal) before symptom onset. None had another known infectious etiology, but testing for infectious etiologies was limited. One patient was intubated. All have recovered or are recovering.

All these events occurred 2-6 weeks post-vaccination, paralleling the time course of GBS during the 1976-1977 swine influenza vaccination program. The latter's attributable risk was finally determined to be about 1:100,000. The two week latency of several cases is consistent with a causative role for vaccination, and is further supported by a statistical disproportionality of VAERS GBS reports after Menactra,® compared to other vaccines.

GBS incidence in 11-19 year-olds. Data from the VSD and the Health Care Utilization Project (HCUP, tracking hospitalization) indicate a GBS incidence of ~1-2/100,000 person-years. That rate is consistent across countries and seasons for this age group, making the GBS rate inferred from VAERS similar to the expected background rate. But the timing of symptom onset remains of concern and VAERS' underreporting is unknown. During the era in which oral poliovirus vaccine (OPV) was still used in the U.S., a study published in 1996 (Rosenthal and Chen, American Journal of Public Health) found that 68% of vaccine-associated paralytic poliomyelitis (VAPP) were reported to VAERS; as this is a clinical syndrome similar to GBS, that might be the upper confidence bound. The lower bound may parallel that of influenza vaccine-associated GBS studied with a capture/recapture methodology ─ ~5%.

Data relevant to this issue were outlined.

- Pre-licensure studies did not indicate any GBS incidence. VSD data were queried for any incident cases of GBS following administration of Menactra. No such cases were found at any VSD site; at two sampled sites, 85-95% of vaccines had at least six weeks of follow-up. However, such data cannot rule out a rare association, such as 1:100,000.
- U.K. data cover three different (tetanus-toxoid, nontoxic diphtheria toxin mutant, CRM) meningococcal C conjugate vaccines used between 1999-2005. Of 30 million doses to persons aged <18 years, only five GBS reports emerged from enhanced spontaneous reporting ─ significantly less than expected.

In view of insufficient evidence that MCV4 causes GBS and an ongoing risk of serious meningococcal disease, CDC advised continuation of the current vaccination strategies, except to avoid vaccination of persons not at high risk who had a prior history of GBS. The ongoing investigation was made part of the vaccine-risk communication process. CDC encouraged health departments to strengthen surveillance and to report possible cases of GBS after MCV4 vaccination to VAERS. GBS surveillance among adolescents was enhanced consistent with state and local disease-reporting guidelines. There are currently a small number of states in which GBS is a reportable condition.

Aside from the *MMWR* notice, Sanofi pasteur has written to providers, updates its web site information regularly, and has updated the package insert to add this possible association. A revised interim vaccine-information statement (VIS) has been disseminated.

MMWR reported in October another confirmed GBS case under investigation; one additional unreported case, with confirmed EBV infection, had onset >4 months after Menactra® administration. No additional GBS reports have been received by VAERS, although one confirmed and one suspected report of transverse myelitis were reported.

The interim GBS case definition developed by the GBS investigation team includes clinical case definitions stratified by levels of diagnostic certainty, clinical and laboratory elements, and a surveillance case definition to aid active case-finding, and will be disseminated to key partners and stakeholders.

Planned studies. This potential VAERS signal will be evaluated in several planned controlled studies: a national retrospective cohort study using multiple, large managed-care databases, and a national-case control and case-series analysis. Both the large cohort study and expanded active and case-finding surveillance will be used to identify cases.

The study protocol is in development and an oversight committee will review it. The primary objectives are to determine whether an association exists between GBS and Menactra® administration, and if so, to quantify the attributable risk. Secondary study objectives will assess non-vaccine risk factors for GBS and attempt to assess the degree of underreporting to VAERS of MCV4-associated GBS. Key communication resources were outlined, such as a new NIP Website portal and new links on the Sanofi pasteur site.

Discussion:

- Dr. Paul Offit asked about the post-administration timing for the confirmed transverse myelitis case (it was within the 2-6 week window), and whether transverse myelitis is part of the GBS investigation. Both are demyelinating diseases, one affecting the CNS and the other the peripheral nervous system. Dr. Iskander responded that the approach would focus on GBS, but also consider transverse myelitis.
- Dr. Allos raised GBS' year-to-year clustering, as well as its seasonality. She also noted that, although it has a culture-proven association with *Campylobacter*, infected individuals can be asymptomatic, so a diary of illness may not be valid. Finally, she commented that the cases' disease concentration in young males greatly paralleled that of *Campylobacter jejuni*. The sex, age, and seasonal similarities need to be examined before any conclusions can be drawn. Dr. Isakander clarified that the broader analysis smooths out incidence over geographic areas. While relatively little year-to-year variation arose, there were gross ecologic similarities between the groups that might be at risk for *Campylobacter* and GBS.
- Dr. Cherry noted the same similarities with enteroviruses and asked if serology looked for that. Dr. Iskander said that even the fairly large studies found no serologic antecedents to infection 60-70% of the time.. However, not all cases in VAERS had a full battery of tests and there were reporting delays. But, since the average GBS case does not have proven antecedent etiology, the absence of one on an individual level neither argues for nor against a vaccine etiology for that particular case.
- The encouragement to report GBS cases produced almost no increase. The signal could have been false or could represent a rare association on the order of 1/100,00 or less

- Dr. Baker congratulated CDC for its response to this signal. She asked what the set point for the attributable risk would be to determine that this was a vaccine-associated event, rare as it is. Frank DeStefano, of the Immunization Safety Office, related that perhaps ~200 GBS cases have occurred in the ~6 months since the vaccine's release. Even if all those cases could be enrolled, at best the detectable relative risk would range from 2.0 to 4.0. More realistically, the 50-100 cases that may emerge from the large managed-care organization and extensive case finding could produce a relative risk of 5.0-10.0. While there may not be sufficient power to determine a statistically significant association, there may be enough to set an upper bound.
- Dr. Turner reported the ACHA's email about the enhanced GBS-Menactra® surveillance to their college health associates. No cases were reported among the ~6-7 million college students in their care. He offered access to the ACHA's large centralized database of several million students for future CDC studies.
- Dr. Geoff Evans asked about the role of CISA, a CDC-funded group of academic vaccine specialists who conduct case-level investigations. They act as CDC's "clinical eyes and ears" to accumulate the best possible case histories and case reviews, operating in a research framework and an informed consent setting. If there are no reporting delays, they can get critical information such as serologic samples, but it is very hard to get real time information. The IOM found a possible association between tetanus toxoids and brachial neuritis and GBS through a case series approach, but it cannot be shown in controlled studies. Investigation at the individual patient level may be needed to find patient level risk factors, if that cannot be done on a population level. Another approach that could be of value is to proceed from the genetics perspective. Dr. Colin Marchant, a CISA investigator at Boston Medical Center, reported protocols under development to look intensively at other cases and this current case, using both genetics and immunology.
- Dr. Phil LaRussa, of Columbia University, asked how many cases would be necessary to exceed the background rate. Dr. Iskander replied "nine,", but added that that would not change the qualitative conclusion.

Update on Isolation of Vaccine-Derived Polioviruses from Five Children in Minnesota
Presenter: Dr. Harry Hull, State Epidemiologist, Minnesota Department of Health

Overview: Minnesota's response to detection of vaccine-derived polioviruses

An investigation of a poliovirus infection in Minnesota was begun when the state laboratory isolated a vaccine-derived poliovirus from a seven-month-old Amish girl. The child had three healthy siblings, and she had traveled to Wisconsin to visit relatives at age two months. From age five months, she was repeatedly ill with fevers, diarrhea, pneumonia, conjunctivitis, and bronchiolitis. After numerous hospitalizations (attended by her mother and grandmother, who changed her diapers) and outpatient visits, she was admitted at the age of 6 months to a Twin Cities children's hospital. The child was diagnosed to have severe combined immunodeficiency (SCID), and is scheduled to undergo bone marrow transplantation. Viral culture of her stools was positive for a poliovirus, which was determined to be a vaccine-derived poliovirus (VDPV), with 2.3% divergence from the Sabin (vaccine) poliovirus.

Because polioviruses mutate at ~1% a year, CDC epidemiologists and virologists suspected that the virus may have originated from a child who had received oral poliovirus vaccine (OPV) 2-3

years previously. Laboratory data also indicated that this virus has been replicating in at least one other immune-deficient person who was on IGIV therapy. Because administration of OPV in the U.S. was discontinued in 2000, the originating child must have received it in a country that is still using OPV. It appeared to have come from an immunodeficient individual, but how this child was infected remains unclear.

Health Department staff members explored whether there was evidence of transmission within the small Amish community of 24 families in which the index child resided. Door-to-door requests for stool cultures and sera yielded four positive cultures in addition to the index child, among three families. The contact may have occurred in school, where the water supply was inadequate and outhouses were used. Genetic sequencing of the subsequent isolates suggested that the virus had circulated in the community for ~2 months.

Thirty-five patients and 23 staff were tracked from the child's hospitalizations, but cultures were negative. Look-backs at other hospitals she visited detected no other individuals with illness consistent with poliovirus infection. Because the child was already infected on admission to the Children's Hospital, Health Department staff searched for immunosuppressed individuals on the staff of these hospitals or in the medical community, but found no immunosuppressed individuals among healthcare workers. In the Amish community surrounding the index patient, Some children were rumored to have died in infancy, but that seems not to be unusual in the Amish population. This child was the 29th documented immunocomprised person in the United States to be infected with poliovirus. Most of the other immunocompromised persons were hypogammaglobulinemic and were chronically infected with poliovirus, and some of those were diagnosed only when they developed vaccine-associated paralytic polio (VAPP).

Control measures. The risk of spread of the VDPV to the general public was felt to be minimal, because 98% of Minnesota schoolchildren are vaccinated and therefore presumed to have immunity to polioviruses. This Amish community was receptive to immunization; 53 individuals in nine families were vaccinated, and 14 adults had previously received OPV. Both parents of this child had been immunized previously.

Concern remains regarding the possibility of polio transmission within the Amish communities nationwide and abroad. The Amish travel nationally and often gather from across the country (as well as in and from other countries with large Amish populations, e.g. Canada) for special occasions such as large weddings. The Minnesota Health Department is working with local health departments to identify all the Amish communities in seven Minnesota counties and to immunize them. Response has been variable. Some entire communities and schools have volunteered for vaccination; in other communities, only 25%-50% of people have been immunized. It was fortunate that the hospital that took the viral culture routinely sends all enteroviruses to the Minnesota State Laboratory for typing; this is not necessarily standard practice across the country.

Dr. Jane Seward reported CDC's role in coordinating information-sharing across all states in the country and internationally, especially Canada. CDC staff have also been working with the WHO to explore the availability of monovalent OPV for an emergency IND, if needed for an outbreak. CSTE has held two national conference calls to share information, and Health Canada has participated. Dr. Seward outlined the tracking done of the parents and grandparents involved in this case, from Michigan, Wisconsin, and Ontario. Cultures and blood test results are pending.

An *MMWR Dispatch* was published on October 14 to increase awareness in the states of an increased risk of poliovirus transmission in unvaccinated communities. CDC has called for heightened surveillance for clinically compatible syndromes (e.g., acute flaccid paralysis, GBS, transverse myelitis), and collection of specimens. Information on EpiX is being updated and PAHO and European nationals have been informed due to transmission risk during travel.

Discussion:

- If this virus was one of the strains that has circulated in under-vaccinated communities, it would not have the mutation found. Vaccinated individuals can be transiently infected with polioviruses, but they excrete it for very short periods of time at low titers, so a virus circulating in the U.S. for long periods of time seems improbable. OPV may be more effective in halting circulation, but IPV does so as well. None of the five individuals documented as infected have developed paralysis. Nonetheless, the response has been aggressive because the virus is considered to be as virulent and transmissible as a wild poliovirus. It is also the first time a circulating vaccine-derived polio virus has been isolated in an immunodeficient person who had not traveled overseas or been vaccinated overseas. This seven-month-old child had no apparent contact with anyone from abroad, and the virus appears to be of a genetic derivation that arose well before this child was born.
- Dr. Katz commented that most of the source cases are now vaccine-related, and with jet travel, a person vaccinated in the last 2-3 weeks could easily enter the U.S. still shedding the virus. The IOM was planning to discuss this the following week, including whether antivirals could be used in cases such as this.
- Dr. Seward reported CDC's close work with the FDA on this child's treatment. FDA was very helpful in identifying and arranging one-day delivery of an IVIG product with high titer, type 1 polio antibodies.
- Dr. Halsey commented that all the OPV viruses in the human intestine can revert back to the wild type in terms of neurovirulence, with only a 1% divergence from the vaccine type. That is the essential difference from the virus shed by a child vaccinated two weeks earlier. He recommended a detailed 2005 review article on VDPVs (Kew et al, *Annu Rev Microbio* 59:587-635).
- NIP is planning a cost analysis of the investigations with all the states involved, to further persuade the public of the benefits of immunization.

PUBLIC COMMENT

Dr. Stan Plotkin warned of a "public health disaster," which he defined as "when a means of prevention goes unused, owing to a failure of the system to appreciate the seriousness of an endemic or epidemic disease." The disaster of which he spoke was Lyme disease. His son developed a rash that resolved, but days later he collapsed while walking his dog. The hospital diagnosed Lyme disease.

GSK withdrew its Lyme vaccine, Lymerix, ® after a "tepid ACIP recommendation" but, he emphasized, the FDA had licensed the vaccine as effective and safe. It was Dr. Plotkin's opinion that decisions on vaccine use should be based on individuals' assessment of their own exposure risk to ticks.

The ACIP recommendation advised that vaccination against Lyme disease *should* be considered for persons aged 15-70 years who engage in activities that result in frequent or prolonged

exposure to tick habitats. Vaccination *may* be considered for persons aged 15-70 years exposed to tick-infested habitat but for whom exposure is neither frequent nor prolonged. The benefit of vaccination beyond that provided by basic personal protection and early diagnosis and treatment of infection is uncertain.

In 2004, there were 18,500 cases of Lyme disease in the U.S., at least 4500 in Pennsylvania alone, where some counties have reported rate exceeding 150/100,000. Safety problems identified with Lymerix® were being studied by GSK, as is done with all new vaccines. Ironically, he noted, there is a commercial Lyme vaccine sold for dogs. He related all this to questions of "life style vaccines." Vaccination is done for West Nile disease, which causes fewer total cases, and Lyme vaccination compares favorably to the cost-benefit of other vaccines.

Dr. Plotkin suggested that the ACIP reestablish a Lyme Working Group to solicit interest from manufacturers, or that NVAC be asked to examine this and report back to the ACIP. At least one company is developing a new vaccine, and two companies can produce the old vaccine.

Mr. Peter Khoury, of Baxter Healthcare, reported their development of a chimeric Os-A vaccine to prevent Lyme disease, in collaboration with Stonybrook University and the Brookhaven national labs, which should be in trials in 2006.

Mr. Andrew McNight, of GSK, stated that GSK withdrew Lymerix® in 2002 due to poor sales, in part because Lyme disease was not well understood by the public. GSK was proud that their vaccine's development had advanced public awareness and the science in that regard. Nonetheless, when it was estimated that <10,000 people would be vaccinated in 2002, they decided that their resources could be better used elsewhere,

With no further comment, the meeting adjourned at 6:10 p.m., and reconvened on the following morning at 8:00 a.m.

OCTOBER 27, 2005

VFC VOTE ON HEPATITIS A VACCINE

Presenter: Dr. Gregory Wallace, NIP

Changes to be voted on, for the recommendation for routine vaccination with hepatitis A vaccine in the Vaccines for Children program, were as follow:

- Clarification, by the asterisk under Eligible Groups, that Havrix® and Vaqta® are licensed for persons aged ≥12 months.
- Clarification, also asterisked, that all children should be vaccinated at one year of age (i.e., 12-23 months).
- Routine catch-up or vaccination of those older is not being recommended, but those not vaccinated by age two years can be vaccinated in subsequent visits. Continued routine vaccination of those aged >1 year in areas where it is currently recommended is encouraged.
- Clarification that the minimum age for vaccination is 12 months.

Dr. Ban Allos **moved to approve the VFC resolution as presented.** Mr. Beck seconded the motion.

Vote
In favor: Allos, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Womeodu, Abramson.
Opposed: None
Abstained: Treanor (conflict).

The vote passed.

UNIVERSAL INFLUENZA VACCINATION
Presenters: Dr. Walter Orenstein, Emory University School of Public Health and Dr. Ben Schwartz, NVPO

Overview: Influenza vaccination strategies, information gaps, challenges to implementation of universal vaccination, Canadian data.

Emory University, CDC and the NVPO called a meeting of government, professional medical societies, academia, school health, and industry to discuss the possibility of universal influenza vaccination. Although influenza vaccination coverage has improved, its mortality, hospitalizations and morbidity continue to be a burden. The present strategy is focused on persons at high risk of complications from influenza, particularly those ≥65 years, but this meeting discussed others aged 2-49 years. This group is not currently recommended for universal immunization, but 4%-44% already are vaccinated, being household contacts and others of high-risk individuals.

Presentations were provided on the disease burden and program impact, information gaps and possible studies, and proposed potential strategies to phase in universal vaccination. Consideration of expanded influenza vaccination is being driven by the continued disease burden, particularly among the elderly and those at high risk; by low coverage among some of the recommended populations; and by the need to increase disease prevention and cost savings, strengthen the public health infrastructure, and improve pandemic preparedness.

The information gaps identified in the science of influenza and its prevention were:
- Whether current influenza vaccine antigen content is optimal for elderly populations and if it should differ according to population (e.g., LAIVC or TIV vaccine type).
- Influenza disease burden and program impacts.
- Indirect effects of vaccination.
- Safety/effectiveness of repeated annual vaccination.
- Cost- and prevention effectiveness.

Despite these gaps, several findings are well supported: the validity of a "U" shaped curve for hospitalization and mortality, significant illness burden throughout the population, higher rates in children than adults, a substantial role of children in transmission, reasonable VE in children and healthy adults, and better than reasonable VE among the elderly.

The challenges to implementation of universal influenza vaccination include a greater burden on the public health infrastructure and resources, since more doses of influenza vaccine would be delivered than all other vaccines combined. Universal vaccination may impose unintended opportunity costs to both current and new vaccines. The site of vaccine delivery was discussed, since this expansion would place a considerable burden on medical homes. Vaccinating in schools has its own set of challenges, as do other possible settings, and the role of public health in vaccine delivery is unclear.

Even without universal vaccination, there have been supply interruptions in the past, and the supply and demand issues are not likely to disappear in the time needed for manufacturers to build their production capacity. The public sector's purchasing (or assured purchase) role continues to be debated. Public and health care sector acceptance will be essential to success, as will be settling the questions of financing. Ethical issues to ensure equitable distribution to all sectors of the population will require attention.

The experience was shared of Ontario's universal influenza vaccination program, instituted in 2000. The program has increased vaccine coverage in all age groups surveyed (although there are no data on those aged <12 years) and lowered respiratory disease hospitalizations in all age groups. A media campaign facilitated its general acceptance. Further evaluations are being done. Still to be determined are the program's impact on disease in children, its indirect effects, the potential of a coverage plateau, and the need for funding support and new delivery strategies. This program was implemented as part of their standard coverage without new funding.

In general, the expansion to universal vaccination was favored by all involved. Many of the latter at this meeting favored a stepwise approach to implementation, which could be more realistically consistent with vaccine supply. The approach would begin with universal vaccination of children, where there may be greater direct and indirect effects.

Several factors were acknowledged in the discussion of potential implementation strategies:

- Improved coverage among the elderly and those at high risk must continue.
- Monitoring of the implementation and its impacts must continue, with improved surveillance and diagnosis/diagnostic testing.
- A reassessment of the disease burden and the cost effectiveness of expanded vaccination in adults (after the initial pediatric focus) should be done.

Discussion:

- Dr. Cochi's commented that the consolidation and extension of discussions of the last few years is a clear signal to ACIP and the Influenza Working Group of a consensus to begin moving forward in a phased manner to expand influenza vaccination in the U.S. Vaccine supply remains a "third rail," but indications are that >100 million doses will be produced next year. The Influenza Working Group will continue to discuss these matters.

HARMONIZED SCHEDULE

Presenter: Dr. Julie Morita, Harmonized Schedule Working Group Chair

Overview: Time line of the Working Group meetings, its members and consultants; proposed new harmonized schedule

Since its formation in February 2005, the Working Group has held monthly conference calls. The members revised the graphic and footnote portions of the harmonized schedule based on recommendations made over the last year. Revisions were reviewed by the CDC leads of the hepatitis, pertussis, meningococcal and influenza Working Groups.

The committee was provided with two different versions of the schedule, addressing first the second draft of the universal hepatitis recommendations. A few edits to the hepatitis A footnote provided at this meeting would be incorporated later as well.

General format changes to the childhood schedule included:

- Format: Adolescent ages were redefined to include the 15 year-old quadrivalent meningococcal vaccine recommendation. The age groups were previously delineated as 11-12, 13-18.
- Yellow bars that denoted a single point in time were removed, because they were intended to represent a range of recommended ages when they should be administered.
- Doses of vaccines hepatitis B and Hib vaccines that were permissible but not required (depending on the vaccine used), were italicized.

Changes made to the childhood/adolescent schedule, by vaccine, were:

- The graphic and footnote for hepatitis B were altered to recommend strongly the birth dose, rather than extending from birth to age 1-2 months. There is stronger language for administering the birth dose, based on the mother's maternal hepatitis B surface antigen status.
- The graphic and footnotes for tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap) were modified to replace tetanus and diphtheria toxoids (Td) for routine vaccination at age 11-12 years and catch-up at age 13-18 years.
- The graphic and footnote for meningococcal vaccine were modified to recommend routine vaccination with MCV4 at age 11-12 years and at age 15 for those still unvaccinated. The use of MPSV4 and MCV4 among special populations was included, and marked with a pink broken line that is now used to denote vaccinations routinely recommended for selected populations.
- The influenza vaccine footnote was updated to include the new risk groups of persons with conditions that can compromise respiratory function, and persons handling respiratory secretions. The *MMWR* reference was updated .
- Hepatitis A's bar for a new universal routine recommendation extends from age 12-23 months with no routine catch-up recommendation.

The *catch-up schedule* was modified as follows:

- The footnote for hepatitis B catch-up for children aged 7-19 years was simplified to advise administering the three-dose series to all unvaccinated children and adolescents aged <19 years.
- The Td recommendations were simplified to define the minimum interval for a vaccination, depending on the age of the first dose and the current age of the person being vaccinated. This allows for catch-up, including Tdap as one dose when an unvaccinated child is vaccinated.

Discussion:

- The special population indication for MCV4 did not extend back to age 11 because all children should be receiving it. However, those aged 12-14 years are not covered by the routine recommendation, nor are those aged 16-18 years. To show that, a dotted line indicated that only selected populations in those groups would receive MCV4.
- Dr. Middleman discussed the delineation of 11-12 year-olds as "pre-adolescent" and, essentially, treating them differently than the rest of the population. There is no similar variation for the 4-6 year-old group's pre-K visit. She suggested that the schedule be updated to parallel the advances in the field of adolescent medicine. The standard terminology is "early adolescent," but not every child enters the stages of adolescence at the same age. She strongly recommended eliminating the developmental terminology for 11-12 year-olds, as was done for the other age groups, as well as the purple bar denoting them. Considerations offered by the committee included:
  - The 11-12 year-old visit should be highlighted to ensure attention to the necessity of that visit, the importance of which may not be recalled by parents as easily as those of early childhood. However, Dr. Middleman hoped that pediatricians and physicians would consider catch-up at all ages.
  - The schedule is admittedly complex, and will be field tested.
  - Dr. Wallace stated that the purple bar is a visual method of emphasizing the recommended routine visit at age 11-12 years. NIP is also considering a field test of separate adolescent and childhood schedules, in view of the growing adolescent schedule.
  - Dr. Baker reported the AAP's decision to use the descriptor "young adolescent" for this age group, rather than "preadolescent."
- It was clarified that the hepatitis A and B bars differed to comply with the previous day's vote to allow, without a specific catch-up recommendation, immunization of unvaccinated children aged 12-23 months with hepatitis A vaccine before preschool or school entry.
- Dr. Helms expressed concern that people with color blindness may not be able to see the entire schedule.
- Dr. Friedland, of GSK, advised attention during the schedule's field test to the readers' comprehension of the time period of the bars. For example, he cited the DTaP bar's ending at 24 months, but it should be given at 15 to 18 months. Dr. Morita responded that this is a problem with other vaccines as well (e.g., influenza's recommendation is from 6 to 23 months). Since one schedule cannot give that level of detail and remain readable, complete detail is provided in the footnotes.
- Dr. Whitley-Williams noted the recommendation to vaccinate adolescents at high school entry. She suggested a focus on "unvaccinated adolescents" instead, since not all adolescents may be in high school and in view of states' varying vaccination mandates. Dr. Abramson agreed; this was another reason to move from descriptive terminology and toward the use of age groups as descriptors.

Dr. Allos **moved to accept the harmonized schedule**, with edits to change the terminology from developmental to age-based, and retaining the purple bar. Dr. Gilsdorf seconded the motion.

Discussion:

- Dr. Wallace reminded the committee that the schedule should not be used to change recommendations; that should be done independently.
- Dr. Lieu favored conforming the schedule to the AAP's language.
- Dr. Naus thought that finalizing the schedule before field testing would be premature. However, Dr. Pickering noted the necessity of a rapid turnaround, since the harmonized schedule must be approved by the AAP and AAFP as well.
- Dr. Cochi saw the purple bar's intent as to highlight the increasing importance of this visit for immunization as part of the adolescent visit, and to point out somehow that this is not a usual visit. Several members agreed that emphasis was needed, particularly since this period of time also will be the entrée for pending new vaccines. Dr. Tan stated the AMA's support of a specific delineation for the 11-12 year-old visit on the schedule.
- Dr. Middleman agreed that the purple bar highlighted a visit that has been recommended for several years by the AAP and AAFP. She requested clarification that this approach be used for all ages, to guide providers during healthcare visits that are not solely for immunization.
- Dr. Barbara Kuter, of Merck, suggested further harmonization of the MMR and varicella lines, to accommodate the new MMRV vaccine.
- Ms. Murphy supported the use of the purple bar to highlight the visit at age 11-12 years, particularly since the vaccinator is generally the nurse or other staff, not the physician.
- Dr. Middleman agreed to the schedule with the age definition replacing a developmental terminology.

Vote
In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Treanor, Womeodu, Abramson
Opposed: None
Abstained: None

The vote passed.

ROTAVIRUS

Background
Presenter: Dr. John Treanor, Chair, Rotavirus Working Group Report

Overview: Background of ACIP recommendations regarding rotavirus vaccines; CDC economic analysis; draft recommendations; in preparation for likely February 2006 recommendation vote.

The ACIP recommended universal rotavirus vaccination to address the disease burden of rotavirus disease. Another ACIP vote to recommend a rotavirus vaccine may be taken in February 2006. The disease impact estimates have not changed since last the ACIP decision, except perhaps to correct a slight underestimation. The disease burden is still significant in terms of total cases and their impact on families, hospitalizations, and deaths.

Merck has developed a new vaccine that is perhaps safer, with lower rates of excretion in stool, absence of intussusception, and lower rates of side effects such as diarrhea, vomiting, and fever. Efficacy is high in the prevention of rotavirus gastroenteritis of all levels of severity and in the prevention of related hospitalizations and utilization of medical services. A draft of the Working Group's findings will be sent to ACIP members as soon as possible for their comment. The proposed recommendation should be ready when the vaccine is licensed, probably in February.

Cost Effectiveness of Rotavirus Vaccine
Presenter: Dr. Marc-Alain Widdowson, NCID

Overview: Cost Effectiveness analysis methodology, disease burden data, data sources used, analysis results.

The last cost effectiveness (CE) analysis of rotavirus vaccination was done in 1998. An update was needed to assess the anticipated new vaccine and its different biologics, to include current disease burden estimates, and the cost of the vaccination's possible side effects. New techniques were also in hand with which to model data uncertainty.

Methodology. A fictitious cohort of 100,000 children was followed from birth to age five years. The number of likely rotavirus cases was calculated, as was the number of outcomes if the cohort was fully vaccinated at 2, 4, and 6 months. The medical and non-medical costs for each outcome were estimated, along with the cost of a vaccine program and that of potential adverse reactions. This produced a cost-effectiveness ratio (net savings minus net program costs divided by the number of outcomes saved) for any one outcome. The CE ratio was calculated from the perspective of the health-care payer (including only medical cost savings) and the societal perspective (including medical and non-medical cost savings).

A probabilistic Monte Carlo distribution technique was used to calculate multiple variables of disease burden distribution, multiplied by cost, to produce values for the median, 5^{th} and 95^{th} percentiles. This is done hundreds of times until the final distribution is a stable result.

Disease burden. The model first assumed that 75% of the cohort has one episode of rotavirus diarrhea by age five years. From that total is subtracted the number who die or have nonfatal outcomes requiring health care (e.g., hospitalization, ED, outpatient, and physician visits). The residual number is the number of rotavirus disease episodes not requiring any medical care. Distributions were charted of rotavirus cases and rotavirus deaths in children from birth to 5 years.

Data sources and their use were charted.

- To estimate the number of episodes that would require healthcare, NCHS data from 1992-2002 were used to calculate the cumulative probability of a healthcare visit for diarrhea attributable to rotavirus, from birth to age five years.
- The MarketScan database provided four years of employer medical cost data representing ~5 million enrollees. That was discounted by 3% for the societal and health-care perspectives. A chart of the disease model input illustrated the estimated number of cases equivalent in the U.S. birth cohort.
- Bureau of Labor Statistics data were used to chart the median, mean, and range of non-medical cost data.

- Vaccine efficacy inputs were based on data from Merck's (public domain) clinical trial.
- The program costs used were illustrative only. The hypothetical vaccine price was derived from the cost of the three required doses of oral rotavirus vaccine, plus an assumed $10/dose administration factor, and an assumed cost for adverse reactions. The latter assumed a small risk of intussusception (or something similar), estimated at 1:50,000 vaccinees. The overall impact on the model of intussusception was ~$0.25.

Analysis results were presented and diagramed, assuming 100% compliance.

- *Health care perspective*. Vaccination resulted in an estimated 63% reduction of all rotavirus diarrhea cases.. It was also estimated that hospitalizations would decrease by 79%. The CE ratio per case averted from the health-care perspective was charted against total cost per vaccinee, with the breakeven threshold (when cost just equals benefits) at $67total cost per vaccinee (range of $37-$149). Above $67 total cost per vaccinee, the vaccine is likely to have a net cost from the health-care perspective.
- *Societal perspective.* The significant impact of days lost from work was clear in the charted results. The breakeven threshold was $167 per vaccinee (three doses and administration costs), with a range of $110 (or $41 for children) to $241. Net costs are increasingly likely above $157 total cost per vaccinee. When considering the outcome of costs per life year saved, the breakeven threshold values were similar to those calculated when considering cost-per-case averted as the outcome. However, whenever the thresholds were exceeded, the net cost per life year saved was approximately 1,000 times greater than the net cost per case averted.

The charted data of a sensitivity analysis demonstrated the dominance, , of hospitalization and ED visits. From a baseline of days of work lost, 50% more and 50% fewer days lost were factored to assess the societal impact. The result increased and reduced the baseline best-case estimate for the two different inputs by $32, which remained within the baseline estimate's 5th and 95th percentiles.

The analysis' conclusions were that, with 100% compliance with rotavirus vaccination, the rate of rotavirus-attributable diarrhea would drop an estimated 63%, and related hospitalizations by 79%. There would likely be a net cost from the health-care perspective whenever vaccination cost exceeds $67 per vaccinee,. From the societal perspective, a cost of vaccination exceeding $157 per vaccinee will likely pose a net cost to society,.

Rotavirus Vaccination Related To Other Selected Childhood Immunizations
Presenter: Dr. Martin Meltzer, NCID

> Overview: CE of rotavirus vaccination compared to MMR, DTaP, hepatitis B, varicella, pneumococcal conjugate and IPV vaccination.

In general, the newer vaccines are less cost saving than older vaccines. Because most averted rotavirus cases are uncomplicated, rotavirus vaccine's cost per QALY averted is likely to exceed that of meningococcal vaccine (which is $138,000/ QALY averted). In terms of $ per case averted, the cost of rotavirus vaccinations will be between that of pneumococcal and pertussis vaccinations.

One way to measure the values placed by society on an intervention is to calculate the time trade-off that is acceptable to avoid the disease's effect on daily life, versus that to avoid a vaccine's adverse effects. When the trade-offs to uncomplicated influenza cases and vaccine adverse events are compared, little time would be traded for the former while for the latter, long periods would be sacrificed. This indicates that those surveyed did not value greatly, in the units considered, avoiding an uncomplicated case of influenza, but greatly value avoiding vaccine-related side effects – even though the latter are very rare (and the low probability of such vaccine-related side effects was carefully explained to those surveyed). Including the value of time lost from work, a median of approximately $150/vaccination cost for rotavirus would not likely be cost saving. When the value of avoiding vaccine related side effects is added to the analyses, the use of the vaccine becomes even less cost effective. Data supporting the idea that the public greatly values avoiding vaccine-related side effects, however small the probabilities of such events, can be drawn from several vaccine experiences (e.g., smallpox, swine flu, GBS, the move from DTwP to DTaP, and from live to inactivated polio vaccine).

Anonymous peer review of this analysis was mostly positive, although some critical suggestions are now being examined. Those include clarification of methods, allowance for regional differences in rates (lost wages, reimbursements rather than true costs), and inclusion of the impact of herd effects.

Discussion*:*

- General appreciation of this analysis was expressed by the committee.
- Dr. Treanor related the Working Group's thinking that, beyond the important economic factors, a vaccine recommendation is based on the ability to reduce case totals. He found it hard to believe that parents would not value prevention of a case. If that were so, they would not even take the child to the doctor.
- The assumption that only 75% of children will have at least one case of rotavirus by age five was thought to be conservative. Dr. Widdowson clarified that that the proportion of children having at least one episode of rotavirus diarrhea by the age of 5 years ranges from 65% to 95%, but even at those ranges, the model's results changed little.
- Dr. Offit agreed that the difficulty in finding a child aged <5 years who is seronegative suggests that the assumption of 2.7 million cases of rotavirus per year is an underestimate. Current studies by David Matson are likely to demonstrate that. He also questioned estimating the vaccine's cost between that for pneumococcus and pertussis, when it has not yet been priced.
- Dr. Plotkin asked why the model's 79% hospitalization reduction was so much lower than the most valid figure to date, from the REST study, of 97%. Dr. Widdowson explained that the REST figure was for vaccine efficacy, which would not include children aged <6 months who are unvaccinated. Including them dropped the VE. Dr. Plotkin objected that this risked an incorrect inference of lower vaccine efficacy. He also noted that the numbers of the analysis indicate rotavirus vaccine to be a reasonable investment, and he questioned the analysis' value in any decision about using the vaccine.
- Dr. Laura York, of Wyeth Pharmaceuticals, noted that the characterization of the cost of pneumococcal vaccination stemmed from older economic studies, which would likely have a different conclusion today. She urged inclusion to this analysis of the

herd immunity effect and a more holistic view of vaccines' beneficial impact on communities as a whole.

- Dr. Lieu appreciated the thoughtful and methodologically well-constructed analysis. However, she expected the current information to be inadequate for an ACIP decision. The unknown vaccine price defeats any realistic CE determination, and the cost per case (termed by Dr. Meltzer as between pneumococcus and pertussis,) will not be clear to many but clinicians who know those illnesses' severity, so those relative values remain unclear. While economics are not the dominant factor in ACIP decisions, this analysis needs to go further to be more useful. The time trade-off, for example, includes a tremendous variation among people relative to prevented influenza. That is true for most minor illness, but when the illness' complications are presented (e.g., otitis media or pneumonia), they raise the time value traded. The study needs to be more systematic and refined to address rotavirus in particular.
- Dr. Roger Glass, of CDC, pointed out that epidemiologic data indicate the asymptomatic character of infections in the first two months of life. Since those are not counted, there is no 100% disease incidence measured. He also noted that this vaccine requires three doses to be fully effective. That is not completed until 6 months of age, leaving the infant potentially vulnerable over three rotavirus seasons.
- Dr. Penny Heaton, of Merck, clarified that their REST efficacy studies were of children vaccinated year-round, so they would be protected through the current and following season.

Draft Recommendations for Pentavalent Bovine-Human Rotavirus (PRV) Vaccine

Presenter: Dr. Umesh Parashar, NCID, for the ACIP Rotavirus Working Group

Overview: Background on rotavirus vaccine (PRV) development, vaccine characteristics; draft recommendations: contraindications, precautions, special situations.

PRV, under the trade name Rotateq®, is an oral vaccine with a two-year shelf life when refrigerated. It contains five human bovine reassortants (a human P and four common human G serotypes) that are premixed with a buffer that resists gastric acid. It can be given orally to infants and the full series consists of 3 doses. The first of the three doses can be given at 6-12 weeks of age, and two subsequent doses at 1-2 month intervals after the preceding dose.

Rotavirus Efficacy and Safety (REST trial. The 2001-2005 PRV clinical trial included slightly more than 70,000 infants aged 6-12 weeks. Results are summarized as follows:

- *Overall VE* monitored among 7000 infants for all outcomes was 74%, and 98% for severe disease outcomes (e.g., dehydration, hospitalization). Efficacy in reducing healthcare utilization was measured by hospitalizations and emergency department (ED) visits among all 70,000, and office visits in a subset. More than 90% of hospitalizations and ED visits were eliminated, as were ~85% of office visits.
- *Intussusception* was monitored for 42 days following vaccination; six cases were identified in vaccinees and five cases in placebo recipients. Because the first few weeks after dose 1 was the critical window for intussusception clustering with Rotashield®, that period was closely studied. No cases of intussusception were observed in the REST trial among vaccine recipients after dose 1, and a few cases were observed following doses 2 and 3. The overall relative risk was calculated at 1.6; the confidence interval included 1.0 but was not statistically significant. The trial concluded that the vaccine was not

associated with intussusception among the infants in this trial.

Working Group discussions. Three options for recommendations were discussed: routine or universal use, a permissive recommendation, and a targeted high-risk recommendation. The Working Group suggested recommending routine immunization of infants with three doses at 2, 4, and 6 months of age, based on the large disease burden, particularly of hospitalizations, among U.S. children. One in 70 children will be hospitalized by age 5 years, constituting 5% of pediatric (to age 5) hospitalizations (total of 55,000-70,000 rotavirus hospitalizations each year).

Risk groups for severe rotavirus disease include low-birth weight or premature infants and certain maternal social characteristics (youth, smoking, unmarried). However, limiting vaccination to these risk groups would exclude a large number of infants who develop severe rotavirus disease requiring hospitalization, so a targeted vaccination strategy is not a practical option.

Draft Recommendations. Dose 1 should be limited to the age given during the REST trial (6-12 weeks of age) since vaccine safety was not evaluated for Dose 1 among those aged >12 weeks, whose background rates of intussusception and natural disease are higher. The second and third doses should be given within the first year of life, with a four-week minimum interval between doses, as in the REST trial.

To resolve the quandary that the narrow dose 1 window might exclude the many children who are vaccinated at an older age, NIS data were analyzed. The analysis showed that ~88% of infants aged 3 months received their first dose of DTP vaccine and by age 12 months 96% of infants had received at least 1 dose of DTP. Thus, the 6-12 week age for dose one would miss only ~8% of infants who receive DTP-1 later. This is still a large number of infants, but weighed against the limited data on safety of dose 1 in infants >12 weeks, the Working Group thought it acceptable.

General recommendations: PRV is recommended for both breast-fed and bottle-fed infants, as data show similar efficacy for both. Concomitant administration with other childhood vaccines is acceptable, and it can be given to infants with transient, mild illnesses.

Contraindications are altered immune competence (T- or B-cell deficiency), since this is a live (although attenuated) virus vaccine; and severe allergy to a vaccine component.
Precautions included moderate- to severe acute gastroenteritis or moderate- to severe febrile illness, pre-existing chronic gastrointestinal disease, and previous history of intussusception. For these, vaccination benefits and risks should be assessed on a case-by-case basis.

Special situations discussed include:

- Considerations for premature infants who are clinically unstable and at an increased risk of severe disease from rotavirus infection. There is no restriction for infants who had recent administration of any antibody-containing blood products.
- Infants with immunocompromised household members. Exposing the latter to even an attenuated virus with low shedding rates is not desirable, but vaccinating the infant reduces their risk of being infected with and transmitting wild virus. The Working Group concluded that these infants can be vaccinated to protect the household member.
- Infant regurgitation of vaccine dose during or shortly after administration: re-

administration is not recommended. There are few data, but it is thought that even a partial dose will provide some immunity.

Next steps. FDA licensure is expected early in 2006. The Working Group will refine the recommendations and circulate them for comment in the next 60-90 days. All the data will be reviewed at the February 2006 ACIP meeting.

Discussion:

- Merck conducted surveys of provider end-users and CDC is planning the same. An Immunization Safety Office (ISO) contractor is surveying pediatricians, and family practitioners will be surveyed in the first quarter of 2006.
- The Working Group considered a recommendation to immunize premature but stable infants in the nursery who are 6 chronological weeks of age. Dr. Baker urged that this be included and clearly stated to avoid any confusion.
- Dr. Neuzil suggested that the Working Group carefully consider the risk benefit of the relative contraindications based on immunogenicity, since that may essentially prevent the child from ever beginning the vaccination series.
- Dr. Baylor reported that post-licensure studies are in discussion. FDA will require sub-studies as well.
- Dr. Lieu requested greater clarity on the economic analysis of vaccine cost and CE for PRV, and for a comparison between the likely number of rotavirus hospitalizations and cases versus that of influenza (with a universal immunization recommendation pending) and other existing and prospective immunization programs.
- A two-dose schedule of a monovalent, G-1 serotype (the most common attenuated) vaccine made by GSK is used mostly in Latin America. Its VE is good against severe disease, very comparable to Merck's. One question is about its efficacy with serotype G2, which is from a different genogroup than G strains 1, 3, 4, or 9. However, G2 is a less common serotype in most settings. That vaccine appears to be safe.
- Dr. Penina Haber cited VAERS' sensitivity to detect rare events, and reported their plans to use rapid-cycle analysis.
- Dr. Penny Heaton, of Merck, reported that they will conduct the post-licensure study, which is in design with FDA. More information will be available in February. She also noted that REST required the premature infants to be healthy, so they have no data on giving the vaccine to neonates in the hospital.
- Dr. Mark Feinberg, of Merck, stated that the vaccine price was not yet set, but will be provided before FDA licensure and an ACIP recommendation request.
- Dr. Jim Alexander, of NIP, reported the Working Group's debate over age at vaccination. They discussed how the tight time limits could miss vaccination opportunities, which is a concern. Dr. Neuzil agreed. She would not make moderate fever a relative contraindication in a two-month-old, because the infant could potentially not return until after the time frame, resulting in no vaccination at all.
- Dr. Heaton described the administration of the vaccine. It is stored refrigerated in a plastic tube with a twist-off cap which, when twisted, breaks the seal. The end of the cap is tapered for direct administration to the infant; a good method has been to give half in one cheek and half in the other. The vaccine is stable for 24 months, of which ~3-6 months is in the manufacturing and shipping process, leaving 18 months in the clinic.

- Dr. Andrew McKnight, of GSK, confirmed that GSK is discussing licensure requirements for Rotarix® with the FDA.

MEASLES, MUMPS, RUBELLA and VARICELLA COMBINATION VACCINE
Presenter: Dr. Dalya Guris, NIP

Overview: Composition of ProQuad®, the combination measles, mumps, rubella, and varicella vaccine; licensure basis; indications for use.

The ProQuad® combination measles, mumps, rubella and varicella (MMRV) vaccine has the same attenuated MMR virus composition and strength as MMR vaccine. It has a higher varicella zoster virus component than Varivax® (3.99_{10} versus 3.13_{10} PFUs). FDA licensure was based on the antigenic components' equivalent immunogenicity rather than the clinical efficacy.

An *MMWR* Notice to Reader will be issued to summarize the licensure data, the recommended routine schedules for MMRV; and MMRV's indications, vaccination intervals, simultaneous administration, storage and handling. The current MMR and varicella recommendations are two routine doses of MMR vaccine and one of varicella vaccine, and a second dose of varicella vaccine in outbreak settings. MMRV is indicated for simultaneous vaccination against measles, mumps, rubella and varicella among children aged 12 months through 12 years. ACIP heard Merck's data on ProQuad's® immunogenicity, safety and concomitant administration in October 2004.

In 1999, ACIP stated a preference for licensed combination vaccines by the use of licensed and antigenically equivalent combination vaccines. MMRV can be administered for the first dose of MMR and varicella vaccines, and can also be used for MMR dose two and, in an outbreak, for the second varicella dose. It may be used whenever any components of the combination vaccine are indicated and the other components are not contraindicated, in the absence of products containing only the needed antigens or when administration of antigens would result in extra injections, and when the potential benefits of vaccination to the child outweigh the risk of adverse events associated with the extra antigen(s).

In the MMRV clinical trials, ProQuad® was administered to 4497 children aged 12-23 months and compared to MMR vaccine and varicella vaccine (Varivax®) given separately and concurrently. The children were monitored to day 42 post-vaccination.

MMRV had a higher rate of reactions than that of the concurrent administration group, in fever (~50% higher, posing a greater risk of febrile seizures), measles-like rash (0.9%) and injection-site reactions (2.3% versus 1.5%). Data from VAERS, VSD, and Merck are being assessed in an ongoing manner in post-licensure monitoring of serious adverse events (i.e., hospitalization, prolonged hospital stay, death or life-threatening illness, permanent disability), as well as other medically important conditions (OMIC) such as febrile seizures.

VAERS post-marketing surveillance will include daily alerts of new or follow-up data (age at vaccination; onset interval in days; vaccination site, gender, symptoms, pre-existing conditions). These are immediately reviewed by CDC and FDA. Higher priority will be given to serious and OMIC reports. VAERS nurses will obtain hospital discharge data and other relevant lab data. Additional monitoring tools will be used to compare the safety profiles of MMRV with MMR

vaccine and varicella vaccine, stratified by age at vaccination, onset interval, reporting period, serious and non-serious reports. An example was shared of how this was done for Menactra® versus Menomune®, which provided the first GBS signal. Code-reporting rates are also monitored to calculate an advance signal detection, by comparing one vaccine with all others in the same age group. Any unexpected outcome increase prompts a VSD rapid cycle analysis of HMO data, using maximized sequential probability ratio testing and SCAN statistics to look for time clustering.

The Vaccine Safety Datalink (VSD) is planning to monitor selected adverse event reports applying the rapid cycle analysis. The aim will be to identify any association of MMRV vaccine with adverse events among children vaccinated between ages 1-2 years and 4-6 years, compared to those vaccinated separately at the same visit in the five years before MMRV introduction. The rates of serious events 42 days post-vaccination will be compared with the age and season-adjusted expected rate of the baseline time period. The VSD cohort includes ~90,000 children. An example was shared of the rapid cycle analysis done to examine rotavirus vaccine and intussusception, when the system successfully detected a rate increase at about week three post-vaccination.

The MMRV adverse events to be monitored are febrile seizure, thrombocytopenia, ataxia, encephalitis, arthritis, rash, rash and fever in 7-14 days of vaccination, and allergic reactions, including anaphylaxis, hives, and angioedema. Any other outcomes appearing at a higher rate will also be referred to the VSD rapid cycle for further analysis.

VFC Resolution
Presenter: Dr. Greg Wallace, NIP

> Overview: Changes to the VFC varicella resolution to authorize the purchase and use of MMRV in the VFC program.

Dr. Wallace summarized the suggested changes to consolidate the ACIP's MMR and varicella VFC resolutions, to incorporate the new MMRV vaccine and the two-dose varicella recommendation in outbreak settings. The changes were as follow:

- MMRV can be used for the two recommended doses of MMR-containing vaccine among those aged 12 months to 12 years. It is not indicated for those aged <1 year, even during measles outbreaks.
- *Precautions*: Tuberculosis was added for those who have not yet started active treatment. For the MMR component: cytomegalovirus immune globulin therapy was added to text on time intervals for certain immunoglobulins before MMR can be given.
- MMRV vaccination eligibility is stated for those aged 12 months-18 years without evidence of varicella immunity.
- *Dosage.* A single routine dose is recommended, or two doses for catch-up of those age ≥13 years. In varicella outbreak settings, a second MMRV dose may be administered to children aged ≥12 months who need additional protection from varicella disease. MMRV should not be administered for the second dose of MMR except when a dose of varicella vaccine is also indicated or if no MMR is available at the time of the second dose. (This text was added to avoid missed opportunities and to include those who lack the first dose of varicella and who are indicated for both the

first dose of varicella and the second dose of MMR.)

- *Intervals.* The differing intervals for those older and younger than 13 years are detailed; reference to the package inserts for dosage information is advised.
- *Contraindications:* The specific contraindications for AIDS and certain other immune deficiencies was removed; text on vaccine use by nursing mothers was added.

Discussion:

- Dr. Lieu asked about the practical connotations of this vote; that is, the amount to be spent and the rationale for such an expenditure. Dr. Wallace responded that the grantees' uptake would determine that, as well as the VFC vaccine contract price, which cannot be negotiated before the VFC resolution passes.
- The second dose of varicella vaccine is likely to be discussed at the February or June ACIP meeting. The workgroup is evaluating that and other issues.
- The time intervals since receipt of immune globulin for the MMR and varicella components was taken from those vaccines' respective tables. That can be updated when the recommendations are updated.
- The minimum interval difference was taken from the package insert; a three month minimum interval for those aged <13 years and requiring two doses. The time period is shorter for those aged ≥13 years. Dr. Kuter reported Merck's need to fit the vaccine into the routine immunization schedule's 3-month interval, but their studies looked at 4-8 weeks. The European label has a one-month interval for the product despite the lack of data. Dr. Marcuse raised the risk of confusion if the ACIP recommends differently than the package insert. In terms of immunogenicity, Dr. Abramson thought that separating two live viral vaccines by a month would provide reasonable immunogenicity. Dr. Pickering added that the three month interval was licensed based on active disease, but felt that six months would make little difference. Dr. Abramson asked the workgroup to look at that issue and recommend on it to the full committee.
- Dr. Barbara Watson, of the Philadelphia health department, reported that of their 400 VFC providers, only two are fully private, and they already have MMRV. She hoped that the measles vaccine experience of coverage disparity, which led to 30% coverage and outbreaks, would not be repeated.

Dr. Campbell **moved to approve the VFC resolution** and Dr. Gilsdorf seconded the motion.

Vote
In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Morita, Treanor, Womeodu, Abramson
Opposed: None
Abstained: Marcuse

The vote passed.

HUMAN PAPILLOMAVIRUS VACCINE

Gardasil™ HPV Vaccine
Presenter: Dr. Eliav Barr, Director, Vaccine Clinical Program

Merck Research Laboratories

Overview: Data of the Phase III clinical trials for Gardasil™ HPV Vaccine

Human papillomaviruses (HPV) cause anogenital cancers and benign lesions such as genital warts. Gardasil™ is a quadrivalent vaccine (HPV types 16,18, 6,11) and is administered in a three-dose schedule. . The vaccine was developed to reduce the incidence of these viral subtypes, which cause:

- HPV 16 and 18 *in women*: 70% of cervical cancers, anal and HPV-related genital cancers, and CIN 2/3 (high-risk, high-grade precancerous lesions) and ~25% of CIN 1 (low-grade lesions clinically indistinguishable from those of higher risk HPV types). *In men:* (primarily MSM): 70% of anal cancers and precancerous lesions; genital warts.
- HPV 6 and 11 *in women and men:* 90% of genital warts. *In women:* 10%-20% of CIN 1 lesions.

Target populations. The inclusion of HPV 6 and 11 was designed to reduce the incidence of the common but low-risk CIN 1 lesions that cause significant healthcare expenditures and anxiety among women. Other than cancer, inclusion of both types was designed to prevent the transmission of the virus to women. The populations targeted are adolescents aged 9 to <18 years, as a prophylactic vaccine before sexual debut, and sexually active adults aged 18-45 years, all of whom are at lifelong risk for sexually-transmitted HPV infection.

The Papanicolaou (Pap) test for cervical cancer screening routinely identifies the disease before invasive cancer develops. With the disease's ~20-year incubation period, HPV prevention can be demonstrated by use of the Pap smear in clinical trials through surrogate markers. HPV infection, as cervical cancer's etiology, is the primary marker; it and CIN 1 lesions, are important relative to the health and economic standpoint of disease burden. But since they both clear quickly, vaccine efficacy in clinicial trials is demonstrated by prevention of CIN 2/3 lesions, which typically develop from 0-5 years after infection. Screening and the uniform removal of CIN 2/3 lesions has dramatically reduced cervical cancer rates in the U.S.

The prevention of CIN 2/3 lesions was selected as the primary efficacy endpoint. Since 1997, four clinical efficacy studies have been conducted. Phase III data were presented during this ACIP meeting session.

Methodology. Lesions are removed, fixed and sectioned. Histological studies are conducted on the first and last sections and HPV-DNA testing is conducted on the central section. A case is defined as a lesion positive for a vaccine genotype and with positive histological diagnosis. The trial included ~20,000 women world-wide; mean age was 20 years, with sexual debut at ~17 years; most were sexually active and had two lifetime partners at enrollment. History of past pregnancy was variable, as was history of chlamydia and baseline HPV disease. Importantly, 75% of the women were naïve to the vaccine's four HPV genotypes, a factor relevant to vaccine implementation considerations.

The per protocol analysis included those who remained uninfected during the vaccination period and received all three doses - 71%-81% of the entire Phase II/III efficacy population.

Overall prophylactic efficacy was measured in a modified intention to treat (MITT) cohort. These were also naïve to the vaccine HPV genotypes at Day 1 and constituted 80%-91% of the entire Phase II/III efficacy population.

Findings were as follow:

- *VE.* A VE of 100% was found, with a p value of <0.001 in the per protocol analysis, and a 99% VE (93% lower bound) among the MITT cohort.
- *Burden of disease* due to the four vaccine types was measured by overall cervical intraepithelial neoplasia (CIN), , external genital lesions caused by these four types, and evaluation of cervical and genital pathology. The vaccine efficacy was 100% (lower bound of 87%) overall and 97% for the MITT cohort (one of the cases was a misidentified placebo subject), for all vaccine types. VE for *external genital lesions, genital warts, and other lesions (*vulvar intraepithelial neoplasia [VIN] 2/3, immediate vulvar/vaginal cancer precursors),was 100% (lower bound, 88%) and 95% (lower bound 84%) in the broader MITT population..
- *Other findings.* Efficacy begins during the course of the vaccination and is comparable across variations in dosing intervals. No differences were seen by regional origin or ethnicity, sexual behavior, or use (or non-use) of hormonal contraceptives. Therapeutic efficacy modestly reduced the progression to CIN 2/3 among those with early HPV infection who were still seronegative. But the vaccine was not effective among those infected who had mounted an immune response. Infection with one HPV type does not impact efficacy for other 3 HPV types.

Long term surveillance. Duration of immunity has been observed through 3.5 years after dose 3 and long term surveillance is planned. A (unneeded) booster dose will be administered to participants of protocol 007 to evaluate response to revaccination and to evaluate immune memory.

Scandinavian studies will extend the Phase III studies:

- A registry (the Nordic Cancer Registry Program) will draw on the Norwegian cervical cancer screening program data and follow women to provide interval VE updates. Norway now mandates registry participation for all vaccines.
- Disease burden/VE study has already begun. This population survey of 14,000 women measures sexual behavior and genital wart disease burden. Subjects will have HPV PCR testing on liquid-based cytology specimen, and results will be linked to the survey and registry data. This will be repeated regularly over time. The data generated will provide an HPV-type distribution in the general population with negative and positive cytology diagnoses, provide a baseline, and evaluate VE over the long term.
- *Extended adolescent immunogenicity study*. HPV vaccine has demonstrated high efficacy and no minimal protective level is known. Titers are very high; anti-HPV GMTs exceed by 10- to 40-times those after natural infection. They wane over time, but post-dose 2 HPV levels are higher than those from dose 1. Data were charted to demonstrate:
    - Anti- HPV16 antibody declined but then stabilized out to 48 months post-vaccination. A similar plateau was charted for anti-HPV 18 GMTs, where levels remained higher than those from natural infection. No late breakthroughs for HPV 18 have been seen.

- The impact of age at vaccination in the GMTs measured in month 7 post-vaccination. The levels achieved for those aged 9-11 years were much higher (in some cases, 2 or 3 times higher) than those of the 16-23 year-olds enrolled in the efficacy trial.

- The integrated safety database showed little difference in adverse events between the vaccine and placebo groups, other than somewhat higher injection site reactions in the vaccine group than the placebo group. Of four serious adverse events among the >6000 Gardasil™ subjects, two (bronchospasm and gastroenteritis) were possibly related, one (injection site pain/impairment) was probably related, and one (headache/hypertension) was definitely related. The placebo group had two adverse events (hypersensitivity and chills/fever).

Summary. Gardasil's™ prophylactic efficacy in 16-26 year-olds was high against development of cervical cancers caused by HPV-16 and -18; and, for all four HPV types, it was effective against the overall CIN disease burden and that of condyloma, VIN, and VaIN. Duration of efficacy has been shown for >2.5 years post-vaccination and the Scandinavian registry cohort will provide still more data four years ahead of those vaccinated post- licensure.

Population efficacy was presented to the HPV Working Group the previous day, which showed reductions in overall incidence of CIN 2/3, CIN, and many of the procedures related to screening (e.g., abnormal Pap tests, excision of genital warts). More data on the vaccine's impact on HPV 16 and 18 will be available soon.

Discussion:

- The homogeneity of the Scandinavian population was noted. Dr. Barr reported an unsuccessful attempt to study women of minority populations in the U.S. This was followed by a large and successful trial among Latina women, African-American and white women in Bahia, Brazil. The VE calculated for Brazil was comparable to that of the Scandinavian trials. Anti-HPV levels also were found to be comparable between women of African descent and of Caucasian descent.
- The Norwegian study will include the impact of the vaccine's introduction on sexual behavior, which is more discussed in Scandinavia than the U.S. The incidence of genital warts and other conditions will be investigated and a baseline of sexual behaviors has been established by a survey. This will be repeated after vaccination among that group and younger groups as well.
- Efficacy after two doses (and possibly three in view of the lifelong threat posed by HPV) will be determined over time.
- It was noted that the period of greatest risk among women is from ages 15-25 years, when most HPV infections occur.
- Data on the duration of antibody response among vaccine recipients who had a higher response to begin with, has been broken out through month 18 post-vaccination and the study was extended through month 36. Preliminary data will be available sometime in mid-2006.

CDC Survey of Sentinel Pediatricians on HPV Vaccine Acceptability

Presenter: Dr. Nicole Liddon, Division of STD Prevention

Overview: Preliminary data from a national study of pediatricians and HPV vaccine acceptability.

A national survey of pediatricians, to determine their receptivity to an HPV vaccination recommendation, was conducted by the University of Colorado, Denver, Health Sciences Center, the NIP and the Division of STD Prevention.

A sentinel network of pediatricians selected from the AAP was surveyed on 1) their knowledge of HPV, 2) their attitudes regarding introduction of an HPV vaccine, and 3) their intentions to recommend an HPV vaccine to adolescent patients. These pediatricians are surveyed 2-4 times a year on various topics relevant to clinical practice and immunization; they were drawn from a stratified sample of AAP members to resemble the general membership in terms of geographic location, practice setting and type. They are also comparable to AMA members in terms of sex, mean years since graduation and practice location. The survey was conducted in September-October, 2005, prior to the IDSA conference and publication of Merck's vaccine trial results.

Of 431 surveyed pediatricians, 298 (69%) responded. They were about equally distributed by sex. The mean period since medical school graduation was 21 years; 44% had an urban practice, ~50% were suburban, and ~15% were rural. For ~33%, >25% of their patients were aged 13-18, and 41% of practices had ≥25% of patients on Medicaid or CHIP.

HPV Knowledge. When asked: 1) if genital warts and cervical cancer are caused by the same HPV types (false) , 20% were correct, 54% incorrect and 26% did not know; 2) whether incidence of HPV in women is highest among women in their 30s (false), 29% answered correctly, 23% were incorrect and 48% did not know; 3) if HPV vaccines under development appear to be highly effective at preventing cervical cancer precursors (true), 56% were correct, 1% incorrect, and 43% did not know; and 4) that almost all cervical cancers are caused by HPV infection (true), 68% were correct, 12% were incorrect and 20% did not know.. Almost all knew that HPV can be asymptomatic and represents a common cause of STD (83% for both) and can cause genital warts in both males and females (97%).

Beliefs about HPV Vaccine: Few (11%) thought that the vaccination may encourage more risky sexual behavior; 54% cited the difficulty in maintaining continuity of care with adolescent patients (a potential implementation problem): 64% thought that the introduction of other adolescent vaccine recommendations would ease introduction of an HPV vaccine; 84% expected to have to talk about sex when discussing the vaccine; and 88% were comfortable doing so with their female patients.

Expected barriers to HPV vaccine administration were: lack of adequate reimbursement (77%); parental refusal (57%) or concern about vaccine safety (53%); up-front vaccine purchase (51%) and vaccine supply problems (42%).

Results: Intent to vaccinate. Responses were as follow on aspects of intent to vaccinate:

- *Overall* intent to vaccinate females with an FDA-approved HPV vaccine showed high acceptance for 16-18 year-olds (89%); 77% for 13-15 year-olds; and 46% for 10-12 year-old patients. There were no significant differences in intent to vaccinate by sex of provider, practice location, or % adolescent patients.

- Of the 187 pediatricians who thought 10% or more of their 13-15 year old patients were sexually active, 51% would vaccinate at age 10-12, versus only 39% of those who thought that <10% of their patients are sexually active ($p \leq .05$).
- The only significant difference in intent to vaccinate was related to provider's knowledge of an efficacious vaccine; those who knew (55%) that HPV vaccine is highly efficacious would vaccinate versus those who did not know (36%), for a p value of <.001.
- Intent to vaccinate was higher among those who thought: 1) that other adolescent vaccine recommendations would make HPV vaccine implementation easier (52% would vaccinate versus 37% of those who did not believe this); and 2) that discussion about sex would not be necessary before recommending an HPV vaccine (67% would vaccinate versus 42% who thought sexual discussion would be necessary).

Barriers: Perception of parent refusal significantly affected intent to vaccinate (36% would vaccinate versus 61% among those who did not see parent refusal as a barrier).

Conclusions of the analysis were as follow:

- Pediatricians are willing to administer an HPV vaccine, particularly to older adolescents.
- Overall knowledge of HPV and HPV vaccine is low in some areas; pediatricians would benefit from education.
- Increased intent to vaccinate overall is related to:
- knowledge of the development of an efficacious vaccine, as is
- the perception that a discussion of sex is not necessary for vaccination of 10-12 year-olds;
- Absence of parental refusal;
- belief that other adolescent vaccine recommendations would ease HPV vaccine delivery
- perceived patient sexual activity at age 13-15. This may indicate that pediatricians see a need for vaccinating prior to sexual initiation.
- The major barrier to HPV vaccination is perception of inadequate reimbursement, even though it did relate to intent to vaccinate.

Some of these results may pertain more to adolescent vaccination in general than HPV in particular. A study of meningococcal conjugate vaccine administration also found problems with reimbursement as a barrier.

Among ongoing and developing research projects to look at these and other issues related to HPV vaccine acceptability is a CDC/NIP study of the acceptability of HPV and other adolescent vaccines to family physicians, internists, pediatricians and samples of parents and adolescents. Other studies about vaccinating children, by industry and academia, are underway.

Preliminary Considerations for U.S. HPV Vaccine Recommendations

Presenter: Dr. Lauri Markowitz, NCHSTP

Overview: Vaccine licensure/production assumptions; disease burden and epidemiology; vaccine acceptability; programmatic issues; vaccine impact/CE; potential recommendation strategies

The HPV Working Group has met several times over the 18 months. The current assumptions made by the Working Group include: 1) the mid-2006 licensure of quadrivalent HPV 6,11,16,18 vaccine for use in females aged 9-26 years; its potential later licensure for use in males; and still later, licensure of a bivalent HPV 16,18 vaccine for use in females.

The data presented at this meeting showed the vaccine's efficacy and safety, with local reactions as the primary side effect. Immunogenicity was well demonstrated by very high seroconversion rates in those aged 9-26 years. The vaccine's GMTs exceeded those after natural infection and were highest in those vaccinated at younger ages; its level of immunity also exceeded that of natural infection, even with a plateau at 18 months post-vaccination. The duration of protection and need for a booster dose remain unknown and there is no known serologic correlate of protection.

The burden of HPV-related disease was presented at the June 2005 ACIP meeting. Cervical cancer cases and deaths in the United States during 2005 are estimated to be >10,000 and 3700, respectively, aside from other HPV-caused conditions requiring medical attention. An estimated >50% of sexually active adults will have HPV at some point, most being asymptomatic and naturally resolving. Data indicate that HPV is acquired soon after sexual debut, 39% within 24 months of first sex. Vaginal sexual activity among U.S. females has been estimated at 26% by age 15 and 77% by age 19.

Vaccine acceptability. Vaccines targeting control of STDs have the potential to raise social concerns, but education about HPV and HPV vaccine may lead to increased acceptability. Providers and parents appear to be more likely to accept vaccination of older adolescents.

Programmatic issues include accommodation of HPV vaccination in the ever expanding list of priorities for the 11-12 year-old preadolescent healthcare visit. Studies of vaccine impact and cost effectiveness are published and ongoing, and will be presented at the next ACIP meeting. The economic analyses to date have estimated a cost of ~$300 for three doses, including administration cost. Recommendations for vaccine use must take into account several *Potential strategies*, including recommendations for routine use, catch-up, or permissive recommendations. The current HPV vaccines will not eliminate the need for cervical cancer screening, since types other than HPV 16 and -18 cause ~30% cervical cancer. This was a basic assumption in the models developed to evaluate HPV vaccine's expected impact.

Strategies discussed for routine recommendation included several considerations. Vaccination of *early adolescents* aged 11-12 years (or younger) would allow vaccination before sexual debut for a larger number of persons. The data indicate higher antibody titers at this age, which also fits the current adolescent immunization schedule. Vaccination of *older adolescents* may provide better protection in the high-risk years, if there is waning immunity (which is unknown) , without requiring a booster. There also may be less social resistance to a recommendation for vaccination at this age, and therefore higher coverage.

At the ACIP meeting to be held in February 2006 the Working Group will present analytical data on vaccination CE and impact, presuming further information data from GSK and Merck. Preliminary recommendations can be discussed then and in June, and perhaps a vote on the quadrivalent HPV vaccine can be taken at the ACIP meeting to be held in June 2006. Subsequent meeting topics will include discussion of the use of HPV vaccine in males, and a bivalent HPV

vaccine. In the meantime, the NCHSTP Website has information on HPV disease and cervical cancer, at www.cdc.gov/std/hpv/, for women, patients and health-care providers. The site also links to the American Cancer Society and the National Cancer Institute.

Discussion:

- Dr. Mark Feinburg (Merck) reported their building of production facilities which have been operating for the last two years. Merck expects to have no problem supplying HPV vaccine for the populations studied.
- Dr. Katz commented on the survey of practitioners at 21 years post-graduation. Given that >66% of young pediatricians today are female, the data might be more accurate if they are surveyed. And, to overcome social discomfort with STDs, he also urged that this vaccine be promoted as a cancer prevention vaccine rather than one for prevention of STDs.
- Pediatricians' reluctance stemming from expected parental objections may not be warranted. Research in general and by Merck on this HPV vaccine in particular indicate that parents rely on and will be influenced by the advice of the pediatrician, and that they will accept the vaccine when they understand the outcomes of HPV infection. Pediatricians could be further educated to these facts. Dr. Murphy added that many parents already have HPV and do not want their children to be infected.
- The two imminent HPV vaccines differ in that Merck's quadrivalent vaccine includes the two genotypes that cause genital warts, and so targets males and females, while GSK's bivalent vaccine targets only cervical cancer in women. The Working Group is focusing on developing proposed recommendations for the vaccine that will be licensed early in 2006.
- The Working Group has not formally communicated with ENT physicians to determine their attitude to HPV, in view of the patients they treat for laryngeal papillomatosis due to HPV 6 and -11. But Dr. Markowitz reported great interest on the part of NCID researchers who are working on recurrent respiratory papillomatosis (RRP) with a network of ENT specialists.
- Dr. Eliav Barr, of Merck, commented that HPV 6 and -11 cause the precancerous dysplasia CIN lesions that are histopathologically indistinguishable from the higher risk HPV types. Eliminating those types will also reduce the "noise in the system." Merck has also had preliminary inquiries from the RRP network. They plan to evaluate that issue, and expect that the high VE for HPV 6 and -11 will also benefit those with RRP.

REVISION TO THE 2002 ACIP GENERAL RECOMMENDATIONS

Presenter: Dr. Andrew Kroger, NIP

The General Recommendations Workgroup met by teleconference 11 times in 2004 to update the ACIP General Recommendations document. The updated draft is expected to be presented at the February meeting and be published by the *MMWR* in summer of 2006. The revised sections on vaccine administration and storage/handling of immunobiologics have already been presented to ACIP. On this day, the draft section on altered immunocompetence was outlined, which was expanded to include the 2002 document's section on hematopoetic stem cell transplants. Discussion of the timing and spacing of immunobiologics, which was scheduled for this meeting, was deferred to February.

Changes made to the altered immunocompetence text included:

- Recommendation that providers order lab tests to assess altered immunocompetence. Several tools are suggested: 1) for *humoral immunity*, immunoglobulin and Ig subsets, specific antibody levels, antibodies for tetanus, diphtheria, and pneumococcal vaccine; 2) for *cellular immunity*, lymphocyte numbers, complete blood count with differential, and lymphocyte subset concentrations and proportions (to determine B-cell deficiency versus T-cell deficiency and then to subset T-cells for CD4+ versus CD8+); and 3) lymphocyte proliferation assays, to measure T-cell proliferation in response to specific or nonspecific stimuli. Finally, since not all laboratory tests are available to all immunization providers, text is added to encourage "consultation with an infectious disease or an allergy/immunology specialist."
- Added a new section on vaccine indications for people with altered immunocompetence (i.e., safety of use of vaccines in general and live vaccines in particular). This is a new section, but the information comes from vaccine-specific ACIP statements' recommendations for people with altered immunocompetence.
- Provides a permissive recommendation to use varicella vaccine and pneumococcal conjugate vaccine following hematopoetic stem cell transplantation, which provides guidance on which restorative vaccines should be given. This references the 2000 document co-authored by CDC, the IDSA and the American Society for Blood and Marrow Transplantation, which does not recommend revaccination with varicella or pneumococcal conjugate vaccine. While noting the lack of evidence to recommend varicella and pneumococcal conjugate, there is an acknowledged substantial risk from infection with varicella and *Streptococcus pneumoniae* during the post-transplant process; this risk is addressed though a permissive recommendation for the use of these two vaccines, based on the physician's assessment of the patient's immune status and risk of infection.
- Provides an option to revaccinate after immune ablation from chemotherapy following acute lymphoblastic leukemia. The text says: "People vaccinated prior to chemotherapy for leukemia, lymphoma, or other malignancies generally are thought to retain immune memory following treatment although revaccination following chemotherapy for acute lymphoblastic leukemia may be indicated." This was based on only one 2005 paper in the *Journal of Pediatrics* by Brodtman, but the evidence was found to be strong.
- Cautions against the use of live vaccines in patients on long-term therapy using therapeutic monoclonal antibodies such as tumor necrosis alpha inhibitors and other isoantibodies. It cites the anti-tumor necrosis factor agents adalimumab, infliximab, and etanercept, which can reactivate latent TB infection and disease and also predispose the patient to other opportunistic infections. It also notes the unknown safety and efficacy of concurrent vaccination of live attenuated vaccines with recombinant human immune mediators and immune modulators. Interferons and immune modulators used as therapeutics, such as Lavamisol and BCG, are cited as examples.
- Inserted a table of contraindications, vaccine effectiveness, and vaccine indications for specific categories of primary and secondary immunodeficiency, and other disease conditions that confer altered immunocompetence. This is a combination of the AAP's 2003 *Red Book* recommendations and the ACIP 1993 table on immunization of individuals with altered immunocompetence. It is indexed in grouped disease conditions according to primary (humoral or cellular) or secondary

immunodeficiency conditions, and mostly defines contraindications according to general classes of vaccines. Comments on disease category and vaccine efficacy will be added as will specific vaccines; and indications.

Discussion:

- After further research, the document will be clarified as to the extent of revaccination being advised after chemotherapy.
- Dr. Abramson suggested further review of the vaccines listed for primary humoral and complement deficiencies. He also expressed concern about including live attenuated influenza virus with all live viruses, since it cannot replicate in cold temperatures, and this could further discourage uptake. Further, he asked for a time designation for safety (e.g., ≥1 year) to the statement advising varicella vaccination for bone marrow transplant patients.
- Ms. Sandra Jo Hammer, of the California immunization program, suggested that this level of discussion of complex issues affecting only a minimal number of patients might make the General Recommendations less user-friendly, and perhaps should be published elsewhere and referenced. Dr. Kroger responded that the concept of inserting the content of the 1993 Altered Immunocompetence ACIP document into the 2006 General Recommendations document were strongly encouraged by ACIP at the February 2005 meeting. It greatly parallels the content of the 2002 document, which also condensed part of the 1993 information.

A vote was deferred to the February 2006 presentation.

HERPES ZOSTER VACCINE

Presenter: Dr. Kenneth Schmader, MD, Duke University/Durham VA Medical Center

Overview: Epidemiology of herpes zoster and post-herpetic neuralgia; risk factors; disease impact in older adults

Herpes zoster is principally a disease of the elderly. Incidence among older adults (age >60 years) ranges from 7.2 to 11.8 cases per 1000 person-years. Retrospective studies estimate U.S. annual incidence at 500,000-1 million cases. The zoster vaccine's Shingles Prevention Study prospectively surveyed people monthly and reported an incidence of 11.1/1000 person-years.

Epidemiology. Zoster's two major risk factors are aging and suppression of cellular immunity. While the lifetime zoster risk is ~20%, it is ~50% in those living to age 85. And, although the risk of recurrent herpes zoster is low (1.7%-5.2%) in the immunocompetent host, rates are highest among immunocompetent older adults compared to immunocompromised individuals. The zoster rate is also high in all age groups among those with HIV/AIDS, lymphoproliferative cancers, immunologic malignancies, lymphomas, organ transplant recipients, lupus patients, and those receiving immunosuppressive treatment. Data charted from the Hope-Simpson study (*Proc R Soc Med* 1965;58:9-20) dramatically illustrated increased zoster incidence with increasing age, beginning at 60-65. Why the risk is higher in females is unclear (studies have conflicting results); blacks have lower risk than whites; and some data indicate a doubled risk for zoster with psychological stress and, some believe, physical trauma.

Morbidity. Zoster morbidity is significant, imposing acute pain in elderly patients. Pain burden

data from the Katz and Dworkin et al study (*Clin Infect Dis*. 2004;39:342-348) measured pain intensity by duration linked to physical roles and social and emotional functioning. About 72% of the patients were aged >50 years. Increased pain burden was paralleled by increased pain intensity and duration, described by 42% of patients as horrible or excruciating.

Lydick et al (*Qual Life Res* 1995;4:41-45) measured the devastation to zoster patients' quality of life by comparing their mean SF-35 (quality of life) scores to those of hypertension, congestive heart failure, diabetes, myocardial infarction, and depression. Two weeks after zoster rash onset, zoster scores often exceeded those of the other serious conditions.

Postherpetic neuralgia (PHN) has no consensus definition. Its diagnosis differs according to the time after rash onset (the literature ranges from 30-180 days) and pain intensity (any pain to clinically meaningful pain). Most recent definitions factor pain 90-120 days after rash onset. The Bennett study (*Hosp Prac*. 1998;33:95-98;101-104;107-110) compared and charted neuropathic pain in the U.S. Significantly, the incidence of only two conditions -- low back pain and painful diabetic neuropathy -- exceeded that of PHN. As the two most common pain states, the last two are intensively researched, but incidence data remain sparse.

Dworkin and Schmader (*Herpes Zoster and Postherpetic Neuralgia*, 2nd ed., 2001) charted the proportion of zoster patients aged >50 years, who were given antivirals in the major antiviral trials within 72 hours of rash onset (something that occurs in clinical practice only ~50% of the time). The data demonstrated some efficacy of antivirals to reduce acute pain and pain duration; however, a substantial proportion (~30%) still have PHN.

Risk factors. The most important risk factor by far is increasing age. The duration of pain in the elderly is worse: what lasts a month or less in younger groups (e.g., 0-39) can go on for years among the elderly. Age ≥60 years with severe acute pain and severe rash and prodrome plus rash, carries a positive predictive value of 47% for PHN. In the absence of these risk factors, the negative predictive value is 88%.

Data from Whitley et al (*J Infec Dis*. 1999;179:9-15) were charted of zoster in adults aged >50 years, with severe, incapacitating pain and an extensive rash (>47 lesions), versus those who had no or mild acute pain and a less extensive rash. The former group had a ~75% likelihood of pain remaining at six months after rash onset.

Common complications of zoster include PHN, ocular complications of ophthalmic zoster, scarring, and bacterial superinfection. Even those complications that are uncommon are not rare. Particularly among immunosuppressed patients, the following can emerge: cutaneous dissemination, herpes gangrenosum, pneumonitis, hepatitis, encephalitis, motor neuropathies, myelitis, and hemiparesis (granulomatous CNS vasculitis). In particular, motor neuropathies are more common than had been thought. The virus can often transfer from the dorsal horn to the ventral horn and causes painful Bell's palsy, a paralytic limb, or weakness in the thoracic or abdominal musculature.

Ophthalmic zoster is also an important contributor to disease burden, as ~15% of cases involve the ophthalmic division of the trigeminal nerve. Without antiviral therapy, 50%-70% of patients with HZO develop ocular complications that can proceed even to blindness. The pain has been compared to an ice pick stabbing behind the eye.

Quality of life is dramatically affected in the zoster patient's physical, psychological, social, and functional life, because they experience many different types of pain. It begins as a spontaneous, constant aching or burning and proceeds to the kind of intermittent shock-like pain that can bring individuals to their knees. Many PHN patients have allodynia, pain prompted by even such gentle stimuli as a breeze or the touch of a soft cloth. The fatiguing pain brings on weight loss and sleep deprivation, lack of physical activity, depression, and isolation.

The basic activities of daily living are significantly impaired. A Liverpool pain clinic study determined that 59% of PHN patients could not pursue their usual activities for up to 16 years, with the average being 1.4 years. The Mauskopf et al (*Quality Life Res* 1994;3:431-435) and Coplan et al (*J Pain* 2004; 5:344-356) studies confirmed the drastic effect of PHN on the elderly with multiple co-morbidities, and confirmed the strong association between pain severity and duration with interference in living their normal life.

Hospitalizations/economic impact. Three studies were cited[1] that demonstrated the increase of zoster hospitalization rates with age. In the CDC-funded Lin study, the mean hospitalization costs over a ten-year period were $12,834 per patient. By 1995, a decade ago, the cost had risen to $16,000. In ~40% of the hospitalization studies, the primary cause was herpes zoster, and it was a secondary diagnosis in the remainder. In the Lin study, ~30% were immunosuppressed; the balance was mostly older immunocompetent adults. The mean length of stay in the MacIntyre study in Australia was 12 days, and ~11 in the Lin study.

There was no discussion following this presentation.

INFLUENZA

Vaccine Supply
Presenter: Dr. Greg Wallace, NIP

> Overview: Projected 2005-2006 influenza season vaccine distribution, compared to past representative years

A line graph of the cumulative influenza vaccine distribution for 2000, 2002, 2004-05, and 2005-06 was presented. This season's August/September dose numbers were accurate, and reflected >80 million doses already distributed. The doses for October through January were projections of vaccine that could be obtained if needed. The data presented clearly demonstrated the greater quantities available for this year than at any time since 2000. However, there still could be spot shortages depending upon which supplier is selected.

Discussion:

- ACIP members were assured that there should be no shortage of supply for the pediatric vaccine formulations (2.5cc dose) for those aged 6-23 months of age. That

[1] Coplan P et al. Pediatr Infect Dis J. 2001;20:641-645; Lin F et al. J Infect Dis. 2000;181:1897-1905; MacIntyre C et al. Epidemiol Infect. 2003;131:675-682.

vaccine, and FluMist,® have less demand than supply this year. Dr. Kathy Coelingh reported that FluMist® distribution data were not yet available, but MedImmune's orders were higher than last year.

- There is no way to determine how many doses were unused last year; only distribution data are available.
- As of October 23, there were no restrictions for vaccination.

Influenza Resistance to Antiviral Drugs
Presenter: Dr. Alexander Klimov, NCID

Two classes of drugs are available for influenza prophylaxis and/or treatment: the adamantanes (amantadine and rimantadine, for influenza A only) and neuraminidase inhibitors (oseltamavir and zanamivir). CDC tested for resistance more than 6500 human influenza A (H3N2) viruses that were collected globally from 1994-2005 (Bright et al, 2005: *Lancet* 366; 1175-1181):

Adamantanes

- *H3N2 resistance to antiviral drugs*: In some areas of Asia, such as China and Hong Kong, resistance to the adamantanes exceeds 70%; in others (e.g.,. Singapore, South Korea), it is lower but still significant (35%-45%), and is 12% in the U.S.. Of H3N2 viruses tested at CDC, , most (88%) have developed resistance since 2003.
- *H1N1 resistance*. Three of 678 influenza H1N1 or H1N2 viruses were shown to be resistant
- *Avian H5N1 virus resistance:* Based on sequencing data available, 17 of 19 (89%) H5N1 viruses isolated from humans were resistant. Resistance in H5N1 isolates from birds is 58% (119 of 206 isolates)

Neuraminidase inhibitors. CDC has found no resistance to NIs in 1444 H3N2 samples isolated in 2004-2005. Two of 164 H1N1 samples tested in 2004-2005 were resistant, but neither had the mutations known for previously characterized NI-resistant strains. For the B strain, one of 304 samples in 2004 and three of 1224 samples in 2005 were resistant. One virus contained mutations in the neuraminidase genes, which previously has been associated with resistant neuraminidase inhibitors.

- *Oseltamivir.* Use of oseltamivir has dramatically increased in Japan. Resistance to date is rare: 0.4% in adults, but rising to ~4% in children and up to 18% in very young children (6-18 months)
- *Zanamivir:* No resistance to date has been seen among immunocompetent individuals, but one B virus was isolated from an immunocompromised person.

H5N1 resistance has been tested in 97 isolates from both humans and birds. All of both were still sensitive to both NIs. One strain, A/Vietnam/30408/2005/H5N1, which came from a Vietnamese child treated with oseltamivir, had a mix of , resistant and sensitive virus. However, the sensitivity of the virus to oseltamivir was only slightly increased

Conclusion: An alarming increase in the proportion of adamantane-resistant influenza A(H3N2) viruses has occurred over the past several years, but the proportion of human influenza viruses resistant to neuraminidase inhibitors is low. Continued surveillance to track the emergence and spread of drug-resistant viruses will continue.

Discussion:

- There has been no evidence to date of relapse or treatment failure among immunocompetent individuals who developed the resistant viruses.
- There are geographic differences in N2 resistance and the frequency of resistance to H5N1. Two genetic clades are circulating in Asia. Human cases in 2003-2005 in Vietnam and Thailand were caused by Clade 1 viruses, while the new cases in Indonesia were caused by viruses from Clade 2. All known H5N1 viruses from clade 1t have the mutation at position 31 of the M2 gene that is typical for viruses resistant to adamantanes. Most of Clade 2 isolates are sensitive to adamnatanes, although not all of them.
- Because only one case of resistance to oseltamivir has been seen, and was borderline, nothing can yet be definitively said about the correlation between pathogenicity and resistance to neuraminidase inhibitors.

AVIAN INFLUENZA H5N1

Update on H5N1
Presenter: Dr. Nancy Cox, NCID, Chief, Influenza Branch

Enhanced surveillance of avian influenza H5N1 in Asia by HHS/CDC is ongoing through bilateral agreements with 11 Asian countries and one WHO Regional Office. In the future, surveillance will be expanded into rural areas and additional geographic areas. HHS is supporting the WHO's Western Pacific Regional Office (WPRO). CDC is strengthening its emerging infectious diseases program in Thailand and is supporting work in Cairo and Jakarta. Those networks have resulted in a large number of H5N1 samples for analysis. WHO's animal/human interface influenza network is being enhanced, as are communications between public health and veterinary agencies. CDC is supporting the shipment of isolates and specimens.

Maps detailed the location of the national influenza centers, WHO collaborating centers, surveillance sites, nations with bilateral agreements, avian outbreaks and human cases. Migrating birds spread the infection to Russian, Mongolia and Kazakhstan. An infected bird imported to the U.K. was quarantined, and H5N1 was detected in swans in Croatia and wild birds in Romania. More reports of bird infections are expected in the coming weeks, as are more reports in humans. There are unconfirmed reports of human cases in China.

The bilateral agreements, so far concentrated in Asia, will be expanded with the virus's spread. The northern and southern American migratory flyways have less intersection than those in Asia, except for Alaska, where surveillance has been increased. There is a high probability that the H5N1 virus will be introduced into Africa and India.

The case fatality rate (CFR) fluctuates but remains high; the CFR currently is 51% overall, regardless of age. The clinical symptoms are similar to those of earlier cases, although diarrhea has become prominent in some. The second wave of infections occurred from August 2004 to the present; this is probably the third wave now. Only one (Thai) family cluster has confirmed human-to-human transmission, but such is possible in other cases.

A dendrogram illustrated the phylogenetic tree of the human glutenin genes of the viruses examined to date. Those causing the human infections in 2004 were in Clade 1, some of which

were used to make candidate vaccine reference strains. Pilot lots of some are in trials. Clade 2 viruses are those seen this year in Turkey and Mongolia, and in the Indonesian human isolates. They also have been used previously to make reference vaccine viruses. No viruses from either clade yet spreads easily from person to person.

Conclusion. Avian influenza viruses pose a major risk to global public health. Early detection of human-to-human transmission is essential, and is very difficult in some rural areas of Asia. The heterogeneity of the Asian H5N1 viruses from 2003 through 2005 make the ongoing international collaboration even more important. Ongoing vaccine development, antiviral stockpiling, and pandemic preparedness is building. Animal surveillance and human-veterinary communication is essential.

Discussion:

- To anticipate human-to-human transmission, researchers are looking for a genetic reassortment to a virus better adapted for human-to-human transmission, changes in the virus receptor binding areas that would facilitate transmission, and in other areas.
- Dr. Lazlo Portman, of ID Biomedical, reported their work on Clade 1 viruses and hoped to get some Clade 2 isolates to continue their work. Dr. Cox will follow up on this matter.
- Dr. Coelingh asked how different the antigenicity of the two clades would be, if cross-tested. Dr. Cox reported 8-fold or better, although this varies from virus to virus.
- Dr. Turner asked if modeling is being done to estimate the relative risk of a pandemic at a particular point in time, perhaps based on past pandemic experience. Dr. Cox answered that the 1918 and 1950 H2 pandemic viruses were not highly pathogenic in birds (one advantage of that is the ability to track the virus's development), and there are no data on how widespread H2 viruses were before those pandemics, nor H3 before the 1968 pandemic.
- The reason that flock culling has not eliminated virus transmission is due in part to the common possession of backyard flocks and pet birds in Asia, and different methods of animal husbandry.
- No large scale seroprevalence studies in Asia have been done; these are being encouraged by CDC.

Update on H5N1 Vaccine Clinical Trial

Presenter: Dr. John Treanor, University of Rochester

The inactivated vaccine candidates undergoing clinical trials now include:

- The Clade 1, A/Vietnam/1203/04 strain is being manipulated with reverse genetics at St. Jude to replace the primary pathogenic factor, so that the seed virus can be handled under normal conditions for manufacture.
- Egg-grown subunit vaccines have been produced by licensed manufacturers (sanofi pasteur and Chiron); these vaccines are developed in a very similar material to that used for conventional annual influenza vaccine production. Licensure would be sought for a strain change.
- The University of Rochester is working on a subunit vaccine with no adjuvant, like the current influenza vaccine, to determine dose related safety and immunogenicity. But, rather than seeking a set point for the latter, they are looking for a

seroneutralizing antibody level that, in the 1997 Hong Kong samples, seemed to differentiate infected from uninfected individuals.

The initial study of this was the NIH DMID 4-063 trial at several of their VTEUs (Baylor College of Medicine, Cincinnati Children's Hospital, St. Louis University, UCLA, University at Maryland, University of Rochester, and Vanderbilt University). They evaluated the vaccine for safety and immunogenicity among healthy adults aged 18-64 years in a prospective, randomized, double-blind trial with a placebo group. Two IM vaccine doses (7.5, 15, 45 and 90 mcg, not all of hemagglutinin antigen) were given 28 days apart. Endpoints were safety, as measured by solicited and unsolicited adverse event reports, and immunogenicity, as measured by a neutralizing titer (i.e., the reverse genetically engineered vaccine seed virus) of 1:40. The results of the immunogenicity assessment were used to proceed with planned studies in the elderly and among children, just now beginning.

Preliminary results of DMID 04-063 show that the vaccine was well tolerated at all doses. There was a dose-related increase of local pain/tenderness. Some neutralizing responses were seen at all doses, and the best responses were seen at high doses. The hemagglutination inhibition test, which was previously ineffective, became very sensitive to detecting response to the H5 virus. When chicken erythrocytes were replaced by horse erythrocytes, the hemagglutination inhibition test became sensitive to detect responses to the H5 virus, and correlated well with neutralizing response. Results and the trial database are expected to be finalized this November. That will provide a better idea of dose-related immunogenicity.

The status of several H5 vaccine trials was outlined:

04-063: Vaccine use in healthy adults: completed. A revaccination study of this cohort to assess immune memory is also planned.

05-0015: Vaccine administered ID versus IM for dose saving: complete.

04-076: Evaluation of 45 mcg and 90 mcg doses in the healthy elderly.

04-077: Vaccine for healthy children: beginning.

05-043: Revaccination of 1997 H5 Hong Kong vaccine recipients (Hong Kong 15697 virus, an antigenic variant different from the current 5 virus).

Future studies of dose-saving strategies include:

- Evaluation of adjuvants (alum, MF59, MPL, and others).
- Evaluation of administration route.
- Evaluation of potential interaction with TIV, toward a quadrivalent with a pandemic component.
- Live attenuated (cold adapted) H5 or H9 vaccines like FluMist, as vaccines or to verify protection (mock challenge). A collaboration of MedImmune, Janta Subbarao and others, this will be tested at Johns Hopkins.
- Development of unconventional approaches such as DNA vaccines boosted by inactivated vaccines (farther in the future).

CLOSING COMMENTS

Dr. Abramson reported for Dr. Gellin that the next version of the influenza pandemic preparedness plan was due to be released in the next few weeks. Then, with no further comment, the meeting adjourned at 2:58 p.m.

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

Jon S. Abramson, MD, Chair

Date

Attachment #1: Attendance

ACIP Members

Jon S. Abramson, MD, Chair
Ban Mishu Allos, MD
Mr. Robert Beck
Judith R. Campbell, MD
Reginald Finger, MD, MPH
Janet R. Gilsdorf, MD
Harry Hull, MD
Tracy Lieu, MD
Edgar K. Marcuse, MD, MPH
Julia Morita, MD
John J. Treanor, MD
Robin J. Womeodu, MD

Members Dr. Dale L. Morse, Dr. Gregory A. Poland, and Ms. Patricia Stinchfield, NP, were absent.

***Ex Officio* Members**

Centers for Disease Control and Prevention
Stephen L. Cochi, MD, MPH
Frank DeStefano, MD
Alison Mawle, MD
Larry Pickering, MD, Executive Secretary
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), National Institutes of Health (NIH)
Geoffrey S. Evans, MD, National Vaccine Injury Compensation Program (NVICP)
Bruce Gellin, MD, Director, National Vaccine Program Office (NVPO)
John Grabenstein, MD, for Wayne Hachey, DO, MPH, Department of Defense (DOD)
Linda Murphy, RN, Center for Medicare and Medicaid Services (CMS)

Kristin L. Nichol, MD, Department of Veterans' Affairs (DVA)

Liaison Representatives
Carol J. Baker, MD, and Keith Powell, MD, American Academy of Pediatrics (AAP); Lorrie Rubin, MD, AAP Committee on Infectious Disease (COID)
Nancy M. Bennett, National Association of County and City Health Officials (NACCHO) Charles Helms, MD, National Vaccine Advisory Committee (NVAC)
Richard Clover, MD, and Jonathan Temte, MD, American Academy of Family Practitioners (AAFP)
Stephan L. Foster, PharmD, American Pharmacists Association (ApharmA)
Andrea Gelzer, MD, America's Health Insurance Plans (AHIP)
Steve Gordon, MD, Hospital Infections Control and Prevention Advisory Committee (HICPAC)
David Johnson, MD, MPH, Pharmaceutical Research and Manufacturers of America (PHARMA)
Samuel Katz, MD, Infectious Disease Society of America (IDSA)
Clement Lewin, PhD, MBA, Biotechnology Industry Organization (BIO)
Amy B. Middleman, MD, MPH, Society for Adolescent Medicine (SAM)
Monica Naus, MD, National Advisory Committee on Immunization, Ontario, Canada
David A. Neumann, PhD, National Coalition for Adult Immunization (NCAI)
Kathleen M. Neuzil, MD, MPH, American College of Physicians (ACP)
William Schaffner, MD, National Foundation for Infectious Diseases (NFID)
Litjen Tan, PhD, American Medical Association (AMA)
James C. Turner, MD, American College Health Association (ACHA)
Patricia Whitley-Williams, MD, National Medical Association (NMA)

Liaison representatives absent:
Stanley Gall, MD, American College of Obstetrics and Gynecology (ACOG),
Romeo S. Rodriquez, National Center for Health of Infancy and Adolescence, Mexico
David M. Salisbury, MD, London Department of Health
W. Paul McKinney, MD, Association of Teachers of Preventive Medicine (ATPM)
Robert Scallettar, MD, MPH, American Association of Health Plans (AAHP)

Agency Staff

Department of Health and Human Services (DHHS): Julie Schafer

Food and Drug Adminstration (FDA): Margaret Bash, Karen L. Goldenthal, Nancy Miller, Dorothy Scott

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

Office of General Counsel: Kevin Malone

National Center for Infectious Diseases (NCID):
Miriam Alter

Larry Anderson
Beth Bell
Niranjan Bhat
Kanfee Billah
Brendan Camp
Nancy Cox
Roz Dewart
Kathleen Gallagher
Laurie Kamimoti
Alexander Klimov
Eric Mast
Martin Meltzer
Dick Moyer
Elizabeth R. Unger
Susan Wang
John Ward
Annemarie Wasley
Mark Widdowson

National Immunization Program (NIP):
James P. Alexander
William Atkinson
Kip Baggett
Achel Bhatt
Willie Bower
Karen Broder
Angela Calugar
Bo-Hyun Cho
Margaret Cortese
Lauren DiMiceli
Gary Euler
Susan Farrell
Mary Fleming
Sandra Gambescia
Paul Garguillo
Edith Gary
John Glasser
Holly Groom
Dalya Guris
Penina Haber
Sonya S. Hutchins
Lisa Jacques-Carroll
Laurie Johnson
Archana Joshi
Tamara Kicera
Duane Kilgus

Katrina Kretsinger
Andrew Kroger
Lara Leidel
Jessica Leung
Pengjun Lu
Mona Marin
Stacy Martin
Gina Mootrey
Trudy Murphy
Rick Nelson
Carolyn O'Mara
Ismael Ortega-Sanchez
Joe Perz
Bette Pollard
Susan Reef
Sandy Roush
Alison Rue
Tammy Santibanez
Jeanne Santoli
Judy Schmidt
Jane Seward
Kate Shaw
Tom Shimabukuro
Jim Singleton
Barbara Slade
Jean Clare Smith
David Sniadack
Pamela Srivastava
Stephanie Steele
Shannon Stokley
Ray Strikas
Tejpratap Tiwari
Claudia Vellozzi
Greg Wallace
Bruce Weniger
Melinda Wharton
Amanda Whatley
Eddie Wilder
Bayo Willis
Skip Wolfe

Unidentified C/I/O:
Eileen Dun
Anthony Fiori
Eileen Lau

Food and Drug Administration (FDA): Teresa Finn**,** Karen Goldenthal, Ann T. Schwartz

National Institute for Allergies and Infectious Diseases (NIAID): Carolyn Deal, Jean Hu-Primmer

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

Members of the public or presenters to the committee in attendance were:
Vincent Ahonkhen, GlaxoSmithKline (GSK)
Shahlad Ali, Suntrust Robinson Humphrey
Donna Ambrosino, MBL
Lisa Amrani, Merck
Paula Annunziato, Merck
Phyllis Arthur, Merck Vaccine Division
Lynn Bahta, Minnesota Department of Health, Minneapolis, MN
Donna Ambrosino, MBL
Philip Basek, Henry Schein, Inc.
Joan Benson, Merck & Co., Inc.
Maryanna Brooke, Samford University, Birmingham, AL
John Boslego, Merck
Andrew Bowser, Internal Medicine World Report, Brooklyn, NY
Damian Braga, Pharmaceutical Researchers and Manufacturers of America
Ana Chevez, Emory University
James D. Cherry, UCLA, Los Angeles, CA
Joseph Collins, sanofi pasteur
Lenore Cooney, Cooney/Waters Group, NYC, NY
Dack Dalrymple, Dalrymple & Associates, LLC
Michael Decker, sanofi pasteur
Shelley Deeks, Public Health Agency of Canada
Derrick Demmon, Emory University
Richard Dinovitz, Wyeth
Erik Dorbach, Merck
Mark Feinberg, Merck Vaccines
Christine Fanelle, Merck & Co., Inc.
Leonard Friedland, GSK
Jeffrey Fu, Merck Vaccine Division
Julie Gabil, Georgia Division of Public Health
Diane Gaffoglio, CCR, CVR-CN
Matt Garrett, Wyeth
Diana Gaskins, Georgia Immunization Program
Ruth Gilmore, Georgia Immunization Program
Michelle Goveia, Merck
Cleveland Grady, Jr., GSK
Jackie Gress, Merck
Jesse Greene, SCDHEC, Columbia, SC

Kenneth P. Guito, sanofi pasteur
Neal Halsey, Johns Hopkins University, Baltimore, MD
Feng Han, Henry Schein
Claire Hannan, Association of Immunization Managers (AIM)
Rick Haupt, Merck & Co., Inc.
C. M. Healy, Baylor College of Medicine, Houston, TX
Penny Heaton, Merck & Co., Inc.
Teresa M. Hesley, Merck & Co., Inc.
Craig Hett, Cooney/Waters, NY, NY
Rachel Hlay, GSK
Micheal Hogue, PharmD, Samford University
Philip Hosbach, sanofi pasteur
Barbara Howe, Merck
John Hunsaker, A.H.I.P
Gina Hunt, Merck & Co., Inc.
Melonie Jackson, Mableton, GA
Rudolph E. Jackson, MD, Morehouse School of Medicine
Kathleen Jakus, Columbia University
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Barbara Kuter, Merck Research Laboratories
Philip LaRussa, Columbia University
François Lebel, MedImmune
Marie-Michele Leger, AAPA
Susan Lett, Massachusetts Department of Public Health
Michele Marill, Hospital Employee Health, Decatur, GA
Dean Mason, Sabin Vaccine Institute
Carmen Mejra, AAP
Joanne Monahan, Merck
Sarah Montgomery, Samford University
Fabienne Moore, Constella Group (CDC/INFO), Silver Spring, MD
Marie Murray, Recorder, Atlanta, GA
Karen Nielsen, GSK
Paul Offit, Children's Hospital of Philadephia, PA
Walter Orenstein, Emory University Vaccine Center
Will Page, GSK
Diane C. Peterson, Immunization Action Coalition
Stanley Plotkin, MD, sanofi pasteur, Doylestown, PA
Mila Prill, Emory University
Jane Quinn, GSK
James Ransom, National Association of City and County Health Officers (NACCHO)
David Rein, RTI International, RTP, NC
Angela Richards, Merck
Beth Rowe-West, North Carolina Division of Public Health
Judith Rusk, Infectious Diseases in Children, Thorofare, NJ
Kim Rincava, University of Maryland Center for Vaccine Development

Patricia Saddier, Merck Research Labs
Debbie Saslow, American Cancer Society
Carlos Sattler, Merck & Co.
Anne Schvind, GSK
Jane D. Siegel, MD, University of Texas, Dallas, TX
Dr. Alan J. Sievert, AAP Georgia Chapter, Braselton, GA
Ben Sloat, Georgia Department of Human Resources
Robert C. Sparks, Vanderbilt U niversity
Jeffrey Stoddard, MedImmune Vaccines
Pati Stoliar, TrialTech
Silvija Stoprans, PhD, Emory University Vaccine Center
Walter Straus, Merck Research Laboratories
Stacy Stuerke, Merck Vaccine
Joseph Sullivan, Merck & Co., Inc.
Michelle Tidwell, Georgia Chapter, AAP
Karen Townsend, GA Chapter, AAP
Timothy Townsend, Johns Hopkins University School of Medicine
John Trizzino, ID Biomedical
Andrew F. Trofa, GSK
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Amanda Welsh, GSK
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Celia Woodfill, California Department of Health Services
Laura York, Wyeth
John Zahradnik, sanofi pasteur
Rick Zimmerman, University of Pittsburgh
Jane R. Zucker, Department of Health and Mental Health, New York City, NY