DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Advisory Committee on Immunization Practices
October 25-26, 2006
Atlanta, Georgia

Record of the Proceedings

TABLE OF CONTENTS

Page

Attachment 1: List of Participants A1.1

Attachment 2: Acronyms Used In This Report A2.1

Minutes of the Meeting 1
October 25, 2006
Opening Session 1
HERPES ZOSTER SHINGLES VACCINE 2
Overview 2
Epidemiology and Impact of HZ and Postherpetic Neuralgia in Older Adults 3
Results of the SPS 4
Review of VZV Economic Studies 5
Overview of Vaccine Financing by Medicare 6
Public Comment Period 8
Proposed Recommendations and ACIP Vote on Use of Zoster Vaccine 8
RABIES VACCINE 16
Overview 16
Review of Human Rabies Prevention in the United States 16
Review of Rabies Biologics 17
Cost-Effectiveness of Rabies PEP 18
Proposed Recommendations and ACIP Vote on Rabies PEP and Preexposure Prophylaxis 19
CHILD/ADOLESCENT IMMUNIZATION SCHEDULE 21
Overview 22
Results of the Immunization Schedule Focus Groups 22
Update on the 2007 Immunization Schedule for Ages 0-18 Years 23
ACIP Vote on the 2007 Immunization Schedule for Ages 0-18 Years 24
INFLUENZA VACCINE 25
Overview 25
Update on Cumulative Monthly Influenza Vaccine Distribution 27
Manufacturer Reports on the Future of Influenza Vaccine 27
CAIV-T Safety and Efficacy Data 29
Public Comment Period 32

TABLE OF CONTENTS

Page

October 26, 2006
VACCINE FINANCING 34
Implementation of New Vaccines and Vaccine Recommendations 34
Overview of the NVAC Financing Workgroup 36
Guidance on Use of Zoster Vaccine [continued] 38
MENINGOCOCCAL VACCINE 39
Overview 39
Update on the MCV4 Supply 40
Overview of GBS in MCV4 Recipients 40
Decision Analysis of Meningococcal Disease Vaccination in the Presence of GBS 41
ISO Update 43
HPV VACCINE 45
Update on the Quadrivalent HPV Vaccine 46
Overview of the GARDASIL® Population Impact Analysis 47
Cost-Effectiveness of a Quadrivalent HPV Vaccine in the United States 48
Update on the Mumps Outbreak 49
Update on the Vaccine Supply 52
Update on the Global Polio Eradication Initiative 53
Ex- Officio Reports 56
Public Comment Period 57
Closing Session 57

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ATTACHMENT 2

Acronyms Used In This Report

AAFP	—	American Academy of Family Physicians
AAP	—	American Academy of Pediatrics
ACIP	—	Advisory Committee on Immunization Practices
AIM	—	Association of Immunization Managers
AIS	—	Adenocarcinoma *In Situ*
ALA	—	American Lung Association
BLA	—	Biologics License Application
BOI	—	Burden of Illness
CAIS	—	Childhood/Adolescent Immunization Schedule
CAIV-T	—	Cold-Adapted Influenza Vaccine
CDC	—	Centers for Disease Control and Prevention
CIN	—	Cervical Intraephithelial Neoplasia
C. jejuni	—	*Campylobacter jejuni*
CMS	—	Centers for Medicare and Medicaid Services
DSMBs	—	Data Safety Monitoring Boards
FDA	—	Food and Drug Administration
FFF	—	Families Fighting Flu
FQHCs	—	Federally Qualified Health Centers
GBS	—	Guillain Barré Syndrome
GMP	—	Good Manufacturing Practice
GSK	—	GlaxoSmithKline
HDCV	—	Human Diploid Cell Vaccine
HepA	—	Hepatitis A
HepB	—	Hepatitis B
HHS	—	Department of Health and Human Services
Hib	—	*Haemophilus influenzae B*
HMO	—	Health Maintenance Organization
HPV	—	Human Papillomavirus
HRIG	—	Human Rabies Immune Globulin
HRSA	—	Health Resources and Services Administration
HUI	—	Health Utility Index
HZ	—	Herpes Zoster
IC	—	Immunocompromised
IDSA	—	Infectious Disease Society of America
IgG	—	Immunoglobulin G
IgM	—	Immunoglobulin M
ILI	—	Influenza-Like Illness
IOM	—	Institute of Medicine
ISO	—	Immunization Safety Office
MCO	—	Managed Care Organization
MCV4	—	Meningococcal Conjugate Vaccine
MMRV	—	Measles, Mumps, Rubella, Varicella
MMWR	—	*Morbidity and Mortality Weekly Report*
mOPV1	—	Monovalent Polio Vaccine Type 1
MSW	—	Medically Significant Wheezing
NCIRD	—	National Center for Immunization and Respiratory Diseases [proposed]
NCVIA	—	National Childhood Vaccine Injury Act
NIH	—	National Institutes of Health
NIS	—	National Immunization Survey

NSFG	—	National Survey of Family Growth
NVAC	—	National Vaccine Advisory Committee
NVPO	—	National Vaccine Program Office
P&I	—	Pneumonia and Influenza
PCECV	—	Purified Chick Embryo Cell Vaccine
PCV	—	Pneumococcal Conjugate Vaccine
PEP	—	Postexposure Prophylaxis
PhRMA	—	Pharmaceutical Research Manufacturers of America
PSC	—	Protein Sciences Corporation
QALMs	—	Quality-Adjusted Life Months
QALYs	—	Quality-Adjusted Life Years
RCA	—	Rapid Cycle Analysis
RHCs	—	Rural Health Centers
sBLA	—	Supplemental Biologics License Application
SMEs	—	Subject Matter Experts
SPG	—	Sucrose Phosphate Glutamate
SPS	—	Shingles Prevention Study
TIV	—	Trivalent Inactivated Vaccine
VAERS	—	Vaccine Adverse Event Reporting System
VFC	—	Vaccines for Children
VICP	—	National Vaccine Injury Compensation Program
VNAs	—	Virus Neutralizing Antibodies
VSD	—	Vaccine Safety Datalink
VZV	—	Varicella-Zoster Virus
WHA	—	World Health Assembly
WHO	—	World Health Organization
ZE-1	—	Zoster Episode 1
ZE-2	—	Zoster Episode 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
October 25-26, 2006
Atlanta, Georgia

Minutes of the Meeting

The Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD) [proposed] convened a meeting of the Advisory Committee on Immunization Practices (ACIP). The proceedings were held on October 25-26, 2006 at CDC's Global Communications Center, Building 19, Room 232 in Atlanta, Georgia. The list of participants is appended to the minutes as Attachment 1. [Note: the list of participants only includes persons who introduced themselves for the record, presented, made public comments, or registered prior to the meeting.]

Opening Session

Dr. Jon Abramson, the ACIP Chair, called the meeting to order at 8:03 a.m. on October 25, 2006 and welcomed the participants to the proceedings. He particularly recognized the new ACIP members: Drs. Carol Baker, Susan Lett, Kathleen Neuzil and Ciro Sumaya. Each new member would serve a four-year term from July 1, 2006 to June 30, 2010. Brief backgrounds of the four new ACIP members were included in the meeting packets. Dr. Abramson also announced that Dr. Janet Gilsdorf's term was extended for an additional year to complete her ongoing activities as the Human Papillomavirus Vaccine (HPV) Workgroup Chair.

Dr. Larry Pickering, the ACIP Executive Secretary, made several announcements. ACIP can be contacted through its e-mail address at acip@cdc.gov. The ACIP web site can be accessed at www.cdc.gov/nip/acip to obtain agendas, meeting minutes, copies of slide presentations, future meeting dates and up-to-date information on other ACIP activities. Time would be reserved during the meeting for public comments, but formal comment periods might also be scheduled during the deliberations of specific agenda items. The public was invited to make additional comments during ACIP's open discussions if time permitted. The structure of ACIP meetings would be modified beginning with the current meeting to allow for two regularly scheduled updates. The two new presentations would include a vaccine safety review and a vaccine supply review of each vaccine recently approved by ACIP.

Dr. Pickering noted the following changes in ACIP representation or participation. Dr. Stanley Grogg, of Oklahoma State University, Center for Health Sciences, College of Osteopathic Medicine, would begin serving as a new ACIP liaison to the American Osteopathic Association in February 2007. *Ex- officio* and liaison members for the following organizations would be absent from the current meeting: Health Resources and Services Administration (HRSA); the National Vaccine Program Office (NVPO); the American College of Obstetrics and Gynecology; and the Pharmaceutical Research and Manufacturers of America (PhRMA). Replacements for the HRSA *ex- officio* representative and the NVPO and PhRMA liaison members would attend the meeting.

Dr. Pickering reviewed ACIP's conflict of interest and disclosure policy. Appointed members agree to forego participation in certain activities related to vaccines during their respective tenures in accordance with the conflict of interest provisions outlined in the ACIP *Policies and Procedures Manual*. The goal in appointing ACIP members is to achieve the greatest level of expertise and minimize the potential for actual or perceived conflicts of interest.

CDC has issued limited conflict of interest waivers for certain other interests that may enhance the expertise of a member while serving on ACIP. The following conditions would apply to members with limited waivers. First, members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may serve as consultants and make presentations to ACIP. Second, members are prohibited from participating in ACIP's deliberations or votes on issues related to those specific vaccines. Third, members may participate in discussions on other vaccines of the affected company, but must abstain from voting on vaccines manufactured by that specific company.

The ACIP charter authorizes the Executive Secretary or designee to temporarily designate *ex- officio* representatives as voting members if a quorum of eight appointed members would not be available or qualified to vote due to financial conflicts of interest. *Ex- officio* representatives who are formally requested to vote during these circumstances would be asked to disclose any potential conflicts of interest.

The following ACIP members disclosed potential financial conflicts of interest for the record.

- Dr. Carol Baker serves as an uncompensated member on the Safety Evaluation Committee for Merck's Pediatric Vaccine Programs; received honorarium from sanofi pasteur for attendance at an educational conference; received honorarium from Inhibitex® for participation on an advisory board; and serves as a consultant to the Novartis Group B Streptococcal Vaccine Program.
- Dr. Janet Gilsdorf is an uncompensated independent safety monitor for an influenza vaccine trial sponsored by the National Institutes of Health (NIH).
- Dr. John Treanor's institution, the University of Rochester, receives support for clinical trials or laboratory studies from Merck, ID Biomedical/GlaxoSmithKline, Protein Sciences, sanofi pasteur and AlphaVax. The University of Rochester also has pending support from Biocryst.

HERPES ZOSTER (HZ/SHINGLES) VACCINE

The series of presentations, ACIP discussions and votes, and public comments on the shingles vaccine are set forth below.

Overview

Dr. John Treanor, the Shingles Vaccine Workgroup Chair, reported that the workgroup held about 30 conference calls following the June 2005 ACIP meeting to review information from CDC and manufacturers on economic issues, efficacy, side effects and other outcomes relating to ZOSTAVAX® vaccine. A series of presentations would be made and the workgroup's recommendations would be summarized to facilitate ACIP's discussion and vote on the use of ZOSTAVAX®.

Epidemiology and Impact of HZ and Postherpetic Neuralgia (PHN) in Older Adults

Dr. Kenneth Schmader, of Duke University and Durham Veterans Administration Medical Centers, presented data on the epidemiology and impact of HZ and PHN in older adults. HZ affects ~1 million Americans each year. Data from retrospective case reviews, administrative claims databases and self-reports showed a range in the incidence of HZ of 1.2-4.8 cases/1,000 person-years in adults of all ages and 7.2-11.8 cases/1,000 person-years in adults ≥60 years of age. However, the Shingles Prevention Study (SPS) showed an incidence of 11.1 cases/1,000 person-years based on microbiologic confirmation of 94% of cases in a cohort of 19,247 adults ≥60 years of age.

The lifetime risk of HZ has been estimated at 20%-30%. A projection was also made that 50% of persons who live until 85 years of age would ultimately develop HZ. The number of HZ cases would be highest in immunocompetent older adults and the absolute number of HZ cases would increase as the population ages. Several key risk factors for HZ have been identified, including HIV/AIDS, lymphoproliferative cancers, organ transplants, systemic lupus erythematosus and immunosuppressive treatment.

Common complications of HZ include acute neuralgia, PHN, ocular complications of ophthalmic zoster, scarring and bacterial super-infection. Less common complications of HZ include cutaneous dissemination, herpes gangrenosum, pneumonitis, hepatitis, encephalitis, motor neuropathies, myelitis and hemiparesis. Of all zoster cases, ~15% involve the ophthalmic division of the trigeminal nerve. Without antiviral therapy, 50%-70% of patients with HZ ophthalmicus would develop ocular complications that could lead to reduced vision or blindness.

Acute HZ pain is a major cause of significant morbidity in older adults. A prospective study with a cohort of 110 patients with HZ found that greater pain burden was associated with increased emotional distress, poorer physical or social functioning, and a decreased role. Of the entire cohort, 42% reported acute HZ pain as “horrible” or “excruciating,” while 14.6%-26.3% reported acute HZ pain as a barrier to physical or social functioning and their roles. A study using SF-36 domains showed that HZ resulted in a lower quality of life compared to hypertension, congestive heart failure, diabetes mellitus, myocardial infarction and depression.

With respect to PHN, different studies published in the literature have resulted in variable definitions. For example, time from rash onset could vary from 30-180 days, while pain intensity could vary from any pain to clinically meaningful pain ratings. However, recent definitions focus on any pain 90-120 days after rash onset. Despite the differences in definitions, PHN is an exceedingly common cause of neuropathic pain that impacts the quality of life of older adults in terms of physical, social, psychological and daily functions. The prevalence of PHN has been estimated at 500,000 in the United States and is second only to painful diabetic neuropathy or low back pain.

Data from major antiviral trials with cohorts of adults ≥50 years of age showed that 55% of patients in the placebo group had pain 90 days after rash onset, while 25%-35% of patients in the antiviral group had pain at this same time point. The SPS showed that the incidence of PHN in the placebo group was 1.38/1,000 person-years 90 days after rash onset. For purposes of the SPS, “pain” was rated as ≥3 or more on a worst pain scale of 0-10. A strong association was seen between increasing age and the prevalence of PHN or duration of pain, but other risk factors that were identified included severity of acute pain or rash, painful prodrome and female gender.

Results of the SPS

Dr. Michael Oxman, of the University of California-San Diego, reported that the SPS results were published in June 2005. In 1998, the Food and Drug Administration (FDA) accepted the SPS protocol and primary and secondary endpoints as the principal efficacy study for the investigational zoster vaccine. The SPS was designed as a randomized double-blind placebo-controlled trial to test the hypothesis that boosting waning varicella zoster virus (VZV)-specific cell mediated immunity in older persons using a live attenuated VZV vaccine would protect this population against HZ and PHN. The SPS enrolled and actively followed 38,546 subjects ≥60 years of age at 22 study sites across the United States.

The primary endpoint of the SPS was the "burden of illness (BOI) due to HZ" defined as the sum of HZ severity of illness scores in all subjects in the vaccine or placebo group. Subjects who did not develop shingles were assigned an HZ severity of illness score of 0. The secondary endpoint of the SPS was the "incidence of clinically significant PHN" defined as HZ pain or discomfort with a zoster brief pain inventory worst pain score of ≥3 for more than 90 days after onset of HZ rash. Of 38,546 patients enrolled in the study, 41% were female, 46% were ≥70 years of age, 19,270 were given the zoster vaccine, and 19,276 were given a placebo. The SPS female population was only 41% due to the small percentage of female veterans ≥60 years of age. More than 95% of patients were followed until the end of the study.

Data collected from the SPA showed the following results. Vaccine recipients did not transmit a vaccine virus. The vaccine reduced the BOI due to HZ in the vaccine group by 61.1% compared to the placebo group. This decrease represented vaccine efficacy of 65.5% in the younger age strata and 55.4% in the older age strata. Both of these outcomes exceeded the pre-specified criteria for "successful" vaccine efficacy of a 47% point estimate and a lower bound of the 95% confidence interval of 25%. Data presented at a recent Infectious Disease Society of America (IDSA) meeting provided further evidence that the HZ BOI would serve as a valid measure of the total adverse impact of zoster on a population of older persons. The zoster vaccine was found to reduce HZ pain interference with daily living activities by ~66%. This measure was similar to the efficacy of zoster vaccine for the HZ BOI.

The SPS also focused on the incidence of PHN and found that vaccine efficacy was 66.5% overall, 65.7% in the younger age strata, and 66.8% in the older age strata. For purposes of the SPS, "PHN" was defined as significant pain persisting or appearing >90 days after zoster rash onset. Despite this rigorous definition, the vaccine was found to reduce PHN by ~66.5%. The SPS provided a low estimate of HZ severity and zoster vaccine efficacy. All subjects were seen as soon as possible after HZ rash onset and were given state-of-the-art treatment without cost, including Famciclovir and pain management. Of all subjects with HZ, 86%-87% received antiviral therapy. Of this subgroup, 64%-66% received treatment within 72 hours of rash onset.

Adverse events data collected from >98% of subjects 42 days post-vaccination showed that the investigational zoster vaccine was well tolerated. The number of deaths and percentage of subjects with ≥1 serious adverse events were the same in the vaccine and placebo group. The influence of age of the subjects on the results was also analyzed in the SPS. Vaccine efficacy for HZ BOI was well maintained in the older age strata and over all age groups, undiminished in the incidence of PHN, and significantly reduced in the incidence of HZ.

The SPS analyzed severity of illness scores of >600 that represent the equivalent of >2 months in which patients reported the "worst imaginable pain" every day. All but one of the subjects 60-69 years of age with these severity of illness scores were in the placebo group. Much more severe disease was seen in the older age strata. Overall, the zoster vaccine resulted in an 89% decrease of severe cases in subjects 60-69 years of age and a 68% decrease in subjects ≥70 years of age for an overall reduction of 73%. The vaccine maintained efficacy regardless of the age of the subject. The effect in younger subjects was

primarily mediated by preventing HZ, while the effect in older subjects was primarily mediated by attenuating HZ.

SPS data indicated that vaccine efficacy would be well maintained four years post-vaccination. Vaccination of all immunocompetent persons ≥60 years of age in the United States would result in annual reductions of 283,700 HZ cases and 46,400 PHN cases. However, the cumulative impact would be even greater due to underestimates of current data. Of >13,000 placebo recipients who have been vaccinated to date, none have shown adverse events. Follow-up of a large subset of the originally vaccinated subjects is ongoing to analyze zoster rates, examine the same endpoints in the parent study, and determine the duration of vaccine persistence.

Several participants provided additional details on the SPS in response to ACIP's questions and comments.

- A recent search showed that only two of 36 adverse events from the zoster vaccine reported to the Vaccine Adverse Event Reporting System (VAERS) were serious: tachycardia and hospitalization due to zoster one day post-vaccination. Rash, vasal dilation and hypersensitivity of injection site were the top three adverse events from the zoster vaccine reported to VAERS.
- FDA's position was that the data were inadequate to support the use of the zoster vaccine to treat PHN. As a result, FDA approved an indication for use of the zoster vaccine for HZ only.
- A transmission case was reported to Merck, but a specimen has not been obtained to date to confirm the case as an oka strain.

Review of VZV Economic Studies

Dr. Mark Messonnier, of CDC, summarized data from VZV economic studies. CDC's literature review included one study published in September 2006 and three unpublished studies submitted by CDC and two external sources. CDC was aware that another VZV economic study was published in 2001, but this research was based on non-U.S. data and was not included in the review.

All four studies considered in the review performed cost-utility analyses and were based on the Markov model. Only one of the four studies analyzed adverse events. Three of the studies were conducted from a societal perspective, while two of the studies included an additional healthcare perspective. The ages of the populations in the four studies ranged from 60+ to 65 years of age.

CDC also reviewed preliminary data from its cost-effectiveness study of vaccinating elderly persons in the United States to prevent shingles. The study included outcomes and summary measures for quality-adjusted life years (QALYs), shingles and PHN cases, a cost-utility ratio, number of persons needed to vaccinate, and a cost-effectiveness ratio. The study showed that the cost per case of HZ prevented would be $3,330; the cost per case of PHN prevented would be $6,405; and the cost per QALY gained would be $35,000.

The following ranges were observed in the four external studies: (1) vaccination costs of $149-$200; (2) acute HZ costs of $287-$742; (3) HZ incidence rates of 3%-14.29/1,000 person-years based on individuals 60-64 years of age or ≥90 years of age; (4) PHN as a condition of having HZ of 5.1%-32.2%; (5) duration of PHN of eight months up to 4.2 years; (6) duration of waning of 9-30 years; and (7) QALY weights for PHN of 0.106-0.67. Four studies conducted by CDC and three external sources from a societal perspective showed a range in the cost per QALY from $27,000-$112,000.

CDC reviewed other vaccine cost-effectiveness data as a basis of comparison with the shingles vaccine. The influenza vaccine would result in a QALY of $16,500 for persons 50-64 years of age and cost-savings for persons ≥65 years of age. The meningococcal conjugate vaccine (MCV4) would result in QALYs ranging from $138,000-$271,000 for adolescents, toddlers and infants. The second dose of varicella would result in a QALY of $96,000. However, CDC acknowledged the difficulty in comparing cost-utility analyses between childhood and adult vaccines. As a result, CDC intends to conduct a more in-depth mathematical analysis after the studies are published due to differences in methodologies, assumptions and measures.

Based on overall results from the studies, the cost-effectiveness ratio would most likely be <$100,000/QALY gained. At this time, a rule or "gold standard" has not been established for a non-cost-saving intervention to determine an acceptable or unacceptable cost-utility ratio. It is up to decision-makers to determine whether the value of a QALY would be worth the expenditure of resources.

Overview of Vaccine Financing by Medicare

Dr. Jeffrey Kelman, of the Centers for Medicare and Medicaid Services (CMS), described the strengths and limitations in using Medicare for vaccine financing. Medicare Parts A and B cover direct treatment of disease. For example, Part B would cover the rabies vaccine after a dog bite, but would not cover the vaccine for a Medicare beneficiary who is an animal handler. However, three exceptions to this statute were established for the influenza, pneumococcal and hepatitis B vaccines for moderate to high-risk persons.

Medicare beneficiaries are not required to pay a deductible or co-payment for influenza and pneumococcal vaccines. Physicians who administer any one of the three preventive vaccines are allowed to charge current procedural terminology codes under Part B. CMS and HHS extensively discussed whether ZOSTAVAX® could be administered under Part B as post-exposure direct treatment. However, the agencies realized that a regulatory or statutory change would be needed because the existing law could not be interpreted to cover ZOSTAVAX® under Part B.

Medicare Part D covers all FDA-approved drugs defined as "medically necessary" medications. Part D includes network drug providers, such as point-of-sale retail, long-term care, home infusion and specialty pharmacies. However, Part D excludes specific physicians as in-network providers and does not cover vaccines otherwise covered by Part B.

CMS acknowledged that existing statutory language would prohibit coverage of ZOSTAVAX® under Medicare Part B. As a result, CMS proposed several strategies to overcome these regulatory barriers and pay for ZOSTAVAX® in or out of physicians' offices. First, the in-network approach would allow Medicare beneficiaries to obtain ZOSTAVAX® from point-of-sale pharmacies in 44 states. In addition, Part D plans can deliver vaccines to physician offices through in-network specialty distributors. Second, the out-of-network approach would allow physicians to obtain ZOSTAVAX® directly from manufacturers, administer the vaccine to patients, and charge beneficiaries, who would then submit the bills to the Part D plans.

Third, the specialty pharmacy approach would allow Medicare beneficiaries in long-term care and assisted living facilities to receive ZOSTAVAX® from long-term care and home infusion pharmacies. Several in-network chains are planning to administer ZOSTAVAX® at the point-of-sale, but specialty, long-term care and infusion pharmacies would be expected to obtain the appropriate certifications and approval from state pharmacy boards before administering the vaccine.

If ZOSTAVAX® is defined as "medically necessary," the vaccine would be covered by all Part D plans in 2007. Physicians could bill Medicare beneficiaries directly for the drug itself as out-of-network and bill secondary insurance payers or state Medicaid plans that cover vaccines for cost sharing, but would not be allowed to bill an administrative charge for ZOSTAVAX® under Part D. CMS issued guidance encouraging the use of all three approaches and strongly emphasized the need for all plans to provide all medically necessary treatments and drugs. However, CMS is anxiously awaiting ACIP's recommendations because ZOSTAVAX® will be available in plan year 2006 and in all plans in 2007.

Dr. Kelman was pleased to announce that several activities are underway to promote easier access to vaccines. A vaccine-specific web portal was developed to link contracted plans and physicians and facilitate electronic billing. A regulation was recently proposed authorizing CMS to link >4 billion Part D data elements that are submitted each year. This integrated database, if approved, would link data elements from Medicare Parts A and B, hospitals, providers, home healthcare facilities and nursing homes in a fully encrypted and longitudinal system.

CMS is confident that the proposed integrated database would serve as a tremendous post-marketing surveillance tool for vaccines and all other drugs. Most notably, data will be captured, linked and maintained on all 43 million Medicare beneficiaries and vaccine side effects, reactions and efficacy. The integrated database will also allow CMS to conduct clinically significant projects with small and defined patient subsets.

Dr. Kelman confirmed that he would provide CDC with a written list of questions and answers for both healthcare professionals and patients. In the interim, however, he emphasized key points on vaccine financing by Medicare that ACIP should consider in formulating its recommendations on the use of ZOSTAVAX®. Medicare Part B does not cover any preventive vaccines other than the three exceptions defined by statute: influenza, pneumococcal and hepatitis B vaccines. Part D will cover ZOSTAVAX® and other large-scale preventive vaccines.

Medicare beneficiaries will pay on average of 25% for ZOSTAVAX® in addition to an administrative fee, but three categories of enrollees will be exempt from this requirement. First, dual-eligible beneficiaries who receive full benefits from both Medicare and Medicaid will pay $3 for ZOSTAVAX®. Medicaid could pay the administrative fee for beneficiaries in this category, but this decision would be made on a state-by-state basis. Second, certain eligible Medicare beneficiaries at 100%-150% of the federal poverty level will pay $5 for ZOSTAVAX®. Third, Medicare beneficiaries who receive catastrophic benefits will pay 5% for ZOSTAVAX®.

Several ACIP members were pleased with the development of the vaccine-specific web portal to facilitate electronic billing and the strategies CMS outlined to promote easier access to vaccines. However, some members were extremely concerned about unresolved or unclear issues. Most notably, efforts to coordinate Medicare benefits to pay for ZOSTAVAX® will be extremely challenging. Potential problems with network pharmacies providing ZOSTAVAX® to providers have not been sufficiently addressed. Adequate attention has not been given to payment of the administrative fee to date because beneficiaries and employers assume that Medicare would pay its fair share for ZOSTAVAX®. The ACIP members strongly urged CMS to clarify these issues for ZOSTAVAX® at this time to avoid facing similar problems when other adult vaccines are approved in the future.

Several participants provided additional details on ZOSTAVAX® financing and economic issues in response to ACIP's questions, comments and concerns.

- Merck launched its Vaccine Patient Assistance Program in September 2006 to provide ZOSTAVAX® and six other vaccines to uninsured adults with household incomes at or

below 200% of the federal poverty level. Physicians' offices and private clinics can administer the seven Merck vaccines to patients who meet these criteria. To avoid missed opportunities for vaccination, patients would be allowed to enroll in the program and receive a vaccine in the same visit. Merck has initiated dialogue with CDC and other key constituents to explore the possibility of expanding the program to public health clinics.

- Of the total Medicare Part D population of 22.5 million persons, ~40% or 9.3 million qualify for low-income subsidies and would be required to pay a $3 or $5 co-payment. However, some health plans intend to use tier 2 formularies to cover ZOSTAVAX®. This approach would require beneficiaries to pay a co-payment of $30 or less.
- Merck is pleased that many Medicare Part D plans are considering using the vaccine-specific web portal to coordinate benefits in physicians' offices at the time a vaccine is administered to patients.
- Merck incorporated several studies into its models and also performed a medical record review study to investigate a 21-day window prior to stated claimed diagnoses. The overall cost-effectiveness ratios were found to be robust regardless of whether this factor was included in the models.

Public Comment Period

Dr. Herbert Kaufman, of the Louisiana State University Medical School, emphasized that HZ causes ophthalmic zoster and other significant adverse outcomes in patients. Most notably, daily excruciating pain can persist for more than one year, prevent social intercourse and lead to suicide in persons >70 years of age. Dr. Kaufman urged ACIP to approve the use of ZOSTAVAX® to minimize the incidence of this terrible disease.

Dr. William Waters has practiced internal medicine and nephrology for 45 years. He emphasized that PHN causes significant depression in older patients due to decreased quality of life. For example, futile medications do not adequately resolve pain. Diagnostic resources for shingles are inappropriately allocated and lead to unnecessary hospitalizations for abdominal, chest or head pains. Dr. Waters noted that prophylaxis with the promising ZOSTAVAX® vaccine would be a much more desirable approach.

Mr. Robert McDonough, of AETNA Insurance Company, announced that AETNA provides coverage for ZOSTAVAX® because the vaccine offers important and clinically significant benefits to its members. He urged ACIP to also consider the clinically significant benefits of ZOSTAVAX® and approve wide availability of the vaccine.

Proposed Recommendations and ACIP Vote on Use of Zoster Vaccine

Dr. Rafael Harpaz, of CDC, reported that FDA licensed the zoster vaccine on May 25, 2006 for the prevention of HZ in persons $\geq$60 years of age. The workgroup made diligent efforts to formulate comprehensive guidance to meet the needs of providers and patients. Since September 2005, the workgroup has held 30 conference calls to review relevant published and unpublished data on (1) the epidemiology and natural history of zoster; (2) zoster vaccine safety, immunogenicity and efficacy; and (3) vaccine financing, storage, handling and economic issues.

The workgroup considered and extensively discussed questions on the zoster vaccine submitted to CDC, the manufacturer and in response to a survey. The workgroup proposed recommendations based on

expert opinion when data were inadequate and presented its preliminary guidance to ACIP during the June 2006 meeting. The workgroup also asked practitioners to review the proposed recommendations to ensure that clinical needs would be met.

The workgroup acknowledged that ACIP's efforts to provide guidance for specific clinical settings even with incomplete evidence are different than FDA's function. As a result, the workgroup attempted to formulate "off-label" guidance that could rapidly yield data and would be consistent with the label whenever possible and appropriate. However, the workgroup also realized that off-label guidance might dissuade studies on defining vaccine safety and efficacy. Moreover, benefits for studies and the overall regulatory process might be delayed and FDA might provide narrow indications. Overall, the workgroup agreed that off-label guidance should be given judiciously and only in select settings where vaccine safety and efficacy would be likely.

Dr. Harpaz presented the workgroup's proposed recommendations for the use of ZOSTAVAX®. The issues being brought to a vote were selected based on (1) size of the impacted population; (2) degree of the workgroup's discussion; (3) consistency with the package label; and (4) the absence of relevant guidance from existing ACIP statements. He also summarized issues the workgroup considered in support of or against each policy.

Vote 1: "ACIP recommends that adults 60 years and older receive a single dose of zoster vaccine." Considerations against this policy are as follows. The burden of disease is pain and would be borne by an adult rather than a child. Effects on a population would be limited. Decisions could be made from a doctor/patient perspective rather than a public policy perspective. Severe disease or death would not be common in immunocompetent persons. The disease would not result in a significant amount of lost work time due to the primary target population of retirees. Results from economic analyses have shown variations in dollars/QALY by factors of four and also demonstrated strong sensitivity to analytic approaches, types of models and parameter values. Empiric or theoretical consensus is lacking for several key economic issues. The vaccine appears to be expensive.

Considerations in support of this policy are as follows. The burden of disease is substantial and can shatter lives due to depression or suicide. The vaccine is safe and fairly effective. Both providers and patients have expressed an interest in the vaccine. Weak support from ACIP could lead to modest financing by Medicare, private insurers and the VA as well as disparities in poor and vulnerable populations. The disease could result in a significant amount of lost leisure time among the primary target population of retirees. Economic analyses have demonstrated that the vaccine is within the acceptable range of cost-effectiveness.

Dr. Abramson called for a motion on the proposed recommendation for routine zoster vaccination of adults ≥60 years of age. A motion was properly placed on the floor and seconded by Dr. Hull and Ms. Stinchfield, respectively. **ACIP passed the motion by a majority vote:**

- **13 in favor:** Abramson, Allos, Beck, Gilsdorf, Hull, Lett, Lieu, Morita, Morse, Neuzil, Stinchfield, Sumaya, Womeodu.
- **2 abstentions:** Baker, Treanor.
- **0 opposed.**

Vote 2: "ACIP recognizes that it is quite plausible that zoster vaccine is safe and effective in persons under 60 years of age. However, in the absence of adequate data on safety and efficacy for this population and in the absence of an FDA license, ACIP does not routinely recommend the vaccine for persons under 60 years of age." The workgroup considered the following issues in proposing this recommendation. Based on considerations of safety and benefit, the manufacturer requested a ZOSTAVAX® license from FDA for persons 50-59 years of age in addition to those ≥60 years of age who

were studied in the vaccine trial. Both patients and physicians expressed an interest in the shingles vaccines for persons <60 years of age. The workgroup is interested in providing explicit guidance for this common clinical issue.

Considerations in favor of a policy that would extend use of zoster vaccine to persons <60 years of age are as follows. Increased vaccine efficacy with decreasing age observed in the zoster trial suggested efficacy in persons <60 years of age. The association between a decrease in the relative risk of adverse events and decreasing age observed in the zoster trial indicated solid vaccine safety in persons <60 years of age.

The burden of zoster is substantial in persons <60 years of age. National disease rates show that ~180,000 persons 50-59 years of age are affected by zoster each year and 9,000-22,000 persons in the same population are impacted PHN each year. The burden of disease would result in lost work because 70% of the population is employed. Other persons <60 years of age might be especially vulnerable to PHN or shingles, including individuals with depression, pre-existing chronic pain, poor pain tolerance or certain occupations.

Considerations against a policy that would extend use of zoster vaccine to persons <60 years of age are as follows. For persons <60 years of age, limited data have been collected on vaccine safety and immunogenicity and no vaccine efficacy data have been gathered. The risk of PHN would be low in persons <60 years of age. No evidence has been produced to support the concern that the prevention of reactivation of disease in vaccinated persons <60 years of age might shift the risk of zoster to later ages when more PHN would be present. However, persons 50-59 years of age represent a very large cohort of ~37 million, and routine vaccination might be inappropriate for such a broad age-based cohort without a supporting FDA license. Even in the absence of specific FDA approval for use of vaccine in persons <60 years of age, physicians always have the option to offer the vaccine to patients off-label.

Dr. Abramson called for a motion on the proposed recommendation for no routine zoster vaccination of adults <60 years of age. A motion was properly placed on the floor and seconded by Drs. Beck and Neuzil, respectively. Several ACIP members made comments and suggestions to clarify and refine the language.

- The language should be revised to be positive rather than negative. Physicians will most likely only read the last sentence of the recommendation and interpret the guidance to mean that ACIP actively discourages vaccination for persons <60 years of age.
- The language should be changed to “ACIP does not recommend routine vaccination for persons under 60 years of age.”
- More science-based evidence on vaccine safety and efficacy should be gathered to support the recommendation.
- The following new language should be added at the end of the recommendation: “In certain circumstances, however, physician judgement may warrant vaccination.”
- “Absence of an FDA license” should be deleted from the recommendation.
- The recommendation should be revised to clarify that “ACIP does not recommend routine vaccination for persons <60 years of age at this time.”

Dr. Abramson noted that ACIP agreed with the overall sense of the recommendation for no routine zoster vaccination of adults <60 years of age, but the voting members did not reach consensus on specific wording changes. As a result, he asked the members to submit revisions to Drs. Harpaz or Treanor.

ACIP passed the motion by a majority vote with the condition that Drs. Harpaz and Treanor would revise the language based on comments submitted by the members:

- **13 in favor:** Abramson, Allos, Beck, Gilsdorf, Hull, Lett, Lieu, Morita, Morse, Neuzil, Stinchfield, Sumaya, Womeodu.
- **2 abstentions:** Baker, Treanor.
- **0 opposed.**

Vote 3: "ACIP recommends zoster vaccine for persons ≥60 years of age whether or not they report a prior episode of zoster. It would seem the benefit of vaccination may be limited soon after the prior episode, though data do not allow establishment of a threshold of time before which benefits do not warrant vaccination.

Considerations in making this determination of when to vaccinate would include reliability of the zoster history, pain and disability from that episode and any factors that would make the patient particularly vulnerable to a recurrent episode. It is not necessary to specifically ask patients about history of zoster before offering them the vaccine." The workgroup considered the following issues in proposing this recommendation. Prior history of zoster is listed in the package label as a precaution to zoster vaccination with the following statement: "The use of ZOSTAVAX® in individuals with a previous history of zoster has not been studied."

Considerations against this policy are as follows. Approximately 15% of persons will have had a prior episode of zoster by the age of 60, but the percentage would be higher in the entire population of persons ≥60 years of age. The vaccine is not licensed for persons with prior zoster. The initial rate and severity of zoster episode 2 (ZE-2) after zoster episode 1 (ZE-1) is unknown, but would appear to be diminished. No safety or efficacy data have been collected on vaccination of adults with prior zoster.

Considerations in support of this policy are as follows. A 10%-20% error rate has been estimated in the reported history of zoster. Self-diagnosis is questionable, while remote diagnosis might lead to recalls in the target population. A solid methodology has not been developed to confirm zoster history. These uncertainties could result in a burden to physicians and additional barriers to vaccination.

The rate of ZE-2 is not well defined, but appears to be similar to the risk of ZE-1 on an annual basis. Persons with ZE-1 might be predisposed to ZE-2. Confirmed cases in healthy adults have been documented to occur within one to two years in the shingles trial. No factors have been identified to support concerns about vaccine safety. The vaccine would most likely add protection, particularly if a history of zoster is remote.

Dr. Abramson called for a motion on the proposed recommendation for persons regarding prior zoster episodes. A motion was properly placed on the floor and seconded by Drs. Gilsdorf and Hull, respectively, to amend the recommendation as follows: "ACIP recommends zoster vaccine for persons ≥60 years of age whether or not they report a prior episode of zoster. A history of herpes zoster should not influence the decision to offer zoster vaccine."

ACIP passed the amended recommendation by a majority vote:

- **13 in favor:** Abramson, Allos, Beck, Gilsdorf, Hull, Lett, Lieu, Morita, Morse, Neuzil, Stinchfield, Sumaya, Womeodu.
- **2 abstentions:** Baker, Treanor.
- **0 opposed.**

Vote 4: "Vaccination with a single dose of zoster vaccine should be considered in limited clinical circumstances in which an immunocompetent person of any age with a verified history of varicella is anticipated to become immunocompetent due to progression of his or her specific medical condition or specific medical treatments." "Verified history" would require IgG testing with conventional and

commercially available laboratory testing in persons <60 years of age, but testing would not be required for persons >60 years of age.

The workgroup considered the following issues in proposing this recommendation. Many situations occur in which immunocompromised (IC) can be anticipated, including chemotherapy or radiation therapy for solid tumors; organ transplantation for failure of kidneys and other organs; and administration of IC agents for inflammatory conditions, such as rheumatoid arthritis, lupus, Crohn's and psoriasis. The period of time until IC is expected to occur can vary in these situations from days to years. The number of persons anticipating IC is increasing due to an increasing number of indications for IC and also due to better and more intensive treatments. An informal evaluation suggests that at least five million persons are in situations in which they can anticipate IC; most of these persons are <60 years of age.

The magnitude of risk of zoster introduced by IC is typically much greater than that introduced by age. For example, the rate in solid organ transplant recipients is ~10 times higher in IC persons compared to the general population, whereas the rate in persons ≥60 years of age is only two times higher compared to persons 50-59 years of age. The risk of the most severe complications of zoster, including dissemination, neurologic and ophthalmic disease and death, is increased to an even greater degree as compared to age alone.

The workgroup's position is that the risk of zoster vaccination in immunocompetent persons anticipating IC is not increased. Indeed, the risk of zoster vaccination in persons with a history of chickenpox and thus at risk of zoster is very likely not increased even in persons who are currently IC since they appear to retain effective specific immunity against VZV. For example, repeated episodes of chickenpox (caused by wild-type VZV) are rare and generally not severe in IC persons. Also, clinical trials have demonstrated that varicella vaccine was well tolerated in IC patients even without a prior varicella history, including those with leukemia in remission and HIV-positive persons with CD4 counts ≥15%. Finally, antiviral drugs remain an option to treat disseminated attenuated VZV should this very unlikely outcome occur.

Three studies have shown the benefits of zoster vaccination in IC persons. Live or heat inactive attenuated VZV in three different regimens was found to prevent or mitigate zoster in severely IC patients, including persons with leukemia in remission and recent bone marrow or stem cell transplant recipients. These studies provided a proof-of-concept that demonstrated even profoundly IC persons could in theory be protected from zoster with immunoprophylaxis. Most vaccines prevent disease by preventing infections; therefore, IC persons can avoid attenuated vaccines with other strategies to limit exposure. However, almost all older adults harbor VZV. IC rather than exposure is the key risk factor for VZV reactivation. No practical prevention tool has been developed to date other than vaccine.

The zoster vaccine provides no benefit in terms of zoster prevention in persons with no latent VZV or varicella history. Zoster vaccine is safe, but is more likely to replicate as a live vaccine and cause adverse reactions in persons with no varicella history or specific immunity to VZV. Therefore, laboratory confirmation of VZV history would be needed for IC persons who are less able to control replication of attenuated VZV in the absence of specific immunity, and who are younger than 60 years of age and thus more likely to have a false-positive history of varicella.

Considerations against this policy are as follows. Limited or no actual data are available on vaccine safety, efficacy and immunogenicity in immunocompetent persons anticipating to be IC. A post-hoc analysis of a small number of subjects who became IC during the SPS did not demonstrate efficacy between zoster and pain. The vaccine is not licensed for immunocompetent persons <60 years of age who anticipate becoming IC.

Considerations in support of this policy are as follows. Vaccine safety and immunogenicity should be completely unaffected prior to IC. Effectiveness should be retained upon IC based on efficacy of (1) live

VZV versus varicella prior to organ transplantation; (2) live VZV versus varicella in currently IC persons; and (3) a live VZV vaccine or a heat-inactived VZV vaccine, versus zoster in currently IC persons. Regarding the post-hoc analysis of SPS data suggesting lack of efficacy, the study was not designed to precisely assess this group or evaluate the risk of severe complications.

The vaccine is licensed for immunocompetent persons >60 regardless of anticipated immunocompromise and the safety profile should be no different for persons <60 at risk for zoster. Providers are seeking guidance on common and important clinical scenarios. As a result, permissive language should be developed for a narrow clinical indication with uncertainties highlighted in the background. The potential for safely reducing disease burden is large in light of the risk of zoster and its severe complications in this group.

Dr. Abramson opened the floor for comments on the proposed recommendation. Suggestions by the ACIP members and other participants to clarify and refine the language are outlined below.

- ACIP should decide whether to address or remain silent on lower age limits or leave this decision to the discretion of physicians.
- The option of incorporating an age cutoff into the recommendation, such as 18 or 20 years of age, should be explored because vaccine safety would be less of a concern in this population.
- The language should be changed to emphasize a "serologically verified history of varicella disease."
- The routine vaccine safety surveillance system should be designed to follow and monitor vaccine adverse events in the target population.
- Caution should be taken in approving the recommendation due to limited or no vaccine safety and efficacy data in IC populations. ACIP should collect solid data and approve the recommendation at a later time with supporting evidence is available.
- The language should be changed to "may be considered" to acknowledge the lack of evidence.
- The two vaccines should be compared if the incidence of zoster is expected to be high in IC children.
- The recommendation should be revised to include a specific timeline on the length of time a patient would be expected to become IC.
- The recommendation should be changed to explicitly state that data are not available for these age groups. Decision-making should be left to the discretion of providers with experience in treating these populations.
- The language should emphasize the need for studies in the IC population.

Dr. Abramson called for a motion on the proposed recommendation for vaccination of IC persons. A motion was properly placed on the floor and seconded by Drs. Gilsdorf and Lieu, respectively, to amend the recommendation as follows: "Vaccination with a single dose of zoster vaccine may be considered in limited clinical circumstances in which an immunocompetent person of any age with serological evidence of immunity and no documentation of varicella vaccination is anticipated to become immunocompetent due to progression of his or her specific medical condition or specific medical treatments."

ACIP did not pass the amended recommendation:

- **5 in favor:** Gilsdorf, Hull, Lett, Lieu, Morita.
- **8 opposed:** Abramson, Allos, Beck, Morse, Neuzil, Stinchfield, Sumaya, Womeodu.
- **2 abstentions:** Baker, Treanor.

Vote 5: "Vaccination with a single dose of zoster vaccine should be considered for persons infected with HIV with a verified history of varicella. Consideration should extend to persons with CD4 counts ≥200 mm3 and/or ≥15% of total lymphocytes regardless of prior course of their HIV disease so long as these values have been present for ≥3 months and that they have been on stable antiretroviral therapy for ≥3 months. While ZOSTAVAX® is licensed for persons ≥60 years of age, the rationale for considering vaccination of persons infected with HIV extends to persons of any age with a history of varicella."

The workgroup considered the following issues in proposing this recommendation. The label lists "AIDS or other clinical manifestations of infection with HIV" as contraindications for ZOSTAVAX®. However, these conditions do not cover HIV-infected persons with less advanced disease, such as HIV-positive persons without AIDS or clinical manifestations. Persons diagnosed with AIDS remain in this status regardless of current clinical status or CD4 counts, but this status does not reflect the biology or current medical management of HIV disease.

The risk and severity of zoster varies inversely with CD4 count and depends on duration of HIV infection and on antiviral treatment. The age-specific rate in HIV-infected persons is >10-fold higher compared to the general population. HIV-positive persons experience various severe complications of shingles. Safety, immunogenicity and efficacy of the zoster vaccine are likely to vary by the status of HIV infection.

Considerations against this policy are as follows. No safety data have been collected and no efficacy studies have been conducted on zoster vaccine in HIV-positive patients. Considerations in support of this policy are as follows. Trial data have demonstrated the safety of the varicella vaccine in HIV-positive patients with a history of varicella. The varicella vaccine is safe in VZV-susceptible IC and HIV-positive patients with CD4 counts ≥15%.

ACIP now recommends consideration of varicella vaccine in HIV-infected children and adults with CD4 counts ≥15% or ≥200. Use of zoster vaccine in such persons should only be safer since they would have pre-existing specific immunity to VZV. No recurrent varicella has been observed in HIV-positive patients. Antiviral drugs serve as additional insurance in this population. Evidence has shown that various vaccine regimens can protect even highly IC persons compared to zoster.

Dr. Abramson opened the floor for comments on the proposed recommendation. Suggestions by the ACIP members and other participants to clarify and refine the language are outlined below.

- The requirement in the recommendation for persons to be on stable antiretroviral therapy for ≥3 months to receive the vaccine should be clarified. Many HIV patients with CD4 counts of >200 or >500 have no indication for antiretroviral therapy. For example, initiation of antiretroviral therapy would be inappropriate for an HIV patient with a CD4 count of 700 who is regularly seen by a physician.
- The language should be consistent with ACIP's previous decision not to recommend the measles, mumps and rubella vaccine (MMRV) for HIV-positive children. ACIP's decision was partly driven by the lack of evidence on use of MMRV in this population.
- ACIP should take caution in approving the recommendation due to the absence of data and should should call for additional studies in this area. Most notably, Merck is conducting a study on ZOSTAVAX® in persons with HIV and well preserved immune functions.

Dr. Abramson did not call for a formal motion on the recommendation. ACIP supported Dr. Abramson's proposal to revise the text to emphasize the need for additional studies on vaccination of persons with less-advanced HIV disease.

Vote 6: "There is a precaution regarding use of zoster vaccine in the following persons except as noted. Ultimately, the physician must assume responsibility for assessing the immune status of his/her patient based on clinical and laboratory evaluation." The list of persons is included in the section entitled "precaution for use of zoster vaccine among immunocompromised persons." The recommendation also lists eight categories where persons should not receive zoster vaccine. This language was extracted from other ACIP statements and general recommendations.

The workgroup considered the following issues in proposing this recommendation. The package label lists the following contraindications for ZOSTAVAX® and notes that the vaccine should not be administered to (1) individuals with a history of primary or acquired immunodeficiency states, including leukemia; lymphomas of any type or other malignant neoplasms affecting the bone marrow or lymphatic system; or AIDS or other clinical manifestations of infection with HIV; and (2) individuals on immunosuppressive therapy, including high-dose corticosteroids. ACIP previously developed and approved explicit language to clearly define contradictions and precautions to vaccination. The language is posted on the CDC web site and was reviewed by the workgroup.

Zoster vaccine is the only live-attenuated vaccine licensed for potential routine use by older persons. The portion of older IC persons is much higher than IC children and younger adults. The spectrum of IC treatments and conditions is much more varied in older persons. Physicians need guidance on the use of zoster vaccine in IC persons due to the burden of zoster in this population. Measles, polio and other vaccine-preventable diseases are severe in IC persons, but this population is also at risk of adverse reactions to live vaccines and are less likely to respond.

Vaccination of IC persons with live vaccines would involve careful consideration of risks and benefits. A review of risks and benefits is also appropriate for ZOSTAVAX®, but this vaccine is different than other live vaccines and requires decisions to be shifted toward consideration of IC persons. These factors include lack of alternative prevention strategies, high burden of disease, potential for vaccine effectiveness, and evidence of acceptable risks in IC persons.

Dr. Abramson opened the floor for comments on the proposed recommendation. Suggestions by the ACIP members and other participants to clarify and refine the language are outlined below.

- ACIP should not approve the recommendation because the precautions are in direct opposition to contraindications listed on the package label. As an advisory body to CDC, ACIP should not issue guidance that conflicts with recommendations by another HHS agency. FDA would strongly object to this recommendation.
- Language should be incorporated into the contraindications section to reiterate standards for live viral vaccines for IC persons.
- The following language should be deleted from the recommendation: "Ultimately, the physician must assume responsibility for assessing the immune status of the patient." New text should be incorporated as follows: "These contraindications are listed in the product insert. However, any decision to vaccinate would be based on the provider's assessment of the degree of immunocompromised and discussions with the patient about potential risks and benefits."

Dr. Abramson did not call for a motion on the proposed recommendation for precautions for IC persons. ACIP supported the approach suggested Dr. Anne Schuchat of CDC. The statement would contain a section to reiterate the label contraindications, but this language would not be included in the recommendation.

RABIES VACCINE

The series of presentations and ACIP's discussion and vote on the rabies vaccine are set forth below.

Overview

Dr. Harry Hull, the Rabies Workgroup Chair, announced that the workgroup was formed in August 2005 with diverse representation from ACIP, CDC and professional organizations. The workgroup solicited input from industry and state and local public health practitioners; held monthly conference calls to review the evidence; and communicated frequently to revise the recommendations.

The workgroup was charged with conducting the following activities. ACIP's 1999 recommendations on human rabies prevention would be revised to reflect the current status of rabies epidemiology and anti-rabies biologics. Information on human and animal rabies epidemiology would be updated. Evidence on the efficacy, effectiveness, immunogenicity and safety of anti-rabies biologics would be summarized. The cost-effectiveness of rabies postexposure prophylaxis would be assessed. The proposed recommendations for rabies preexposure and postexposure prophylaxis (PEP) would be presented to ACIP for a formal vote. During the current meeting, a series of presentations would be made to facilitate ACIP's discussion and vote on the workgroup's recommendations for rabies preexposure prophylaxis and PEP.

Review of Human Rabies Prevention in the United States

Dr. Charles Rupprecht, of CDC, reported that rabies is an acute and progressive encephalomyelitis with the highest case fatality rate of any infectious disease. To date, 11 known species or genotypes that cause rabies have been identified. The incubation period is typically several weeks to months, but could range from days to years. The United States experienced a marked decrease in rabies cases from domestic animals after World War II and is the most recent country to become canine rabies-free. A decreasing trend in rabies cases among both dogs and cats has been seen. The likelihood of human exposure to a rabid domestic animal in the United States has declined. None of the eight human rabies cases reported in 2004 were acquired from indigenous domestic animals.

Wild animals are the most important potential source of rabies infection for humans and domestic animals. Most reported cases occur in carnivores and bats. Nearly all human rabies cases in recent years were caused by variants associated with bats. Of 11 human rabies cases reported in 2004-2006, five were attributed to bat exposure. Of the remaining six cases reported in 2004, two were caused by canine rabies infections acquired outside the United States and four were caused by transplantation of organs and vascular tissue from a deceased patient.

Each year, ~16,000-39,000 potentially exposed persons receive post-exposure prophylaxis. The United States has faced intermittent shortages of rabies biologics in recent years. The current biologics are safe, but prophylaxis is occasionally complicated by minor adverse reactions that are rarely severe. Clear and specific recommendations regarding appropriate preexposure and postexposure rabies vaccination are critical to reduce inappropriate prophylaxis and maximize prophylaxis when necessary.

Dr. Susan Manning, of CDC, reported that three cell culture rabies vaccines are licensed for use in the United States. The rabies vaccine adsorbed is no longer available. The human diploid cell vaccine (HDCV) is manufactured by sanofi pasteur, prepared from the Pitman Moore strain, and grown on MRC human diploid cells. HDCV is concentrated by ultra-filtration and inactivated with beta-propriolactone. HDCV is formulated for intramuscular administration in a single-dose vial containing lyophilized vaccine and reconstituted with sterile diluent to a final volume of 1 mL prior to administration. The potency of each dose is ≥2.5 IU/mL of rabies virus antigen. Intradermal HDCV is no longer available in the United States.

The purified chick embryo cell vaccine (PCECV) is manufactured by Novartis, prepared from the fixed rabies virus strain Flury LEP, and grown in primary culture of chicken fibroblasts. PCECV is inactivated with beta-propriolactone and processed by zonal centrifugation. PCECV is formulated for intramuscular administration in a single-dose vial containing lyophilized vaccine and reconstituted with sterile diluent to a final volume of 1 mL prior to administration. The potency of each dose is ≥2.5 IU/mL of rabies virus antigen.

Two human rabies immune globulin (HRIG) preparations are licensed for use in the United States. HyperRab™ S/D is manufactured by Talecris Biotherapeutics and Imogam® Rabies-HT is manufactured by sanofi pasteur. Both HRIG preparations are prepared by cold ethanol fractionation of hyper-immunized donor plasma and are standardized at an average potency of 150 IU/mL. The recommended dose is 20 IU/kg body weight. Both HRIG preparations are equally efficacious when used as recommended.

Randomized controlled human trials and cohort studies with untreated comparison groups would provide the best evidence of the effectiveness and efficacy of rabies PEP. However, no controlled studies with unvaccinated groups have been conducted due to nearly universal fatality of human rabies cases. To evaluate PEP effectiveness and efficacy, the workgroup reviewed the available literature, including immunogenicity studies, direct evidence from field experiences with humans exposed to rabies, and direct evidence from controlled animal studies. Key outcomes from the literature review are outlined below.

Three studies published in 1923, 1954 and 1987 demonstrated a substantial protective effect of rabies vaccination. Multiple published studies showed that the cell-culture rabies vaccine plus HRIG was effective in preventing human rabies. Two studies published in 1955 and 1988 showed the importance of RIG administration in conjunction with vaccine. A study published in 1971 demonstrated that anti-rabies serum alone resulted in poor protection from rabies in rhesus monkeys.

Assessments of protective immunity of the rabies vaccine are complex. Virus neutralizing antibodies (VNAs) are believed to have a primary role, but other immunologic factors are important as well. Although definitive protective titers cannot be described, two working definitions of adequate rabies VNA reference values have been developed to define an appropriate intact host response: (1) antibody titer ≥0.5 IU/mL, used by the World Health Organization (WHO) as an indicator or an adaptive immune response and (2) complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focused inhibition test, used by ACIP as an indicator of an adaptive immune response. Several published studies demonstrated the ability of rabies PEP, including a combination of cell-culture vaccine and HRIG to produce VNA ≥0.5 IU/mL by day 14.

Direct evidence of preexposure prophylaxis in protecting against rabies is unavailable. Animal models have shown that primary immunization with HDCV or PCECV provides protection from a productive rabies infection after virus challenge. Multiple studies have demonstrated that three intramuscular doses

of HDCV or PCECV produce VNA titers >0.5 IU/mL by days 14-49 and provide superior long-term immunity compared to a two-dose series.

Several studies have been conducted on the safety of rabies biologics. For HDCV, mild and self-limited local reactions were reported in 60%-90% of vaccine recipients, including injection site pain, redness, swelling and induration. Mild and systemic reactions were reported in 7%-56% of vaccine recipients, including fever, headache, dizziness and gastrointestinal symptoms. Systemic hypersensitivity reactions were reported in 6% of vaccine recipients following booster doses. These reactions were believed to be associated with betapropriolactone-altered human albumin.

For PCECV, local reactions were reported in 11%-57% of vaccine recipients, including injection site pain, redness, swelling and induration. Mild and systemic reactions were reported in 0%-31% of vaccine recipients, including fever, headache, dizziness and gastrointestinal symptoms. Data collected from VAERS from 1997-2005 showed 30 adverse events/100,000 doses, two serious adverse events/100,000, 0 vaccine-related deaths, and 0 vaccine failures. For HRIG, local and mild reactions are common. Systemic reactions are typically mild and self-limited. Four studies showed that no serious adverse events were reported when HRIG was co-administered with HDCV.

Rare, individual case reports of neurologic adverse events following rabies vaccination have been reported. Five cases of neurologic illness resembling Guillain-Barré syndrome (GBS) occurring after treatment with HDCV or PCECV were identified. One case of acute neurologic syndrome involving seizure activity was reported following the administration of HDCV and HRIG. Another case of acute CNS demyelination was reported following the administration of HDCV. In none of these cases has a causal association between rabies immunization and the adverse outcome been established

Cost-Effectiveness (CE) of Rabies PEP

Dr. Martin Meltzer, of CDC, presented a study on the CE of rabies PEP. For the purposes of his study, CE was modeled as “net cost in dollars per life saved due to the administration of PEP.” The model included three CE ratios to demonstrate average, least and most CE. Several assumptions were made in the study. Death would be the only outcome of clinical cases of human rabies. PEP for rabies essentially would be 100% effective in preventing a clinical case of rabies when given as recommended. The study was conducted from a societal perspective over a one-year timeline. No costs were discounted with the exception of value of life lost. All costs were adjusted to 2004 dollars.

Cost data were extracted from public health reports published in 1998 and a study in press. Average, minimum and maximum costs of biologics ranged from $2,315-$4,831; hospital and physician charges ranged from $584-$1,423; and patient indirect costs ranged from $161-$2,161. To determine the dollar value of life, average present values of expected future lifetime earnings and housekeeping services assumed an average life span of 75 years and were discounted at 3%. Based on this formula, the value of human life weighted by age and gender was estimated at ~$1.1 million.

The probability of rabies transmission was difficult to estimate in the study due to the lack of data, except when animals were tested positive. To overcome this challenge, a panel of 10-12 experts used the Delphi technique to estimate potential exposure in seven different scenarios. The expert panel provided a broad range of probabilities of rabies transmission in the various scenarios. In addition to the baseline cost scenario, two sensitivity analyses were performed. In cost scenario 2, all PEP-associated costs were doubled and the baseline value of human life was maintained. In cost scenario 3, the value of human life was doubled and the cost of PEP was unchanged.

Key findings of the study are summarized as follows. Administration of PEP would result in cost savings if a skunk or rabies-positive animal bit an individual. Administration of PEP would result in a baseline cost of $2.9 million-$4 billion from possible bat bite exposure, dog bite or lick, cat bite or lick, or exposure to a rabid human. However, for each scenario depicting potential exposure to rabies, there was a wide range of CE ratios. For example, in the case of a possible bat bite exposure, the CE ratio ranged from net savings to a net cost of $8.4 billion. The sensitivity analyses, involving cost scenarios 2 and 3, also showed wide CE ratios that ranged from cost savings to $17 billion per life saved.

Overall, the study demonstrated cost savings if an individual was bitten by a rabies-positive rabid animal, skunk or another animal from the reservoir/vector species. On average, PEP was not found to be cost saving in the other rabies transmission scenarios. An extremely wide range of CE was observed in most of the scenarios. The study was limited due to three major factors. Efforts to place a dollar value on human life continue to be a source of debate. The probability of rabies transmission was the most important factor input into the model, but these estimates tremendously varied. Some scenarios of rabies transmission were not included in the model.

CDC conducted a peer review of the study. Two major comments by the reviewers focused on cost savings versus CE and the sensitivity analyses. The authors responded to the reviewers as follows. Cost savings do not automatically infer CE. No scientific threshold has been established to date to define CE. Similar to any other scheme, doubling of the values is arbitrary.

Proposed Recommendations and ACIP Vote on Rabies PEP and Preexposure Prophylaxis

Dr. Manning summarized important components of the workgroup's draft revised recommendations. No substantial changes were made to the recommended approach to rabies prophylaxis. Wording changes were made to clarify and specify the prophylaxis recommendations and explain difficult exposure scenarios. No new anti-rabies biologics have been developed for use in the United States since ACIP approved recommendations on human rabies prevention in 1999. No changes to the immunization schedule were recommended.

All tables and text would be updated to reflect that rabies vaccine adsorbed is no longer available for rabies prophylaxis. A systematic review of the available evidence was added to demonstrate the effectiveness and safety of rabies biologics. The number of references in the current draft statement increased from 118 to 215. New data on the economics of rabies PEP were added. New information on human rabies treatment considerations was included.

Dr. Manning's summary of specific changes to the workgroup's draft revised recommendations is outlined below.

Rabies PEP. The introduction will emphasize the following points. PEP administration is a medical urgency rather than a medical emergency. Appropriate management of potential human exposure requires an accurate risk assessment. Because rabies biologics are valuable resources and are periodically in short supply, benefits and harms should be balanced. Clinicians are strongly encouraged to consult with state or local pubic health officials in determining whether PEP would be needed. PEP recommendations depend on associated risks, including type of exposure, animal rabies epidemiology, circumstances of the exposure incident, and availability of exposing the animal for observation and rabies testing. Rabies prophylaxis is not risk-free.

The "types of exposure" section will contain several sub-sections. The two major categories will be "bite exposures" and "non-bite exposures." The workgroup did not propose modifications to these basic

definitions. The "non-exposures" sub-section will highlight situations that do not warrant PEP administration: (1) petting or handling of an animal, (2) contact with blood, urine or feces, (3) contact of saliva with intact skin, and (4) contact with non-mammals.

The "special considerations" sub-section will provide updated information on two types of exposures. First, bat exposures require a thorough evaluation. The risk of rabies from a bat encounter might be difficult to determine due to limited injury inflicted by a bat bite or inaccurate recall of a bat encounter. "Some bat-related rabies viruses may be more likely to result in infection after inoculation in superficial epidermal layers." **(Proposed new language)** Any direct contact between a human and bat should be evaluated for exposure unless the individual is reasonably certain that a bite, scratch or mucous membrane exposure did not occur. Second, human-to-human transmission of rabies has occurred in 16 cornea, solid organ and vascular tissue transplant recipients in the United States and four other countries. No laboratory-confirmed cases from human-to-human exposures have been observed other than the transplant cases.

The "wild terrestrial carnivores" sub-section will emphasize that all bites from raccoons, skunks and foxes should be considered as possible exposures. "PEP should be initiated as soon as possible following exposure to such wildlife unless (1) the animal is available for diagnosis and public health authorities are facilitating expeditious laboratory testing or (2) it is already known that brain tissue from the animal has tested negative." **(Proposed new language)** If PEP was initiated and animal tests were negative based on appropriate laboratory diagnostic testing, PEP should be discontinued.

Rabies Preexposure Prophylaxis. All preexposure tables and text would be updated to reflect the unavailability of intradermal administration of preexposure vaccination and rabies vaccine adsorbed for rabies prophylaxis. Preexposure vaccination should be offered to persons in high-risk groups. There are four risk categories based on the nature of the risk. No changes were proposed for the "continuous" risk category. Typical populations in the "frequent" risk category were expanded to include "all persons who frequently handle bats" regardless of location in the United States or throughout the world because of the existence of lyssaviruses on all continents except Antarctica. Typical populations in the "infrequent" risk category were revised as follows: "Veterinarians and terrestrial animal control workers in areas where rabies is uncommon to rare." No changes were proposed for the "rare" risk category.

Contact information will be provided on indigent patient programs offered by sanofi pasteur and Novartis to ensure that uninsured or under-insured patients receive rabies biologics. Data will be highlighted on the treatment of human rabies patients. Rabies has the highest case fatality rate of any infectious disease. No proven effective treatment is recognized after onset of illness. Of six surviving cases, only one survived without rabies vaccination. Rabies vaccination after onset of illness is not recommended and might be detrimental. At a minimum, primary health considerations should focus on comfort care and adequate sedation of the patient in an appropriate medical facility after a definitive diagnosis is made. Aggressive and experimental therapies are currently under evaluation.

Precautions for safe clinical management of rabies patients will be outlined. Human rabies patients pose no greater risk to healthcare personnel than patients with more common bacterial and viral infections. Routine delivery of healthcare to a patient with rabies is not an indication for PEP unless the healthcare worker is reasonably certain that he or she was bitten by the patient or that his/her mucous membranes or nonintact skin was exposed to potentially infectious saliva or neural tissue. Medical staff should adhere to standard precautions as outlined by the Hospital Infection Control Practices Advisory Committee, particularly during incubation and suctioning. These precautions include gloves, gowns, masks, eye protection and face shields.

The critical components of human rabies prevention will be emphasized, such as enhanced public health education about rabies, domestic animal vaccination, responsible pet ownership, rapid and accurate

laboratory testing, and modern stray animal control. The recommendations will note that timely and appropriate human prophylaxis will prevent human rabies, but is largely unnecessary if these other basic public health and veterinary programs are operative for functional zoonoses prevention and control.

Several ACIP members and other participants made suggestions to strengthen the recommendations.

- The proposed language in the "infrequent" risk category for rabies preexposure prophylaxis should be changed as follows: "Veterinarians and terrestrial animal control workers in areas where rabies is uncommon to rare, including workers who work in areas where rabies is uncommon to rare."
- CDC should frequently update its web site with guidance for front-line workers because ACIP's recommendations on human rabies prevention are only revised every seven years.
- New language should be included in the recommendations to clarify the use of rabies prophylaxis in HIV-positive persons and other IC populations. For example, the new text could specify that "additional doses should be administered to IC persons until an adequate serologic titre is achieved."
- New language should be included in the recommendations to clarify the use of rabies prophylaxis for common and indirect non-bite exposures, particularly those that result in an extensive amount of time for evaluation.
- New language should be included in the recommendations to specify when rabies prophylaxis should be administered following a bat bite.
- The recommendations should be revised to provide specific guidance for persons who travel to or reside in areas where rabies is enzootic, such as Peace Corps workers and their children.
- Contact information for CDC and state health departments should be highlighted or featured in boxes in the recommendations. This approach would allow clinicians to easily and rapidly locate resources and obtain guidance on difficult scenarios.

Dr. Abramson entertained a motion to approve the proposed recommendations for rabies PEP and preexposure prophylaxis. A motion was properly placed on the floor and seconded by Mr. Beck and Dr. Hull, respectively.

ACIP passed the amended recommendation by a majority vote:

- **14 in favor:** Abramson, Allos, Beck, Gilsdorf, Hull, Lett, Lieu, Morita, Morse, Neuzil, Stinchfield, Sumaya, Treanor, Womeodu.
- **1 abstention:** Baker.
- **0 opposed.**

Drs. Manning and Rupprecht explained that ACIP's recommendations on rabies PEP and preexposure prophylaxis serve as a living document. As a result, they confirmed that suggestions made during the meeting to strengthen the recommendations would be considered. They also encouraged the members to submit additional comments for consideration and inclusion in the next iteration of the statement.

CHILD/ADOLESCENT IMMUNIZATION SCHEDULE (CAIS)

The series of presentations and ACIP's discussion and vote on the CAIS are set forth below.

Overview

Dr. Gregory Wallace, of CDC, highlighted key milestones that occurred from 1983-2006 in developing immunization schedules for children and adolescents. In 1983, ACIP published the first schedule for "normal infants and children" through 16 years of age. In 1995, an annual harmonized childhood immunization schedule was created and approved by ACIP, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). In 2003, a new format for the childhood immunization schedule was adopted with catch-up bars and a pre-adolescent assessment. In 2003, the name of the "childhood immunization schedule" was changed to "CAIS" with the addition of a stand-alone catch-up schedule. For the 2007 CAIS, a proposal was made to split the schedule into two, *i.e.*, for children and adolescents and elimination of the red box for selected populations.

The Childhood/Adolescent Immunization Workgroup presented preliminary findings and initial focus group results on the CAIS during the June 2006 meeting. Since that time, the workgroup has been addressing ACIP's comments on the CAIS. The workgroup is currently exploring the potential to harmonize formats between the CAIS and adult schedules; revisiting the possibility of providing a routine-only schedule; identifying strategies to utilize the catch-up schedule more prominently; and developing a separate high-risk schedule. During the current meeting, the workgroup would make a series of presentations and present its proposed recommendations to facilitate ACIP's discussion and vote on the 2007 CAIS.

Results of the Immunization Schedule Focus Groups

Ms. Sarah Clark, of the University of Michigan, announced that focus groups were held with 69 immunization providers following the June 2006 ACIP meeting to obtain input on the proposed two-schedule format and three potential schedules: (1) 0-6 years of age on page 1 and 7-18 years of age on page 2; (2) 0-10 years of age on page 1 and 11-18 years of age on page 2; and (3) 0-6 years of age on page 1 and 11-18 years of age on page 2. Feedback was also gathered from the providers on individual features within the proposed formats and potential formats for the catch-up schedule.

The 69 immunization providers who participated in the focus groups were resident and attending pediatricians and family physicians, nurse practitioners, physician assistants, registered nurses, and licensed practice nurses. The providers represented local health department immunization clinics, urban federally qualified health centers, suburban and rural primary care clinics, and urban pediatric clinics.

Consensus on the format of two schedules was not reached across provider group, setting or type. The preference for the 0-6/7-18 year format was driven by the preference for the 0-6 schedule. None of the providers were in favor of excluding the 7-10 age group. Providers who supported the 0-6/7-18 year format made the following comments. "The 0-6 page is clean and easier to read." "The format is consistent with the concept that one phase of immunization reaches children through kindergarten shots, while the next phase reaches older children." "The format matches the recommendations most closely because some vaccines are not given after this age range."

Providers who supported the 0-10/11-18 year format made the following comments. "The inclusion of all information on one schedule would be the next best thing." "This format would provide more information because my institution's web site would only post one page." All providers were in favor of the yellow boxes for primary recommendations in the 11-12 year age group. Nearly all providers disliked the green and purple bars because the format was viewed as overwhelming and redundant with the catch-up schedule. The majority of providers initially supported the one-table version for the catch-up schedule.

However, most providers eventually preferred the two-table format because agreement could not be reached on an appropriate format for DTaP/Tdap.

The providers made overarching comments for ACIP to consider in formulating its recommendations on the immunization schedules. Recommendations for high-risk populations are typically confusing and do not contain sufficient details. The ranges of recommended ages can be problematic. The intervals between doses with exceptions are unclear. "Catch-up" is not clearly defined as actual catch-up, a recommendation, option or unnecessary action. Overall, the providers generally preferred two schedules rather than one schedule for the 0-18 year age group. Providers who favored two schedules preferred the 0-6/7-18 year format. Providers preferred two tables for the catch-up schedule rather than one table due to complexities associated with DTaP/Tdap.

Update on the 2007 Immunization Schedule for Ages 0-18 Years

Dr. Angela Calugar, of CDC, reported that several factors were considered when changing the immunization schedule, such as its growing complexity, the need for a better and more user-friendly format, and approval of the new vaccines in 2006. A two-phase qualitative research project was conducted with immunization providers. Preliminary findings from this activity and initial drafts of the schedule were presented to ACIP during the June 2006 meeting. Collaborative efforts were undertaken with subject matter experts (SMEs) to refine the content of footnotes. Final drafts of the immunization schedule would be presented to ACIP during the current meeting for review and formal approval.

The current immunization schedule for the year 2006 targets ages from birth through 18 years and includes 14 combined or single-dose antigen vaccines. The current catch-up schedule is split into two tables for children 4 months through 6 years of age and 7-18 years of age.

Immunization providers in the focus groups were most frequently concerned about (1) overcrowding of the immunization chart; (2) the purple bar for the assessment of children 11-12 years of age; (3) confusion in the red box for special populations; and (4) insufficient or an overabundance of details in the footnotes.

The workgroup revised the schedule for consistency with several recent ACIP recommendations, *i.e.*, approved rotavirus and HPV vaccines in February and June 2006, respectively. Influenza vaccine recommendations were expanded to include children 24-59 months of age and the second dose of varicella vaccine was approved.

The current immunization schedule was split to reflect the 0-6 and 7-18 year age groups. The purple bar for the adolescent visit and the red-dotted box for special populations were removed from the schedule. Other major changes were made to the presentation of the fourth dose of the hepatitis B (HepB) vaccine, footnotes for the *Haemophilus influenzae B* (Hib) vaccine, and the overall order of the vaccines. These changes were made in response to the focus group findings and some programmatic considerations. The workgroup performed a thorough analysis when suggestions by the immunization providers widely varied or were contradictory.

The workgroup's next steps will be to address outstanding issues and concerns raised by immunization providers who participated in the focus groups:

- Lack of details for high-risk groups.
- Dislike of the colored bars in the 7-18 year age group schedule.
- Confusion in the recommended age ranges and intervals between doses with exceptions.

- Unclear presentation of the MCV4 for the 15-year-old dose.
- Unclear definitions and indications for using catch-up bars and schedules.
- No harmonization between the CAIS and adult schedule.
- The possibility of developing a special schedule for high-risk children and removing catch-up bars from routine schedules.

ACIP Vote on the 2007 Immunization Schedule for Ages 0-18 Years

Dr. Calugar presented the following proposed drafts to facilitate ACIP's discussion and vote: (1) immunization schedules for the 0-6 and 7-18 year age groups, (2) the catch-up schedule, and (3) footnote formats for all three schedules.

ACIP commended the workgroup on making tremendous improvements to enhance the immunization schedules. The members found the proposed drafts to be clearer and easier to read. Several members and other participants made suggestions for the workgroup to consider in further refining the documents.

- The title should be changed to "11-12 years" on the schedule for the 7-18 year age group. The word "assessment" should be deleted to be consistent with the other titles.
- Dr. Amy Middleman, the liaison member for the Society for Adolescent Medicine, should be engaged in future efforts to revise the schedules. Dr. Middleman's expertise could assist the workgroup in creating a separate schedule for adolescents. This change would be consistent with current efforts to shift toward specific preventive care strategies for this age group. Moreover, ACIP should consider whether a new adolescent workgroup should be formed.
- The web-based version of the schedule should be revised to include hyperlinks to ACIP's recommendations for each vaccine. A separate web page should also be developed specifically for IC persons.
- A uniform abbreviation for rotavirus should be created because both "Rota" and "RV" are used in the field.
- The green and purple bars in the schedule for the 7-18 year age group should be extended to ages 7-10 years for both high-risk and catch-up.
- Focus groups should be conducted with obstetricians, gynecologists and adult physicians because these providers are not typical users of the schedules. Input from these practitioners on the schedule for the 7-18 year age group would be particularly helpful because older adolescents present to these providers rather than pediatricians.
- The contradiction in footnote 10 in the schedule for the 7-18 year age group should be resolved. Most notably, guidance to "administer varicella vaccine at least three months apart" and "not repeat the second dose if administered $\geq$28 days following the first dose" is inconsistent. The contradiction could be resolved with the following revision: "A three-month interval is recommended. If $\geq$28 days have passed, however, repeating the dose is unnecessary."

Dr. Abramson entertained a motion to approve the proposed draft immunization schedules with the condition that the workgroup would address ACIP's comments. A motion was properly placed on the floor and seconded by Dr. Hull and Ms. Stinchfield, respectively. **The motion was unanimously approved by all 15 voting members:** Abramson, Allos, Baker, Beck, Gilsdorf, Hull, Lett, Lieu, Morita, Morse, Neuzil, Stinchfield, Sumaya, Treanor, Womeodu.

Drs. Pickering and Wallace confirmed that CDC would take several actions to address ACIP's comments on the immunization schedules. One, CDC will revise the next version of the web-based interactive child

immunization schedule to allow users to type the child's date of birth, enter the immunization history, and obtain output data on specific vaccines the child would need by a certain date. CDC will continue its internal discussions on potential strategies that could be applied to completely eliminate paper-based immunization schedules in the future.

Two, CDC will consult with its Education Branch and rotavirus SMEs to resolve the discrepancy between the "Rota" and "RV" abbreviations for rotavirus. Three, CDC will initiate discussions with the ACIP Varicella Workgroup and varicella SMES on potential wording changes that could be made to resolve the inconsistency in footnote 10 on the schedule for the 7-18 year age group.

INFLUENZA VACCINE

The series of presentations, ACIP discussions and public comments on the influenza vaccine are set forth below.

Overview

Dr. Joseph Bresee, Chief, Epidemiology and Prevention Branch, Influenza Divisiion, CDC, summarized surveillance data for the 2006-2007 influenza season. Laboratories participating in the WHO National Respiratory and Enteric Virus Surveillance System showed that 1% of samples submitted were positive with a fairly even split between influenza B and H1A viruses. H1 strains detected in the late spring/early summer and into the fall were closely related to vaccine strains. Data collected from sentinel provider networks on pneumonia and influenza (P&I) mortality in 122 U.S. cities showed that 1.3% of all visits to sentinel providers were attributable to influenza-like illness (ILI) less than the seasonal baseline. The P&I systems also showed a P&I mortality below epidemic thresholds.

To date, 40 states reported no influenza activity, six states reported sporadic activity, and two states reported local activity. The CDC laboratory will periodically perform adamantane- and neuraminidase-resistance testing on isolates during the influenza season. CDC does not expect the test results to change influenza recommendations for the 2006-2007 season.

Dr. Ban Allos, the Influenza Workgroup Chair, reported that both ACIP and AAP currently recommend two doses of influenza vaccine for children <9 years of age in the first year they receive vaccine. During the June 2006 meeting, ACIP voted not to change the recommendation for children <9 years of age who received only one initial dose of vaccine. ACIP took this action due to the lack of evidence to support a change in the recommendation.

In October 2006, however, the AAP Committee on Infectious Diseases adopted a different recommendation stating that children <9 years of age should receive two doses of vaccine the following year. The workgroup will collaborate with AAP to develop communication messages or frequently asked questions to address differences between the two sets of recommendations. CDC expects to create the list of questions and answers over the next two to three weeks.

During the June 2006 ACIP meeting, the workgroup also proposed a potential time frame to modify annual influenza vaccination recommendations. Critical issues would be assessed and addressed in 2006-2008. The possibility of expanding the recommendations to include all school-aged children 5-18 years in 2008-2009 would be explored. The recommendations could potentially be expanded to include household contacts and caregivers of school-aged children in 2010-2011. Universal vaccination would be

recommended if necessary and the recommendations would be extended to persons 18-49 years of age in 2012-2013.

Several ACIP members expressed concerns that the proposed time frame was too long, particularly after the inclusion of household contacts of school-aged children. The members also requested clarification on data that would be used to inform ACIP decision-making and whether these data would be readily available. However, feedback from ACIP members to the workgroup to address these concerns was limited following the June 2006 meeting.

The workgroup identified several critical factors that need to be assessed and addressed before the influenza vaccination recommendations are changed. New or existing surveillance systems should be developed or enhanced to assess influenza illness. Vaccine safety and effectiveness should be monitored. Capacity to annually vaccinate school-aged children and working adults should be evaluated. Availability of an adequate vaccine supply should be assured.

In its next steps, the workgroup will meet to discuss vaccine safety and effectiveness, adequacy of supply, and feasibility of expanding the recommendations to include school-aged children. The workgroup will be mindful of the importance of improving vaccine delivery to existing target groups during these efforts. Data collected from 1989-2004 showed that the most progress in influenza vaccination was among persons >65 years of age, while the least progress was among healthcare workers. The workgroup acknowledged that public awareness and education of providers and practices must be strengthened to improve influenza vaccination of existing target groups.

Several ACIP members made suggestions for the workgroup to consider in future efforts to expand the influenza vaccination recommendations.

- The recommendations should be strengthened with the following language to advance toward universal vaccination: "Influenza vaccine would be appropriate for individuals with an interest in decreasing their risk for acquiring influenza in the current season."
- The proposed time frame to expand the recommendations to universal vaccination should be expedited for consistency with the availability of vaccine for pandemic influenza. This goal could be achieved by changing the two-year increments to one-year increments in the proposed time frame. However, the expedited time frame should ensure that the supply can meet the demand.
- Stronger efforts should be made to educate the public on the risks and benefits of influenza vaccination during pregnancy.
- The clinical realities of ordering vaccine should be considered when ACIP's influenza recommendations are developed, expanded or revised. For example, some pediatricians expressed concern that the expanded recommendation to include children 24-59 months of age occurred after pre-booking. As a result, the amount of vaccine was not sufficient to meet the expectations and needs of the expanded population.
- ACIP should be given an opportunity to re-review cost effectiveness data on influenza vaccination during the workgroup's ongoing efforts to expand the recommendations.
- The list of questions and answers that will be developed should contain accurate guidance on the appropriate time to administer influenza vaccine. For example, the public has an incorrect perception that influenza vaccine must be administered in September and should not be given after November.

Update on Cumulative Monthly Influenza Vaccine Distribution

Dr. Wallace reported that 25 million influenza doses were distributed by the end of September 2006 and ~50 million doses were available as of October 20, 2006. By October 31, 2006, up to 75 million doses are projected to be available. More doses were distributed from October 13-20, 2006 compared to the previous week. The peak distribution by month in the current season is projected to be the same as last year, but later than an early season, such as 2002. The actual peak is anticipated to be larger and occur later than any previous season.

The possibility exists of increasing the supply to 110-115 million doses due the recent approval of the GlaxoSmithKline FluLaval™ vaccine. The vaccine could be distributed if the demand is sustained. Overall, manufacturers are making efforts to address concerns about vaccine delays, specific vaccine recipients, and the 0.25 thimerosal-free vaccine for young infants.

Manufacturer Reports on the Future of Influenza Vaccine

sanofi pasteur. Dr. Philip Hosbach reported that sanofi pasteur publicly announced delays in influenza vaccine by ~3 weeks. Of the 59% of vaccine sanofi pasteur will distribute by October 27, 2006, 46% will be to the public sector. Of all targeted doses, 85% will be distributed to private physicians, public health providers and hospitals. By the first week in November 2006, sanofi pasteur will distribute all doses of the 0.25-mL preservative-free influenza vaccine to pediatricians for children ≤3 years of age. To date, >100,000 doses of this vaccine have not been ordered.

A new enclosed facility is under construction that will double sanofi pasteur's capacity in 2008-2009 and allow for production of 100 million doses of influenza vaccine. In 2007 or 2008, sanofi pasteur expects to build a new fill and formulation facility that would allow for an expansion over the current 8-9 million doses of preservative-free vaccine. sanofi pasteur initiated cell culture clinical trials and was awarded six requests for proposals. The new research projects include the stockpile, H5N1 vaccine, and pandemic influenza capability and capacity in clinical trial vaccine production. sanofi pasteur is also exploring the possibility of immunizing children <6 months of age in clinical trials. sanofi pasteur is producing new formulations and methods to deliver influenza vaccine that would assist in improving immune response in elderly persons and other populations.

Protein Sciences Corporation (PSC). Dr. Manon Cox reported that PSC is developing a recombinant hemagglutinin-based vaccine made in cell culture. The vaccine is 90%-95% pure, contains three times more active ingredients than the currently licensed vaccine, and does not contain any preservatives or adjuvants. The vaccine can be used in egg-allergic persons.

PSC has conducted >10 clinical trials on the vaccine to date and published these data in peer-reviewed journals. A field study showed 100% protection of the vaccine against cell culture-confirmed influenza in persons presenting with CDC-ILI.. Solid immunogenicity in elderly persons was observed as well. PSC has been placed on FDA's accelerated approval pass and expects to begin filing its biologic license application (BLA) of the vaccine in the first half of 2007. Depending on when FDA approves PSC's BLA, 5-10 million doses of the vaccine could be available for the 2007-2008 influenza season.

Novartis Pharmaceuticals. Dr. Theodore Tsai reported that the 25 million doses Novartis will have shipped by the end of October represent ~60% of the total production for the year. Novartis expects to ship ~40 million doses in the next influenza season and is making investments to increase the number of preservative-free doses in the near future.

Novartis recently completed Phase III trials on a Madin-Darby canine kidney cell-derived vaccine that is not produced with formaldehyde and contains no antibiotics, thimerosal or preservatives. Novartis is in the process of submitting a BLA for the cell culture influenza vaccine and recently broke ground on a new manufacturing facility in North Carolina that will be dedicated to the production of the vaccine in the United States. Overall, Novartis' position is that the vaccine could have advantages in manufacturing flexibility; might provide an opportunity to include more antigenically representative strains in the seasonal vaccine; and will offer an option for egg-allergic persons.

Novartis is the only distributor of an adjuvant influenza vaccine. Fluad was first licensed in Europe in 1997 and is currently licensed in >20 European countries. To date, 25 million Fluad doses have been distributed. Novartis is now exploring options to introduce an adjuvant vaccine in the United States in the future.

MedImmune, Inc. Mr. Mark Twyman reported that MedImmune acknowledges the merit in encouraging Americans to be immunized early in the season. This approach would facilitate several outcomes: stronger capacity to leverage available vaccine in the July-September time frame; benefits from completing the immunization series prior to the circulation of disease in communities; and greater opportunities for providers to administer two influenza vaccine doses to children.

MedImmune began shipping FluMist® doses to physicians in July 2006 for the current influenza season. All ~3 million doses were available for distribution prior to the end of September 2006. The remaining doses are now available for immediate shipment to physicians. MedImmune has a bulk capacity of 90 million FluMist® doses and will have capacity next year to fill and finish ~7 million doses for market distribution.

MedImmune will increase its production capacity to 20 million doses for the 2008-2009 season and 35 million doses thereafter. Depending on demand, MedImmune has the ability to invest additional capital to increase its fill and finish capacity to meet the bulk capacity of 90 million doses. MedImmune is currently focusing on the pediatric segment with respect to future product label changes, but has not yet determined a specific scope and timeline for other enhancements of the FluMist® label.

MedImmune assessed the potential demand curve if the current influenza vaccination recommendations were expanded to include age groups up to 18 years. The assessment showed that MedImmune could meet most of the vaccine requirement in 2008 to support the expanded recommendations and all of the vaccine requirement in 2009. Vaccine supply issues might not continue to serve as an impediment in the future due to the capacity of MedImmune and other manufacturers to meet demand if the influenza recommendations are expanded to include age groups up to 18 years.

Pending FDA approval of its supplemental BLA (sBLA), MedImmune would make FluMist available to the Vaccines for Children (VFC) eligible population under a contract with CDC. The VFC price would be discounted from the currently contemplated price of $18/dose for the next generation vaccine. As with FluMist®, MedImmune's cold-adapted influenza vaccine (CAIV-T) will also be 100% free from thimerosal and preservatives pending FDA licensure.

GlaxoSmithKline (GSK). Dr. Margaret Rennels reported that GSK has made a significant commitment to expand global influenza vaccine production, introduce influenza vaccine to the United States, and develop new vaccine approaches. GSK has made a $2 billion investment to double manufacturing capacity of the FLUARIX platform in Dresden, German for a total of 60-70 doses per year. GSK's purchase of ID Biomedical in Canada and expansion of this facility will result in production of ~75 million doses annually. GSK also procured the former Wyeth Manufacturing platform in Marietta and will convert and update this facility to produce the cell culture-based influenza vaccine.

Licensure of the FluLaval™ vaccine in the United States will increase the total number of doses GSK can bring into the country to ~25 million doses this year. GSK will launch pediatric studies in the fall and will also introduce a preservative-free vaccine as soon as feasible. The initial pediatric studies will be conducted with FLUARIX that contains trace thimerosal.

GSK has several novel vaccine approaches in early development. HHS awarded a contract to GSK to produce cell culture-based vaccines. GSK has been developing adjuvants for influenza vaccine since 1989 under several ongoing programs, including adjuvant H5 vaccine, adjuvant trivalent inactivated vaccine (TIV) to improve the immune response in elderly persons, and adjuvant intranasal inactivated TIV vaccine.

CSL Biotherapies. Dr. Pickering read a statement that was submitted into the record by CSL Biotherapies. CSL completed the enrollment of 1,300 subjects for a clinical trial of its influenza virus vaccine. The randomized double-blind controlled trial was designed to evaluate safety and immunogenicity of the vaccine in healthy adults and is intended to support accelerated approval for the 2007-2008 season. CSL and the FDA Center for Biologics Evaluation and Research outlined a program to facilitate the submission of a BLA for a thimerosal-free single-dose pre-filled syringe and a multi-dose vial containing thimerosal as a preservative only.

CSL-branded influenza virus vaccines are already approved and marketed in 16 countries worldwide. CSL's thimerosal-free single-dose syringe is approved in Europe for persons >6 months of age. CSL also provides bulk influenza vaccine for sale in 24 countries. CSL is expanding its manufacturing facilities to be able to supply ~20 million doses to the United States by 2010. Pending FDA licensure, CSL's influenza virus vaccine would be marketed by its U.S. commercial vaccine entity.

Baxter Healthcare Corporation. Dr. Peter Khoury reported that Baxter produces its viral cell-derived influenza vaccine in a commercial-scale and good manufacturing practices (GMP) approved facility in Czech Republic. Baxter has two ongoing developmental programs. The seasonal vaccine is a split viral trivalent vaccine that is free from antibiotics and preservatives, independent of egg supply, and packaged as pre-filled syringes. The process to produce the vaccine is ~12 weeks from strain availability to actual availability of the pre-filled syringes.

Baxter intends to formulate the seasonal vaccine for both adult and pediatric use and expects to file an investigational new drug application in the United States over the next two weeks. Baxter will initiate clinical trials of the seasonal vaccine in the first quarter of 2007 with an adult population and in the third quarter of 2007 with a pediatric population. Baxter expects to obtain approval for the adult indication during the second quarter of 2009 and the pediatric indication during the second quarter of 2011.

Baxter developed its pandemic whole virus viral cell vaccine with the Vietnam 1203 strain of H5N1. Baxter recently completed Phase I/II clinical trials of the vaccine in Austria and Singapore. The study showed that the vaccine was safe and had an excellent tolerability profile. No dose response or adjuvant effects were observed. Baxter will initiate clinical trials of the pandemic vaccine in the second half of 2007 with an adult population and in second half of 2008 with a pediatric population.

CAIV-T Safety and Efficacy Data

Dr. Robert Walker, of MedImmune, presented data to demonstrate the safety and efficacy of CAIV-T in young children. FluMist® is currently indicated for active immunization for the prevention of disease caused by influenza A and B in healthy persons 5-49 years of age. FluMist® is a trivalent live attenuated

influenza vaccine that is stored frozen, thimerosal-free, needle-free and administered as a nasal mist. The dose volume of 0.5 mL (0.25 mL per nostril) is administered as a single annual dose in persons 9-49 years of age. However, persons 5-9 years of age with no previous FluMist® vaccination would receive two doses.

Several manufacturing and other developments have occurred since FluMist® was approved in June 2003. A new bulk manufacturing facility in the United Kingdom was approved in December 2005. The new facility provides MedImmune with capacity to manufacture up to 90 million trivalent bulk doses. The plasmid rescue technique for FluMist® manufacturing was approved in June 2006. MedImmune has made this reverse genetics technology available to other influenza vaccine manufacturers. MedImmune received approval from FDA to release the first doses of FluMist" in July 2006 and the remaining available doses by the end of September 2006. MedImmune will continue its efforts to make FluMist® available as early as possible in the season.

Both the frozen FluMist® formulation and the new CAIV-T formulation are preservative-free and contain sucrose phosphate glutamate (SPG) as excipients. However, several characteristics distinguish the two vaccines. FluMist® is licensed in the United States, while CAIV-T is an investigational vaccine. CAIV-T is refrigerator stable, while FluMist® requires storage in the freezer. CAIV-T contains other excipients in addition to SPG, such as arginine and hydrolyzed porcine gelatin. The dose volume of CAIV-T is 0.2 mL (0.1 mL per nostril).

MedImmune filed an sBLA for CAIV-T in September 2005 to provide FDA with Phase III trial data. The study was designed to bridge CAIV-T and FluMist®, demonstrate analytic comparability between the two formulations, and evaluate immunologic and clinical equivalents of the vaccines. MedImmune filed a second sBLA in July 2006 to expand the CAIV-T label to include children 12-59 months of age with no history of asthma or wheezing. This indication was derived from a series of risk/benefit analyses of the comparative study. FDA is currently reviewing the Phase III trial data and has scheduled the Prescription Drug User Fee Act review for May 2007.

A substantial body of data showed that FluMist® and CAIV-T had high efficacy in young children. Cohorts in placebo controlled trials ranged from ~1,600-3,000 children. The efficacy of FluMist® or CAIV-T ranged from 73%-93% and was statistically significant. Both cohorts in two large TIV-controlled studies had ~2,000 children. The studies compared CAIV-T and TIV and showed statistically significant results. CAIV-T would have additional efficacy of 53% and 35%, respectively, compared to TIV. Both studies were recently published.

The CP111 pivotal study was designed as a multinational randomized and double-blind study that used TIV manufactured by sanofi pasteur as an active control. The cohort was 8,475 children 6-59 months of age, including those with underlying medical disorders. However, immunocompromised children and those with severe asthma and recent wheezing within six weeks were excluded from the study. The primary efficacy endpoint was culture-confirmed modified CDC-ILI that required the presence of a fever plus at least one other symptom on the same or consecutive days, such as cough, sore throat, runny nose or nasal congestion.

During the CP111 study, the first immunizations were completed in advance of the onset of the immunization season. Significantly fewer cases of influenza were seen during the onset of the season in the CAIV-T group compared to the TIV group. Differences in influenza attack rates became more pronounced as the season progressed. The relative efficacy of CAIV-T of 54.9% was statistically significant for culture-confirmed modified CDC-ILI caused by any wild-type strain. The relative efficacy of CAIV-T was also statistically significant for culture-confirmed modified CDC-ILI caused by specific strains: 89.2% for H1N1 and H3N2 for 79.2%. However, the strain-specific relative efficacy of CAIV-T for the B strain of 16.1% was not statistically significant.

Rates of serious adverse events were similar in the CAIV-T and TIV treatment groups. CAIV-T was associated with increases in runny or stuffy noses, while TIV was associated with increases in injection site reactions. Children were followed during the study period for medically significant wheezing (MSW) based on a prospective case definition. For purposes of the CP111 study, "MSW" was defined as wheezing documented by a healthcare provider and associated with an intervention.

In children >2 years of age, no significant differences in MSW rates were seen between the CAIV-T and TIV treatment groups. In children <2 years of age in the two-dose group, a statistically significant increase of MSW was seen within the pre-specified safety evaluation period of 42 days after dose 1. CAIV-T was associated with a 3.2% increase in MSW in 55 children, while TIV was associated with a 2% increase in MSW in 34 children. Increases in MSW cases were not observed in the first week following vaccination. MSW rates were not statistically different beyond 42 days post-vaccination through the end of the study period or after dose 2.

The CP111 study did not show differences in the severity of MSW between the CAIV-T and TIV treatment groups among children <24 months. Rates were also comparable between the two groups in terms of hospitalization for MSW and the median duration of hospitalization. MSW was not associated with any deaths, admission to intensive care units or use of ventilators. Recurrent MSW rates were 3.2% in the CAIV-T group and 2.8% in TIV group with $\geq$1 recurrence and 2.6% in the CAIV-T group and 4% in the TIV group with $\geq$2 MSW recurrences.

Post-hoc exploratory analyses were performed for the entire study period to assess MSW, hospitalizations due to any cause, and a potential association from prior history of wheezing or asthma. CAIV-T was associated with an increase in all-cause hospitalization in children 6-11 months of age. CAIV-T was associated with higher hospitalization rates in children 12-47 months of age with a history of wheezing, but these rates were not statistically significant. CAIV-T was not associated with a risk of hospitalization in children 12-59 months of age without a history of wheezing. CAIV-T was associated with higher MSW rates in children 12-47 months of age with a history of wheezing. Overall, the post-hoc exploratory analyses demonstrated that CAIV-T had significant benefits in terms of reducing influenza in all age groups of children with and without a history of wheezing.

The CP123 study was conducted in 2005 with the same vaccine formulations as the CP111 study to analyze immunogenicity. The CP123 cohort was 52 children 6-35 months of age. The children received two doses of either CAIV-T or TIV. Serum hemagglutination-inhibiting antibody responses were assessed following both doses. Seroconversion rates were substantially higher following both CAIV-T doses and some of these rates were statistically significant.

Overall, CAIV-T was associated with superior efficacy against both matched and mismatched influenza. Based on data from the post-hoc exploratory analyses, MedImmune will not recommend the use of CAIV-T in children <12 months of age until additional studies are conducted to better understand the increase in all-cause hospitalization in this population. MedImmune is currently seeking FDA approval of its proposed indication for use of CAIV-T in children 12-59 months of age.

CAIV-T might be associated with a higher rate of all-cause hospitalization in children up to 47 months of age with a history wheezing. CAIV-T appears to have a highly favorable risk/benefit profile in children 12-59 months without a history of wheezing. Children with no history of wheezing accounted for 80% of all children 12-59 months of age in the CP111 study. An ongoing study demonstrated that the duration of protection of CAIV-T extended beyond 10-12 months in one season. MedImmune has submitted the CP111 data for publication.

Dr. Neuzil pointed out that other published data with a large cohort of children showed different immunogenicity results with the H1N1 strain than the CP11 study. Dr. Abramson asked CDC to develop and distribute a table to ACIP by the February 2006 meeting. The table should list all licensed influenza vaccines, the current production status of each vaccine based on the manufacturer reports, and potential outcomes with vaccine production that might occur in the future.

Public Comment Period

Mr. Scott Laster is a parent of a child with autism who is showing phenomenal results from treatment. He pointed out that the manufacturer reports presented during the meeting and several published studies provide ACIP with sufficient information to recommend thimerosal-free vaccine for all doses in the next influenza season. For example, a 1999 study with children who received either thimerosal-free or thimerosal-containing vaccines showed that children with thimerosal exposure were 11 times more likely to develop autism than children with no exposure.

A 2004 study demonstrated that thimerosal interrupts or inhibits the methylation process. This process plays a key role in building neural pathways in the brain. A 2005 study with infant primates showed that thimerosal crosses the blood brain barrier and contains twice as much inorganic mercury compared to methyl mercury after entering the brain. Mr. Laster urged ACIP to recommend the removal of thimerosal from vaccines. He also asked ACIP to reiterate to the public that children and pregnant women should receive thimerosal-free vaccines.

Ms. Allison Davis is a parent of autistic children. She received four thimerosal-containing vaccines *in utero*. She urged ACIP not to recommend mercury-containing vaccines for pregnant women because mercury is the second most neurotoxin on the planet. Ms. Davis reminded ACIP that its guidance and recommendations affect the lives of individuals throughout their entire lives.

Mr. Glenn Moise, of Families Fighting Flu (FFF), is a parent of a child who was nine months of age at the time of his death. His son died from complications due to influenza A prior to receiving his second influenza shot. Mr. Moise emphasized that FFF is a strong national and local advocate for influenza immunization for all children. He thanked ACIP for its continued efforts and focus on universal pediatric immunization.

Ms. Denise Palmer, of FFF, is a parent of a child who was 15 months of age at the time of her death from influenza A. She thanked ACIP for its ongoing efforts to expand the influenza recommendations.

Dr. Kristin Nichol, Chair of the Minnesota Coalition for Adult Immunization, announced that the American Lung Association (ALA) recently launched the national and regional “Faces of Influenza” initiative. The campaign involves the development of educational materials; distribution of public service announcements; creation of a web site; and publication of a portrait gallery book with photographs and personal stories of Americans who are in one of the high-priority groups recommended by ACIP for annual influenza vaccination.

The Faces of Influenza initiative was designed to demonstrate the seriousness of influenza as a potential deadly disease and emphasize the importance of prevention through vaccination. ALA will soon initiate several regional events to support the campaign. Dr. Nichol encouraged the public to view the portrait gallery book and other program materials at www.facesofinfluenza.org.

Ms. Wendy Fournier, of the National Autism Association, is a parent of an autistic child who is six years of age. Her daughter received the HepB vaccine shortly after her birth and 212.5 µg of thimerosal from

other vaccines over the next 15 months. Her daughter was diagnosed with autism at 18 months of age, but was later discovered to have heavy metal toxicity, food sensitivities, gut pain and encephalitis due to IgG and IgM auto antibodies to her brain consistent with vaccine injury.

Ms. Fournier described several milestones that have resulted in poisoning and destroying the immune system of her daughter and an entire generation of children. Merck had knowledge of the danger of mercury in its vaccines, but took no actions to protect the public. A manufacturer informed CDC in 1999 of its capacity to provide a sufficient supply of thimerosal-free vaccine to meet the demand through the first half of 2000, but CDC did not order the thimerosal-free vaccine.

The bulk of thimerosal was removed from pediatric vaccines, but CDC added multiple influenza shots to the child immunization schedule and is still recommending influenza immunization for pregnant women. CDC continues to insist that mercury-containing vaccines are safe. ACIP has refused to state a preference for thimerosal-free vaccines. Studies have not been conducted to demonstrate that vaccines administered to children in a short period of time in accordance with the child immunization schedule are safe. Data have not been presented on the toxic components used in the production of vaccines.

Ms. Fournier urged CDC to reevaluate its vaccine program because the success of the program should be based on the protection of children's health rather than uptake. She also urged ACIP to restore public confidence by creating a safer child immunization schedule and recommending that children and pregnant women receive thimerosal-free vaccines only.

Ms. Lyn Redwood, of Sensible Action for Ending Mercury-Induced Neurological Disorders (SafeMinds), noted that ACIP did not fully respond to the request she made during the June 2006 meeting. Although several vaccine manufacturers reported on future plans to produce preservative-free vaccines, ACIP still did not state its preference for thimerosal-free vaccines for infants, children and pregnant women during the current meeting.

Ms. Redwood noted that the danger of thimerosal-containing vaccines to the unborn child is the primary reason only 10% of pregnant women are vaccinated. A large study was conducted with 50,000 women over five influenza seasons and showed no difference in influenza or influenza-related illness between vaccinated and unvaccinated women. The study also found no difference in vaccinated and unvaccinated infants in the first six months of life. The influenza vaccine is a category C vaccine in pregnant women, but no safety studies have been conducted to date with reproductive animals.

Ms. Redwood's position was that the risk of influenza immunization outweighs the benefits. She repeated her request for ACIP to state its preference for thimerosal-free vaccines for infants, children and pregnant women. She asked ACIP to officially vote on this issue with all members stating their individual preferences.

Dr. Schuchat clarified that ACIP is prohibited from voting on any matter without advance notice to the public. Because an official ACIP vote on thimerosal-free vaccines was not announced, ACIP would be unable to make a decision on this issue during the October 2006 meeting. However, CDC would present a systematic update on immunization safety on the following day and would also continue to discuss this topic at each ACIP meeting.

Dr. Schuchat could not make a commitment on whether ACIP would officially vote on thimerosal-free vaccines during the next meeting in February 2007. In follow-up to Dr. Schuchat's comments, Ms. Redwood announced her intention to notify the media about CDC's refusal to address thimerosal-free vaccines.

Mr. William Kerry is a parent of an autistic child who is nearly eight years of age. He was aware of ACIP's protocols to officially vote on issues. However, ACIP should publicly acknowledge the significant problems with thimerosal-containing vaccines and assure the public that efforts are being made to address this issue. This approach would increase the number of individuals who are willing to be immunized. Mr. Kerry pointed out that anecdotal evidence showed a decline over the last few years in statistical increases in autism in children throughout the state of California. The recent decrease has been associated with the voluntary removal of thimerosal from vaccines.

Cmdr. Stephen Kay, of Generation Rescue, is a parent of an autistic child who received >400 µg of mercury during his first year of life. Mercury poisoning impacted his son's ability to detoxify, but chelation eliminated all of the physical and metabolic conditions he developed. Cmdr. Kay learned that of 12 vaccinations on the child immunization schedule, eight still contain thimerosal and one contains aluminum. His daughter has never been vaccinated and is healthy. He applauded and appreciated the efforts of manufacturers in removing preservatives from vaccines. However, he urged ACIP to formally recommend the removal of thimerosal and preservatives from vaccines to regain public trust and confidence.

With no further discussion or business brought before ACIP, Dr. Abramson recessed the meeting at 5:55 p.m. on October 25, 2006.

VACCINE FINANCING

Dr. Abramson reconvened the ACIP meeting at 8:00 a.m. on October 26, 2006 and yielded the floor to the first presenter. The series of presentations and ACIP discussion on vaccine financing are set forth below.

Implementation of New Vaccines and Vaccine Recommendations

Dr. Lance Rodewald, Director of the CDC Immunization Services Division, described the current immunization program and its stressors; resources that are available to immunization grantees; strategies and challenges in implementing new vaccine recommendations; and potential solutions to resolve the vaccine financing dilemma. The VFC program is an entitlement to children that mandates funding of recommended vaccines. The VFC program was designed to ensure that its implementation would ease the use of services and vaccination opportunities would not be missed. A key provision is that VFC providers are able to determine individual children's eligibility to the program. Having a streamlined program implementation makes vaccine accountability a critically important challenge to be met by the states and by CDC.

ACIP has sole authority in the federal government to add vaccines to the VFC program. ACIP uses vaccine safety, efficacy and economic data to make vaccine recommendations. ACIP applies this evidence as part of the public health perspective. The methods used in economic studies presented to ACIP are now being standardized. However, the Congressional intent and legislative history of the VFC program indicated that ACIP would not use cost as the driving force in its public health determinations to add particular vaccines to the VFC program, even though cost can be a consideration when ACIP adds a vaccine to the VFC program.

At the state level, policies to implement new vaccines are, in part, financed-based. Full access to vaccines is expensive and financing gaps exist for underinsured children. States have options to

implement the VFC program only or implement the VFC program and arrange financing for underinsured children at health departments or private immunization providers. Each state has funding sources to augment the VFC program, such as its individual appropriated funds or Section 317 discretionary dollars. However, Section 317 funds are not an entitlement and have served as a "gap filler" for underinsured children in the VFC program over the past 12 years. No restrictions, such as age or insurance status, have been placed on using Section 317 program funds. Overall, neither state appropriated funds nor Section 317 program funds have kept pace with the VFC needs-based funding. Data showed that the VFC program has been able to meet the needs of children compared to the Section 317 program.

States also have an option to use federal vaccine contracts that are negotiated after ACIP passes a VFC resolution. States must use the contracts with the VFC program and for Section 317 purchases; states may use the federal contracts for state-funded purchases. CDC has prioritized timeliness in the negotiation of federal vaccine contracts, but delays have occurred. For example, shipping issues were a problem with the varicella vaccine and cost was a concern with the RotaShield vaccine.

CDC is experiencing smaller discounts for newer vaccines. Most notably, federal contract prices for vaccines in 2006 included a 51% average discount for vaccines recommended through hepatitis B vaccine, but a 17% average discount for varicella vaccine and subsequently recommended vaccines. States' funding accounted for the lowest percentage of childhood vaccine doses purchased in 2005: 46% by the private sector; 43% by the VFC program, excluding influenza vaccine; 6% by Section 317 immunization grantees; and 5% by states.

Data from 1994-2004 showed that the private sector kept pace with the VFC needs-based funding. To date, private health insurance typically includes an immunization benefit. Private sector financing is largely independent of government purchase policies. Some children have insurance that does not cover vaccines and this requires their parents to pay. The 2003 Institute of Medicine (IOM) report estimated that 5%-14% of the U.S. childhood population would fall into this category. There are additional challenges with private health insurance. Payment for new vaccines might not cover the entire cost of the vaccine. A time lag could occur while establishing a code for the vaccine to be included in health insurance plans. Private health insurance might exclude some vaccines. Insurance plans that are exempt from the Employee Retirement Income Security Act are self-insured and cannot be regulated or mandated by states.

The cost of vaccines is one of the most significant stressors of the immunization program. For example, the federal contract price for vaccines that ACIP universally recommended increased from $45 in 1985 to $894 in 2006. In terms of the development of new vaccines, biotechnological advances and characteristics of the VFC program are the two primary drivers. For example, the VFC program was designed to achieve the "Childhood Immunization Initiative" goal of fostering the development of new and better vaccines. ACIP is a committee of independent scientific experts that passes VFC resolutions and admits vaccines to the VFC program. ACIP's VFC resolutions guarantee a substantial market and its universal recommendations become national objectives under the *Healthy People* initiative. Uncapped prices for vaccines with new biologics license numbers were established as incentives for manufacturers in terms of research and development, funding and profit.

A two-tiered state vaccination policy within local health departments is the major challenge in implementing the VFC program. Health department clinics traditionally vaccinated any child who presented for immunization, but underinsured children are ineligible for VFC vaccines except at ~3,000 federally qualified health centers (FQHCs) and rural health centers (RHCs). The VFC program designated FQHC and RHCs as "safety net" providers for underinsured children. With this approach, state funding and Section 317 dollars would be used to vaccinate underinsured children. However, many states could not purchase vaccines for underinsured children due to inadequate state funding and Section 317 dollars. This process has resulted in a two-tiered policy in which vaccines purchased by the

government would not be available to underinsured children at health department clinics. Therefore, access to new vaccines for some children is based on insurance status, which creates an ethical tension for public health officials, providers and states.

States are challenged by having to implement vaccines in an environment where needs are greater than resources. For example, states are required to implement the VFC program. A minimum time between implementation of ACIP's VFC resolutions and establishment of federal vaccine contracts for states to implement a new ACIP VFC resolution has not been established. The non-VFC population is a significant concern due to the cost of new vaccines, underinsured children and adult priority populations. Immunization programs in states and urban areas are placed in difficult situations of identifying priorities. CDC and ACIP have not prioritized one vaccine over another at this time. States typically prioritize immunizations by vaccine rather than populations, but prioritization based on geography and needs might be an option.

Data from a survey administered in 2003 showed that 20 states were unable to administer pneumococcal conjugate vaccine (PCV) to underinsured children in health department clinics due to two-tiered polices. A study was also conducted on state decision-making in vaccination. The data showed that the provision of vaccines by grantees in 2006 to underinsured children varied based on geography and specific type of vaccine. A review of vaccine purchase data from the Section 317, VFC and state programs in 2005 showed that health department clinics did not purchase PCV7 vaccine for underinsured children in nine states or MCV4 vaccine for underinsured children in 31 states. These states might not have a public health department safety net to vaccinate underinsured children against these diseases.

Dr. Rodewald drew three conclusions. First, the safety net for childhood vaccines is severely challenged by difficulties providing vaccines to underinsured children. Second, this problem goes beyond the desire for a medical home for primary care. Ideally, providers should be able to provide vaccines in the context of comprehensive primary care, but failing that, it would be important to at least have a relatively convenient location to refer a child with financial barriers. The current situation is such that there are areas in the country in which a private provider has no other provider to refer an underinsured children for free vaccination. Third, the current implementation of ACIP recommendations as a "patchwork quilt" among states for underinsured children is troubling.

Dr. Rodewald noted that several groups in addition to ACIP are attempting to identify solutions to the vaccine financing dilemma. IOM published a report on financing vaccines in the 21st century. The National Vaccine Advisory Committee (NVAC) formally responded to the IOM report and established a Vaccine Financing Workgroup to specifically address this issue. The President's VFC legislative proposal of 2003 included health department clinics as safety net providers for the VFC program. The AAP Immunization Task Force is currently focusing on vaccine financing issues.

Overview of the NVAC Financing Workgroup

Dr. Gary Freed, the NVAC Chair, presented an overview of the NVAC Vaccine Financing Workgroup. The purpose of NVAC is to advise and make recommendations to the Director of the National Vaccine Program and the Assistant Secretary for Health. NVAC's current membership is 17 appointed members, including two industry representatives; nine *ex- officio* members or government agency staff; and six liaison members or representatives of other advisory groups. NVAC has no statutory authority, but the members raise issues, propose solutions and drive public debate.

NVAC formed its Vaccine Financing Workgroup with three primary charges. A process would be established to obtain input from stakeholders. A strategy would be developed to select and address two

to three key topics each year. Specific policy options for the key topics would be developed within one year. The workgroup is consistent with NVAC's mandate and defines NVAC's unique role. Because NVAC is not an IOM committee, the workgroup was also asked to establish realistic expectations and achievable goals for vaccine financing in the public and private sector in the United States. As a result, the workgroup will address incremental changes within the current system rather than systematic changes for the entire nation.

The NVAC workgroup is represented by NVAC and NVPO members, CDC and CMS representatives, the ACIP Chair and other invited members. During its first face-to-face meeting, the workgroup agreed that its focus in the first year would be on private sector, delivery and practice economic issues, such as vaccine inventory cost, reimbursement and administration. The workgroup acknowledged the need to be mindful of systematic changes in this effort.

The workgroup also identified several action items that would need to be completed in fulfilling its charge, such as determining information needs; convening stakeholder panels with industry, private sector and public sector representatives; and developing realistic and achievable recommendations to address private sector financing issues. The workgroup is now attempting to define the appropriate role of HHS in identifying solutions and determine the best venue in addressing comprehensive financing issues.

Dr. Freed emphasized that the workgroup welcomes input from all sources, but all recommendations must first be publicly vetted and voted on by the full NVAC membership. Feedback on the workgroup's activities can be submitted to Ms. Angela Shen of NVPO at angela.shen@hhs.gov.

To guide the discussion on vaccine financing, Dr. Abramson asked for input on short-term actions ACIP could take to facilitate full implementation of its vaccine recommendations for children and adults. Suggestions by ACIP members, liaisons and other participants in response to Dr. Abramson's request are outlined below.

- ACIP should become involved with ongoing efforts by the AAP Immunization Task Force. This group identified three major barriers to practitioners delivering vaccine services to the nation: (1) vaccine acquisition costs to private sector physicians; (2) the dilemma between administrative fees and the obligation of physicians to provide vaccines to patients; and (3) the negative role of vaccine supply issues in actual practice. AAP formed three subcommittees to focus on these three issues in more detail, review current data and propose potential solutions. However, AAP will convene a stakeholders' meeting in February 2007 to obtain vaccine financing solutions from a broader audience. AAP is conducting these activities in parallel with NVAC's ongoing efforts, but AAP's priorities are somewhat different than the private sector and other constituencies.
- ACIP should become involved with ongoing efforts by the Immunization Workgroup of the IDSA National and Global Public Health Committee. This group will soon release a set of principles outlining IDSA's position on overcoming existing barriers and improving the delivery of vaccines at all possible visits. IDSA acknowledged that solid coordination among ACIP and other groups would assist in strengthening the capacity of current systems to deliver vaccines, resolve issues with Section 317 funding, and address implementation issues. IDSA is also aware that ACIP and other groups would need to coordinate efforts with Congress to enhance state infrastructures, eliminate two-tiered systems and minimize inappropriate delivery of vaccines.
- ACIP should become involved with AMA's ongoing efforts. AMA is attempting to identify vaccine financing strategies that could be implemented to allocate Section 317 dollars for both adult and pediatric immunizations. AMA made a formal commitment to this activity by incorporating the improvement of the adult vaccine infrastructure into its three- to five-year strategic plan.

- ACIP and AAP should attempt to reach consensus on extending VFC coverage to uninderinsured children.
- ACIP should formally recommend that site visits be made to each state health department director in the country due to inadequate state funding of vaccines at the local level. This approach might influence and improve the allocation of Section 317 dollars.
- ACIP should place more emphasis on addressing the need for vaccines in the adult population. This issue is an increasing problem, but has not been sufficiently addressed by the public sector, private sector or states to date.
- ACIP should assist states in making interim decisions about vaccine implementation.
- ACIP should be involved in ongoing efforts by NVAC, AMA and industry to share information and address vaccine financing concerns. For example, several manufacturers currently support a 317 coalition that lobbies for additional funding. Under this initiative, Section 317 dollars would match needs based on recommended vaccines. GSK is supporting a number of studies to measure pediatric vaccine coverage, better understand coverage issues and focus on adult immunization funding issues.
- ACIP's guidance on vaccine financing should focus on a reasonable level of reimbursement because this issue is a major consideration within the private insurance community.
- ACIP's guidance on vaccine financing should focus on other basic preventive health practices, such as HIV testing and mammograms. This approach might engage other preventive health providers who serve populations that are challenged by access to care issues and health disparities.
- Guidance on vaccine financing should be provided to state and local immunization programs, but ACIP might not serve as the best source for these recommendations. For example, ACIP guidance on prioritizing vaccines might minimize the strength of the recommendations and cause insurance companies to deny coverage of vaccines.
- ACIP's guidance on vaccine financing should strongly emphasize the tremendous amount of dollars that have been saved in preventing disease from mumps, measles, invasive pneumococcal disease and Hib meningitis. ACIP's recommendations on the rising cost of vaccines should be balanced with vaccine cost-savings. This information should be presented to legislators and policymakers to encourage adequate funding of both pediatric and adult vaccination programs.
- ACIP's guidance on vaccine financing should acknowledge adverse outcomes that have occurred at the local level as a result of "flat funding" of the Section 317 program, such as decreased dollars, less staff, no safety net, an inability to deliver vaccines, and a total erosion of services. ACIP should provide national leadership in addressing these local issues.

Dr. Abramson acknowledged the diversity in the suggestions on short-term actions ACIP could take to facilitate full implementation of its vaccine recommendations for children and adults. As a result, he confirmed that ACIP would monitor the ongoing efforts of NVAC and other groups in addressing the vaccine financing dilemma.

Guidance on Use of Zoster Vaccine [continued]

Dr. Abramson announced that CDC would provide ACIP with additional data on use of the zoster vaccine, but the presentation would be for informational purposes only and would not require a vote. Dr. Harpaz reported that guidance on dosage and administration of the zoster vaccine was extracted from the package insert. An assessment of a history of chickenpox was not required for routine vaccination for

adults ≥60 years of age. Details were provided on simultaneous and non-simultaneous vaccination with other adult vaccines.

Routine vaccination of adults ≥60 years of age should include persons with chronic medical conditions. Zoster vaccine should be offered at the first clinical encounter. Strategies to ensure vaccination should include linkages to other adult vaccines and preventive services. Emphasis should be placed on solid adult vaccine delivery practices. Residents of chronic care facilities should be included in vaccination efforts as appropriate. A permanent vaccine record should be maintained for both providers and patients.

Guidance on vaccine storage and handling was extracted from the package label. Unreconstituted vaccine should be discarded if the temperature exceeds 5°F. Providers should take measures to prevent inadvertent freezing of refrigerated vaccine kept in combined refrigerator units. Providers should call the manufacturer's hotline to request additional information on storage and handling.

The challenges of vaccine safety monitoring in the target population were emphasized, particularly the high rate of medical events in older persons. Zoster vaccine is the first live vaccine that was specifically developed for the elderly. Guidance was provided on administration errors and infection control practices for shingles. The zoster vaccine was not recommended for the sole purpose of preventing household or occupational VZV transmission.

Guidance was provided for specific populations: (1) persons receiving blood products or antiviral medications that could interfere with VZV transmission; (2) persons with a history of varicella vaccine; (3) nursing mothers; and (4) vaccinees with household members at high risk for attenuated VZV. No indications were established for use of zoster vaccine to control or prevent current shingles or PHN cases. Allergies to vaccine components and pregnancy were highlighted as contraindications to vaccination, while severe illness and active untreated tuberculosis were noted as precautions to vaccination.

MENINGOCOCCAL VACCINE

The series of presentations and ACIP discussion on the meningococcal vaccine are set forth below.

Overview

Dr. Carol Baker, the Meningococcal Workgroup Chair, highlighted the workgroup's three major recommendations. First, administration of MCV4 should be continued for adolescents 15 years of age, freshmen entering college who will live in dormitories, and persons at increased risk of invasive meningococcal disease. Second, routine MCV4 immunization of adolescents 11-12 years of age should be resumed. Third, CDC should initiate active surveillance studies of vaccine-associated GBS.

The workgroup based its original recommendations on two major factors. Increased rates of meningococcal disease per 100,000 population in serogroups A, C, Y and W135 are observed in persons 11-30 years of age, but sanofi pasteur indicated that MCV4 supply would not support immunization of all adolescents aged 11-18 years. Thus, the workgroup prioritized three cohorts for MCV4 immunization. A three- to five-fold increase was observed in college freshmen living in dormitories. Surveillance data showed a peak in meningococcal disease among persons 15-18 years of age. The adolescent platform at 11-12 years of age would be important because this population typically presents to physicians for immunization and other preventive services. During the meeting, the workgroup presented updates on

the MCV4 supply, the occurrence of GBS in recipients of MCV4, and a decision analysis to support its recommendations.

Update on the MCV4 Supply

Dr. Wallace reported that the high demand of MCV4 in June 2005 resulted in order limits and back orders in both public and private sectors. The demand initially was highest among college freshman. CDC emphasized its initial recommendations for vaccination only of three distinct cohorts. A high demand occurred in the summer following approval of MCV4, but complaints and concerns about supply rapidly diminished in the fall and winter. In year 1, sanofi pasteur distributed ~4.1 million doses and projected that ~6 million doses would be distributed in year 2.

CDC convened a Supply Workgroup with representation by ACIP, CDC, other federal agencies, sanofi pasteur and professional organizations. CDC also published a notice in the May 19, 2006 edition of the *Morbidity and Mortality Weekly Report* (*MMWR*) to alert readers to the limited supply of MCV4 and recommend deferring vaccination of persons 11-12 years of age. Insurance claims data collected through March 26, 2006 confirmed MCV4 use across all adolescent ages, not just the recommended cohorts. However, it appeared that CDC's revised guidance on Menactra® significantly impacted vaccination practice among physicians because use in 11-12 year olds was greatly reduced after the May *MMWR* report.

The distribution of cumulative doses has steadily increased since CDC issued its revised recommendations. Data on the number of doses distributed each month from March 2005 to September 2006 demonstrated diligent efforts by sanofi pasteur to distribute as many doses as possible during the summer demand. In terms of the future supply, sanofi pasteur is meeting its projections for 3.5-4.5 million additional doses through March 2007. Back orders have been filled and restrictions were released on order sizes for the private sector. CDC will collaborate with sanofi pasteur to ease the caps placed on order sizes in year 1 for the public sector.

Dr. Wallace asked ACIP to consider the following issues during its discussion. Significant doses are projected to be available in the future. Adolescents 17-18 years of age likely received a larger proportion of vaccine in year 2 compared to year 1, likely at least partially due to the revised recommendations. The Supply Workgroup has determined that supply is now adequate to return to routine recommendations. An article the workgroup developed is ready for publication in the November 3, 2006 edition of the *MMWR*. Pending the outcome of the current ACIP meeting, the workgroup will coordinate with partners in publishing the announcement to return to routine recommendation.

Overview of GBS in MCV4 Recipients

Dr. Robert Davis, Director of the CDC Immunization Safety Office (ISO), reported that GBS is a serious neurologic disorder involving inflammatory demyelination of the peripheral nerves. Additional cases of GBS after MCV4 vaccination continued to be reported to VAERS following the April 2006 *MMWR* article. CDC assessed the reports to determine whether the new cases indicated an increased risk for GBS after MCV4 vaccination. Three articles were published in the *MMWR* on 17 GBS cases after MCV4 vaccination reported to VAERS from October 2005 to October 2006.

A CDC medical officer and an independent clinical immunization safety assessment investigator reviewed the nine most recent cases reported to VAERS in October 2006. Both reviewers confirmed diagnoses of

GBS in all nine cases. Eight of the nine cases met the surveillance case definition. The remaining case was a sensory variant of GBS that was diagnosed by an attending neurologist and was based on nerve conduction studies consistent with GBS. A case review showed that clinical data for other causes of GBS typically were not available. *Campylobacter jejuni* (*C. jejuni*) is the leading cause of gastroenteritis and is also the most frequent antecedent pathogen in GBS cases.

Of all 17 GBS cases, none reported diarrheal prodromes; three had stool cultures taken; and two tested negative for *C. jejuni* based on either a stool culture or serum sample. None of the states where the patients resided reported outbreaks of *C. jejuni* from June 2006 to September 2006. No evidence was seen of geographic clustering. The onset of the 17 cases ranged from 2-33 days following vaccination. A temporal scan statistic showed a significantly elevated risk for clustering in the period of 9-15 days following vaccination. Data from a managed care organization (MCO) within the Vaccine Safety Datalink (VSD) indicated that ~94% of persons who received MCV4 vaccination were 11-19 years of age. As a result, subsequent analyses were limited to this population and excluded two GBS cases in persons 30 and 43 years of age.

The analysis was designed to determine whether the reporting rate for GBS after MCV4 vaccination was higher than expected. Variables input into the calculation included observed, background and expected reporting rates. The analysis was based on several assumptions, including that all cases were reported and that all vaccine distributed was, in fact, administered. The analysis suggested that there might be a small increased risk of GBS after MCV4 vaccination. The timing of neurologic symptoms within one to five weeks of vaccinated cases is a concern.

Risk estimates using background incidence rates from either VSD or the Healthcare Cost and Utilization Act have substantial uncertainties. The completeness of GBS reporting to VAERS is unknown. Under-reporting of GBS after MCV4 vaccination would increase risk estimates. The absence of any GBS cases after MCV4 vaccination in persons 11-19 years of age would not offer substantial reassurance regarding MCV4 safety.

On the other hand, no surge in GBS cases reported to VAERS was seen after publication of the *MMWR* articles. Overall, the VSD has limited ability to detect rare adverse events. A larger study would be needed to provide a more definitive assessment, but this research would require several years to accumulate cases and attain sufficient statistical power. An evaluation of GBS cases after MCV4 vaccination is underway within VSD.

The additional cases reported do not affect or change CDC's current recommendations due to the ongoing risk for meningococcal disease

Decision Analysis of Meningococcal Disease Vaccination in the Presence of GBS

Dr. Bo-Hyun Cho, of CDC, presented preliminary findings from a cohort simulation model that was developed to compare health outcomes of vaccination and no vaccination in the presence of GBS risk. The hypothetical birth cohort included 4.1 million adolescents 11 years of age who were followed over an eight-year period. The patient perspective was considered in the study. Outcome measures included cases of meningococcal disease and GBS, death and life-months lost, and quality adjusted life months (QALMs).

The study was based on several assumptions. GBS and meningococcal disease would be independent and mutually exclusive events. Only meningococcal disease vaccine-preventable serogroups would be considered. A six-week risk window would be used for vaccine-attributable GBS. The life expectancy of adolescents would be 67.7 years of age. The probability of a vaccine-attributable GBS episode was

calculated with the frequency of GBS episodes among vaccinated persons reported to VAERS and the baseline risk for GBS among unvaccinated persons with data from VSD.

Several parameters were input into the model. A 5% morbidity rate among adolescent GBS patients was used based on a published study. Vaccine efficacy was assumed to be 93%. An incidence rate of 0.77/100,000 was used for meningococcal disease among unvaccinated persons based on unpublished data. The meningococcal disease incidence rate among vaccinated persons was scaled down by 1 minus vaccine efficacy. The vaccine coverage rate was assumed to be 70%. A 10% case fatality rate was used based on unpublished data. The health utility index (HUI) of long-term disability related to GBS was 0.698 based on a published study. The HUI of survival for meningococcal disease was 0.952 based on both published and unpublished data.

Preliminary findings from the study are as follows. MCV4 vaccination would prevent 163 meningococcal events and 16 deaths associated with meningococcal disease in a cohort of 4.1 million. Three cases of vaccine-attributable GBS cases would occur. GBS would cause 37 QALMs lost. Vaccination would prevent 12,488 life months lost and 5,352 QALMs lost.

The following results were seen when the case fatality rate was changed to 20% and the GBS morbidity rate was changed to 10%: (1) an increase from 16 to 32 deaths associated with meningococcal disease; (2) an increase from 12,488 to 24,976 life months lost; (3) a decrease from 5,352 to 4,757 QALMs lost; and (4) an increase from 37 to 85 QALMs lost caused by GBS. Overall, the cohort simulation model showed that MCV4 vaccination is favorable. The period of an increased risk of vaccine-attributable GBS is limited, while the benefit of meningococcal disease prevention is prolonged.

CDC made several remarks in response to ACIP's request for clarification on the analysis of GBS among MCV4 recipients and the preliminary findings from the cohort simulation model of meningococcal disease vaccination in the presence of GBS. However, Dr. Davis emphasized that many of the questions could not be answered at this time because the data are preliminary.

Two key comments were made for the workgroup to consider in its ongoing focus on meningococcal vaccine and vaccine-associated GBS. Dr. Allos advised the workgroup to cautiously consider results of the two patients who tested negative for *Campylobacter* because bacteria were not isolated from stool cultures. For example, persons infected with *Campylobacter* typically excrete bacteria in their stool for a median of 16 days. Most persons who develop GBS following *Campylobacter* have an onset of symptoms at 10-21 days after infection. Due to time lags between the individual seeking medical care and the provider ordering a stool culture, *Campylobacter* would not be detected in stools of GBS patients even if *Campylobacter* was the trigger.

Dr. Michael Decker, of sanofi pasteur, was pleased to announce that progress is being made on the workgroup's request for active surveillance studies of vaccine-associated GBS. A traditional case-control study would be virtually impossible to conduct because VSD is not nearly large enough to undertake a research project of this magnitude. Collaborations are underway between sanofi pasteur and a VSD contract site to coordinate and markedly expand VSD, launch an enormous cohort study, and address vaccine-associated GBS and other issues in the future. CDC, FDA and a number of other groups are also involved in this effort. At least two years would be required to collect a sufficient amount of data for the large cohort study, but the research partners expect to implement a study protocol within the next few months.

Summary. After the above presentations and discussion, Dr. Baker summarized the workgroup's recommendations to resume routine use of MCV4 in 11-12 year olds, to continue MCV4 use in previously recommended cohorts and those at increased risk of meningococcal disease, and to conduct additional research into the possible increased risk of GBS in MCV4 recipients.

ISO Update

Dr. Davis reported that CDC is conducting safety monitoring planning for all new vaccines to facilitate transparency and accountability, promote consistency of safety profiles, and document existing processes. CDC undertook this effort due to existing or pending approval of new vaccines or indications for rotavirus, shingles, HPV, MMRV, meningococcal disease, Tdap and influenza.

CDC will develop a safety profile for each new vaccine with two primary modes of data collection. First, VAERS is a passive surveillance system with capacity to provide signal detection and the potential for reporting from the entire United States. However, the limited, variable, biased and still primarily paper-based VAERS reporting system does not provide epidemiologic data. Diligent efforts are being made to promote an existing web-based system and make other improvements in VAERS. Second, VSD is an active surveillance system that collects data from eight health maintenance organizations (HMOs) or 3% of the United States. VSD captures highly complete outcomes and provides epidemiologic data, but has limited power for very rare adverse events.

For intussusception and other serious gastrointestinal reports, CDC and FDA review VAERS reports on a daily basis. The daily summaries include information on severity of the adverse event, age at vaccination, onset interval in days between vaccination and symptoms, gender of the vaccinee, all vaccines administered, pre-existing medical conditions and known allergies. For serious reports, VAERS nurses obtain radiologic, surgical or autopsy information with medical records confirmation. A Brighton case definition is used to verify suspected intussusception reports. Reporting rates are calculated and compared to background rates. The percent of COSTART codes are compared in children <12 months of age. For example, RotaTeq® and other vaccines are compared to children of the same age who received the same vaccines without RotaTeq®.

CDC uses VSD for safety monitoring because other than VAERS, no routine surveillance system has been developed to monitor vaccine safety signals in the United States. Recent events underscored the need for more timely reporting systems that are able to detect adverse events as closely as possible to real time following the introduction of new or modified vaccines, such as myocarditis associated with the smallpox vaccine, intussusception associated with the rotavirus vaccine, and Bell's palsy associated with the influenza vaccine.

The primary goals of CDC's rapid cycle analysis (RCA) conducted within the VSD are to detect adverse events associated with newly introduced vaccines and monitor adverse events arising with changes in established vaccines. However, the RCA system serves as a denominator-based assessment of whether future investigations would be needed rather than a final answer to an epidemiologic question. CDC collects information on all known vaccinees each week and follows each individual for a six-week observation period. The rate of adverse events is analyzed in the cohort of vaccinees and compared to either a comparison group or historical background rates. A fairly sophisticated statistical analysis is developed each week to determine the presence or absence of a signal for an adverse event compared to historical background rates.

CDC will use VAERS as a front-line monitoring system for gastrointestinal and other unexpected vaccine adverse events related to RotaTeq®. CDC will also incorporate the RCA system into VSD to conduct a real-time assessment of gastrointestinal-related vaccine adverse events among children 2-12 months of age who received RotaTeq®. Rates of intussusception and other serious gastrointestinal conditions will be analyzed and compared to historical rates. VSD will be used to confirm additional unexpected VAERS signals.

Ms. Penina Haber, of ISO, summarized recent RotaTeq® vaccine events that were reported to VAERS. As of September 30, 2006, ~1.7 million RotaTeq® doses were distributed. Of 189 RotaTeq® vaccine events reported to VAERS from March 1-October 23, 2006, 48% were from RotaTeq alone; 61% were after the first dose; 34% did not indicate the number of doses; 57% were among children 2-3 months of age; 5% were among children <2 months of age; 55% had an onset of symptoms within 0-2 days; 5% had an onset of symptoms within 3-7 days; and 16% had intussusception or other serious adverse events.

The most frequent adverse events following RotaTeq® vaccination in children 0-12 months of age were diarrhea in 24%, vomiting in 22% and fever in 17%. Six intussusception cases were reported to VAERS with a range in age of 4-21 weeks and a range in the interval of symptoms of 2-32 days. Of the six cases, four had surgery, two had necrotic bowel resection, and four developed intussusception after the first dose. No deaths have occurred.

To estimate intussusception risk, CDC obtained VSD data from 2000-2004 and used an average background rate in children 6-32 weeks of age. The risk was calculated at 2.98 intussusception cases per 10,000 person-years. The expected number of cases within 21 days after vaccination at any dose was estimated to be 30.7. The observed risk within 21 days was four intussusception reports per ~1.7 million persons. CDC used published data to assume a 47% under-reporting rate. The observed frequency of ~8.51 in the four observed cases was statistically significantly lower than the expected 30.7 cases even after adjusting for under-reporting.

CDC also formed an Intussusception Workgroup to systematically collect clinical data, demographics on intussusception cases, and stool, serum and tissue samples. The workgroup members had expertise in VAERS, rotavirus disease epidemiology, and pathology and virology laboratory procedures. The laboratory specimens were tested for wild-type and rotavirus vaccine strains and adenovirus. Specimens were requested on all intussusception reports regardless of the time since vaccination.

The results of three cases in which intussusception specimens were obtained are as follows. The ages of vaccinees were 11 and 12 weeks at dose 1 in cases 1 and 2, respectively, and 16 weeks at dose 2 in case 3. Necrotic bowels were resected on day 8 and 16 in cases 1 and 2, respectively, and the bowel was reduced in case 3. Tissues were negative for rotavirus and adenovirus in case 1; tissue results are pending in case 2; and stool and serum results are pending in case 3. The stool sample in case 1 revealed a VP4 gene that was identical to the rotavirus vaccine strain.

Reports of 19 hematochezia cases, excluding intussusception, were also submitted to VAERS among children 1-12 months of age after RotaTeq® vaccination. CDC and FDA agreed to characterize “hematochezia” as bloody diarrhea, melena, or colon, gastrointestinal or rectal hemorrhage. Of the 19 hematochezia reports, 37% were after receipt of RotaTeq® only; 68% were made within three days of vaccination; and 68% were among children two months of age. A comparison showed that the 19 hematochezia reports were per 1.7 million RotaTeq® doses distributed, while 60 hematochezia reports were per 1.5 million Rotashield® doses distributed. For other vaccines in the same time period and with the same age group, four hematochezia reports were submitted among 2,248 total reports.

Preliminary results of the RotaTeq® reports submitted to VAERS are as follows. Few serious cases after RotaTeq® were observed when the vaccine was used alone. Intussusception reports were less than the expected rate in the general population. Hematochezia reports were primarily within three days of vaccination, but none of these events were serious. Overall, CDC acknowledges that these findings are subject to limitations of passive surveillance systems.

CDC is using its VSD RCA system to conduct an observational study of RotaTeq® in eight sites that capture ~96,000 births per year. The primary events that will be analyzed in the study include

intussusception, gastrointestinal bleeding, meningitis, encephalitis, seizures, gram-negative sepsis, and other signals which may be identified through VAERS. During post-marketing and other follow-up activities for RotaTeq®, CDC will obtain additional data from Merck's Phase IV study of ~45,000 children and will continue to convene conference calls with FDA and the manufacturer to coordinate the research projects.

Dr. Davis provided an update on ISO's efforts in developing a comprehensive immunization safety research agenda in an open and transparent process with both extensive internal and external input. This activity was triggered by the release of the IOM *Vaccine Safety Research, Data Access and Public Trust* report in February 2005. The entire report included 28 recommendations on vaccine safety research, public access to vaccine safety data and public trust, but Chapter 5 was specifically devoted to an independent review of VSD activities. Chapter 5 noted that "the limited ability of independent external researchers to conduct high-quality corroboration studies or studies of new hypotheses create a special need to involve the public in the priority setting process for the VSD research plan."

Chapter 5 also contained specific recommendations. An NVAC subcommittee should be formed with a wide variety of stakeholders to review and provide advice on the VSD research plan. The existing Safety and Communications Subcommittee could serve as the new NVAC subcommittee. Subcommittee meetings should be public to allow interested persons to observe the process and provide input through established mechanisms.

In response to the IOM report, CDC will develop a comprehensive safety research agenda with both internal and external input. Transparency, standardization and credibility will serve as the guiding principles of the research agenda. The focus and strengths of the research agenda will be to leverage partnerships, invite extensive internal and external collaborations, facilitate efforts with NVAC, produce scientific credibility, and promote public trust.

CDC and Merck made several comments in response to ACIP's questions on safety monitoring of RotaTeq®. First, CDC will use VSD to encourage MCOs to adhere to ACIP's age-based recommendations on RotaTeq® vaccination in the immunization schedule. CDC is aware that ACIP issued this guidance due to its concern about the association between age and intussusception.

Second, CDC will correct the ISO data that showed an infant four weeks of age received a second RotaTeq® dose. The infant was actually six months of age at the time of the second dose. Third, efforts are underway at Merck that are parallel to CDC's activities on safety monitoring of RotaTeq®. For example, Merck is reviewing data from insurance claims and HMOs to determine the actual use of RotaTeq®, specific age groups that are receiving the vaccine, and turnover in use of the vaccine by practice.

HPV VACCINE

The series of presentations and ACIP discussion on the HPV vaccine are set forth below.

Update on the Quadrivalent HPV Vaccine

Dr. Lauri Markowitz, of CDC, announced that ACIP's provisional recommendations on the quadrivalent HPV vaccine were posted on the CDC web site shortly after the June 2006 ACIP meeting. The ACIP statement is currently undergoing the CDC clearance and Office of Management and Budget review processes. CDC expects the statement to be published in the first half of 2007.

The catalog price of the quadrivalent HPV vaccine is $120/dose. ACIP adopted a VFC resolution for the vaccine during the June 2006 meeting; the VFC contract is still being negotiated. Data from the manufacturer showed that 750,000 doses were distributed through mid-October 2006. As of the end of September 2006, 76 adverse events were reported to VAERS with the manufacturer serving as the source of 74% of these reports. Of the 76 reports, 42% were among persons 11-18 years of age; 2 were among males; 86% involved quadrivalent HPV vaccine only; and 50% involved adverse events with onset the day of vaccination.

The five most frequently reported symptoms after quadrivalent HPV vaccine was syncope, pain at injection site, rash, dizziness and fever. Three serious reports were reported to VAERS after HPV vaccination in females 14 and 16 years of age. One of these patients had vasovagal syncope and was hospitalized overnight for observation. Two patients who received MCV4 at the same visit as HPV vaccination developed GBS. Merck established a vaccine in pregnancy registry. No outcomes have been reported to date. There have been nine exposures during pregnancy and seven persons were enrolled in the registry.

CDC will monitor coverage of the quadrivalent HPV vaccine. The National Immunization Survey (NIS) will use its sample frame methodology to conduct a teen module in October-December 2006 through a random digit dial telephone survey. The national sample will include ~5,000 parents of teens 13-17 years of age. Initial data will be available in June 2007. The survey will include questions on specific vaccines, HPV and HPV vaccine knowledge, reasons for not receiving new vaccines, health insurance, VFC eligibility, and the adolescent visit at 11-12 years of age. Provider records will be checked to verify immunizations.

NIS will also conduct an adult module in the second quarter of 2007 through a telephone interview of adults 18-49 years of age. The survey will include questions on HPV and other recommended vaccinations. Provider records will not be checked to verify immunizations. Results of the adult module will be used to guide questions on the 2008 National Health Interview Survey.

The National Survey of Children's Health will provide national and state-based estimates. This survey was conducted in 2003 and will be repeated in 2007. The national sample of ~102,000 children will include ~2,000 children <18 years of age per state. Household interviews will be administered to ~20,000 teens 13-17 years of age. The survey will include questions on HPV, Tdap and meningococcal vaccines. Immunization data will be based on parental recall only.

The Immunization Information System sentinel sites will conduct an adolescent registry model in geographically limited areas in five states and the District of Columbia. Quarterly data will be collected from the third quarter of 2006 to the fourth quarter of 2007. Coverage estimates will be gathered on individual vaccines, vaccine series recommended for adolescents, and concomitant administration of recently recommended vaccines.

The Association of Immunization Managers (AIM) administered a web-based survey in September 2006 to its 64 grantees to identify strategies that would be used to implement HPV vaccine. Of 44 grantees that responded to this question, 20 planned to provide HPV vaccine to VFC-eligible females 11-12 years

of age only; 23 planned to provide vaccine to females in the age groups of 9-18, 11-12, 11-14, 11-18 or 17-18 years; and 1 had no plans at the time of the survey to purchase vaccine.

AIM acknowledged several reasons for grantees providing age ranges for HPV vaccination that were more limited than ACIP's recommendations. Grantees were concerned about the limited inventory of HPV vaccine when the VFC contract initially would be established. Most states have no interest in developing a two-tiered system if funds through other sources would be insufficient for vaccine purchases. States would limit the number of cohorts to ensure that vaccine would be available to all persons within a limited age group. States would fully implement the HPV vaccine recommendations when funding was identified.

Of 44 grantees that responded to this question, 14 would provide HPV vaccine to underinsured females 11-12 years of age in public settings; 16 planned to provide vaccine to females in the age groups of 9-18, 11-12, 11-14, 11-18 or 17-18 years; and 13 had no plans at the time of the survey to purchase vaccine. Of 41 grantees that responded to this question, 30 had no plans to purchase HPV vaccine for females 19-26 years of age and only 6 had plans to purchase vaccine through either Section 317 dollars or state and local funds. However, 17 grantees planned to educate providers or consumers about the vaccine.

Dr. Markowitz announced that the HPV Vaccine Workgroup would continue to review data on both the bilavent and quadrivalent HPV vaccines. GSK recently reached the pre-specified number of events in the Phase III trial and plans to submit a BLA to FDA in the spring of 2007. The ACIP statement would be revised as needed based on new data that become available

Overview of the GARDASIL® Population Impact Analysis

Dr. Eliav Barr, of Merck Research Laboratories, presented data from clinical studies on the disease burden and efficacy of the GARDASIL® quadrivalent HPV recombinant vaccine in North American women. The U.S. population contains a mixture of naive, partially exposed and fully exposed women. "Naive" women are naive to all four vaccine HPV types and would derive maximum benefit from vaccination. "Partially exposed" women have ongoing or prior infection with <4 vaccine HPV types and would derive some benefit from vaccination.

Clinical studies of the GARDASIL® prophylactic HPV vaccine included 5,996 North American women 16-24 years of age. The number of lifetime sexual partners was restricted to <6 in the Phase IIa trial and <5 in the Phase IIb/III trial. Virginal adolescents 16-17 years of age were excluded from the study. Subjects from 35 states, Puerto Rico and three Canadian provinces were enrolled in the study. Most of the sites were on college campuses, but several sites were in inner city settings. The study focused on the primary outcome of prophylactic efficacy of the vaccine in baseline HPV-naive subjects. Additional analyses were done to focus on the secondary outcome of the impact of the vaccine in the general population regardless of baseline HPV status. The current follow-up period of the study is 2-4 years.

Key demographics of the North American cohort of 5, 996 subjects are as follows: the median age was 20 years; 73.4% were white; 15.4% had a pregnancy history; 92% were non-virgins; the mean age at first sexual intercourse was 16.9 years; 9.6% self-reported a history of sexually transmitted infections; and 13% had a previous Pap test abnormality. The sexual behavior of the cohort was compared to data from the National Survey of Family Growth (NSFG). In NSFG, 77% of women 15-24 years of age were sexually active (compared with 92% in the North American cohort in the vaccine trial). Among those sexually active, the median number of sexual partners was 2 (similar to those in the vaccine trial).

In the North American cohort, the prevalence of chlamydia was 3% and the prevalence of gonorrhea was 0.4%. Of 3,587 subjects with serology or PCR test results for HPV types 6/11/16/18, 76.1% were naive to all four types; 23.9% were positive to 1 or more types; and 0.1% were positive to all four types. Few of the subjects ≥23 years of age were positive to both HPV types 16/18. Even if seroprevalence is assumed to be double what was detected, to account for the fact that not everyone develops antibody after infection, a small percentage would have been positive for both HPV types 16/18.

Data from the clinical trials showed several major findings. Most women 16-24 years of age with multiple sexual partners remained naive to at least one of the two cancer causing HPV types. Among women who were positive to one HPV type, prophylactic efficacy against the other types to which they were naive remained high at ~90%. Prophylactic efficacy was not impacted by the presence of at least one positive vaccine HPV type at baseline.

In the North American cohort general population analysis, including all women regardless of HPV status, the proportion of women in the vaccine group with HPV 16/18-related cervical intraepithelial neoplasia (CIN) 2/3 or adenocarcinoma *in situ* (AIS) was reduced by 67% compared with the placebo group. In the same population, the proportion of women in the vaccine group with any CIN 2/3 or AIS lesions was reduced by 32% compared with the placebo group. The benefit of the vaccine became more apparent over time as prevalent disease was identified and resolved and incident disease was prevented. Merck will continue to conduct analyses in Phase III studies to collect data on the overall population impact of the vaccine on rates of CIN 2/3 and type-specific disease.

Dr. Barr summarized the major conclusions based on data from the GARDASIL® clinical studies. In the general population of North American women 16-24 years of age, most subjects were naive to all four vaccine HPV types and few subjects were positive to both HPV types 16/18 even with four lifetime sexual partners or a Pap test abnormality. Event rates were high in the study population. Administration of GARDASIL® would be highly effective in reducing the burden of HPV disease. The benefits of GARDASIL® would become more apparent over time.

Cost-Effectiveness of a Quadrivalent HPV Vaccine in the United States

Dr. Elamin Elbasha, of Merck Research Laboratories, presented data from a study that projected the epidemiologic and economic consequences of a quadrivalent HPV vaccine in the United States. An integrated disease transmission model (which captured direct and indirect herd immunity effects of vaccination) and cost-utility analysis were developed, applying data on demographics, behaviors, and HPV infection and disease. U.S. health system data were applied that assumed existing screening practices would continue after vaccination

Vaccination strategies examined included vaccination of females before 12 years of age and four temporary catch-up programs targeted to females 12-14, 12-17, 12-19 and 12-24 years of age. Vaccine characteristics were based on both data and assumptions of vaccine take, vaccine degree and duration of protection, and breakthrough infections. Vaccine penetration for routine vaccination of adolescents 12 years of age was assumed to increase linearly from 0% in year 0 to reach a maximum of 70% in year 5. For the temporary catch-up program, the ramp-up among previously unvaccinated females was from 0% to 50% over 5 years with a decline to 0% thereafter.

Several efforts were undertaken to validate the model. Persons with expertise in the natural history of HPV infection and disease were consulted. HPV vaccination and cervical cancer screening models were reviewed. Mathematica® was used to program equations and perform all calculations in the model for consistency. All of the model equations and inputs were publicly released for review. Several tests were

performed to establish technical accuracy. The predictive validity of the model was compared to predictions of HPV prevalence, genital warts, CIN 1/2/3, and cervical cancer incidence and death in the published literature. Several analyses were performed with the model to make the following projections:

- The proportion of females currently or previously infected with HPV types 16/18 by age prior to vaccination.
- The incidence of HPV types 6/11/16/18-related CIN 2 by age prior to vaccination.
- The public health impact of various vaccination strategies on HPV types 16/18-related cervical cancer.
- The cumulative incremental impact of vaccination strategies on HPV types 16/18-related cervical cancer.
- The impact of vaccination strategies on HPV types 6/11/16/18-related CIN 2/3 among females.
- The impact of vaccination strategies on HPV types 6/11-related genital warts among males. Although male vaccination was not included in this scenario, a substantial reduction in the incidence of genital warts in males would be expected due to herd immunity effects and the protection of female partners.

The model was also used to demonstrate additional HPV types 16/18-related cervical cancer cases that would be prevented in the United States in the next 25 years. The model suggested that routine vaccination of females 12 years of age would prevent 10,124 cervical cancer cases assuming lifelong duration of protection.

Catch-up programs targeting females 12-17 years of age would prevent an additional 10,181 cervical cancer cases. Expanding the catch-up vaccination to include women 18–19 years of age would prevent an additional 3,980 cervical cancer cases. Expanding catch-up beyond age 19 years to include women 20-24 years of age would prevent an additional 6,134 cases of cervical cancer. The cost-effectiveness of various HPV vaccination strategies was analyzed as well. Overall, the strategy of routine vaccination of 12-year old females plus catch-up vaccination of females 12-24 years of age was found to be the most effective strategy at a cost of $10,362 per QALY.

Dr. Elbasha summarized the major conclusions of the cost-effectiveness study of a quadrivalent HPV vaccine in the United States. A prophylactic quadrivalent HPV vaccine could be efficiently added to current screening programs and also could reduce the incidence of cervical cancer, CIN and genital warts. Catch-up vaccination could provide earlier and greater reductions in HPV-related disease. Vaccination of females before 12 years of age combined with a temporary catch-up program of females 12-24 years of age could be cost-effective relative to many other public health interventions.

Update on the Mumps Outbreak

Dr. Gustavo Dayan, of CDC, provided an update on the mumps outbreak that occurred in the United States in 2006. CDC published dispatches in the March 30 and May 18, 2006 editions of the *MMWR* on the unexpected increase in mumps cases in Iowa and the spread of the outbreak to other states. An update on mumps activity in the United States from January 1-October 7, 2006 is scheduled for publication in the October 27, 2006 edition of the *MMWR*.

CDC used two major sources to collect mumps data. Data from cases with dates of onset from January 1-October 14, 2006 were extracted from the National Notifiable Disease Surveillance System states use to electronically report mumps cases to CDC. Data from patients with dates of onset between January 1-July 31, 2006 were also extracted from databases of seven states with the most mumps cases: Iowa,

Kansas, Illinois, Missouri, Nebraska, South Dakota and Wisconsin. The outbreak peaked in April 2006 and began to decrease in May 2006. The number of cases reported by states ranged from 1-1,971 with the seven highly affected states reporting ≥100 cases each. The incidence of mumps also ranged among states from 3-67 cases/100,000.

Key demographics of the mumps outbreak in the United States were as follows: 63% female, 90% white, 93% non-Hispanic, and a median age of 22 years. The ages of the cases ranged from <1-96 years, but the age group of 18-24 years was most affected. Parotitis was present in 68% of cases. The G strain was isolated from the outbreak and was identical to the G genotype in the mumps outbreak in the United Kingdom. Of nearly 6,000 reported cases, 4% were unvaccinated and 46% had received two vaccine doses. The vaccination status was unknown in 30% of cases.

CDC followed specific mumps clusters in several states. An Illinois cluster included 85 persons 17-30 years of age in a college from August 31-October 13, 2006. Ten students had positive immunoglobulin M (IgM) results, seven had positive PCR results, 93% had received two vaccine doses, and orchitis and myocarditis were each present in one case. A Kansas cluster included 22 persons 18-24 years of age at two colleges from August 7-September 22, 2006. Of these students, 95% had received two vaccine doses. A Virginia cluster included 24 persons 18-22 years of age and one healthcare worker from September 22-October 23, 2006. Of these cases, 96% had received two vaccine doses and aseptic meningitis was present in one case.

CDC learned several lessons from the epidemiology of the mumps cases. Few infants were affected and minimal outbreaks were reported in schools or day care centers. The mumps cases did not spread to unvaccinated populations. Cases with mild clinical presentation among vaccinated persons might have delayed recognition of cases. Congregate settings facilitated transmission. For example, CDC's case-control study in Kansas with 97 cases and 147 controls demonstrated that residence in a dormitory or exposure to mumps increased risk. Several questions remain unanswered about the epidemiology of the mumps cases. Why were females more affected? What was the reason for the outbreak starting in Iowa? Why were incidence rates highest in Iowa?

CDC learned several lessons from the laboratory diagnosis of the mumps cases. The performance of IgM tests varied. IgM responses might not occur or might be delayed. Immunoglobulin G (IgG) acute specimens were positive in many cases. However, efforts to obtain two IgG specimens were difficult, particularly during the outbreak. Real-time PCR had a low yield and was higher when specimens were taken early in the course of disease.

For example, CDC's study in Kansas with 32 students with mumps detected only nine positive results. Real-time PCR samples were positive in 8 out of 9 specimens taken during the first three days following the onset of symptoms. Preliminary data from Iowa showed similar results. The ability to rule out cases on the basis of negative laboratory results was difficult. Several questions remain unanswered about the laboratory diagnosis of the mumps cases. What are the kinetics of serologic response among vaccinated persons? What are the true correlates of immunity for mumps? Is there a protective IgG level of antibody titers?

CDC learned several lessons from surveillance of the mumps cases. The existing surveillance system was not adequate for the mumps outbreak. The current case report form was not sufficient to report the absence of parotitis or asymptomatic cases. The clinical case definition of mumps varied among states. Several questions remain unanswered about surveillance of the mumps cases. Was mumps virus circulating endemically? Were mild symptomatic cases not detected by the surveillance system before the outbreak? Were cases in vaccinated persons ruled out by negative laboratory tests? Were mild symptomatic cases over-diagnosed during the outbreak due to enhanced surveillance?

CDC learned several lessons from vaccine effectiveness of the mumps cases. Efforts to study vaccine effectiveness in settings with high two-dose vaccine coverage were difficult. For example, CDC conducted a study to determine attack rates in two highly affected college campuses in Iowa with a case definition of parotitis, orchitis, culture or submand/mental swelling. The study showed a 2% attack rate in colleges where 97% of students had received two vaccine doses and a 3.8% attack rate in colleges where 77% of students had received two vaccine doses. Attack rates in students who lived in dormitories were approximately twice those in students who did not live in dormitories.

Efforts to measure vaccine performance were challenging. For example, the Iowa college study showed a vaccine failure rate among two-dose recipients of ~8% with a broad case definition and ~3% with a restricted definition of "parotitis or orchitis lasting $\geq$2 days." However, the attack rates of 2%-4% in Iowa were lower compared to previous outbreaks with attack rates of 2%-18% and 25%-49%. Several questions remain unanswered about vaccine effectiveness of the mumps cases. Could mumps outbreaks be prevented in the future with the current MMR vaccine? Could the current MMR vaccine eliminate mumps? Could a third dose of MMR be used for outbreak prevention?

CDC learned several lessons from waning immunity of the mumps cases. Preliminary data did not appear to show that waning immunity played an important role. For example, CDC's study in Nebraska with 450 students who had received two MMR doses demonstrated that 7% were seronegative based on IgG testing. CDC's cross-neutralization studies with FDA did not show evidence of genetic drift or mutations giving rise to vaccine escape. Several questions remain unanswered about waning immunity of the mumps cases. Is IgG a solid correlate of immunity? What are the protective levels of immunity? What is the role of cell-mediated immunity?

CDC learned several lessons from outbreak control of the mumps cases. Intervention strategies were limited to settings of high two-dose coverage. Guidance was provided on isolation. For example, CDC's study in Kansas with 32 students showed that viral shedding appeared to be unlikely after three days following the onset of symptoms. In another study in Kansas with 134 students who were advised to be isolated, 100 adhered to the recommendation. Compliance was higher among students told to be isolated $\leq$ 4 days. Two key questions remain unanswered about outbreak control of the mumps cases. Is isolation useful for mumps control? Do dormitories enhance transmission?

Although a number of questions remain unanswered, CDC identified several potential reasons the mumps outbreak occurred. The importation of cases was unrecognized. Recognition of the outbreak was delayed due to unfamiliarity among physicians of clinical illness and vaccine modified disease. Some early cases may have been ruled out with negative IgM results. College settings played a major role in transmission, primarily because of lower two-dose vaccine coverage compared to other school settings, poor adherence to isolation guidance, and difficulties in truly isolating students in dormitory settings.

Vaccine effectiveness of ~90%-95% and two vaccine doses might have resulted in the accumulation of susceptible persons sufficient to sustain transmission and maintain a sizeable outbreak on a periodic basis. The contribution of waning immunity is still unknown at this time. However, high MMR vaccine coverage levels and vaccine effectiveness mostly likely prevented thousands of additional mumps cases. Incidence of the 2006 mumps outbreak was relatively low compared to previous outbreaks. The disease appeared to be modified with lower rates of complications and hospitalizations.

Dr. Dayan confirmed that several actions would be taken in the future based on lessons learned from the mumps outbreak and current unanswered questions. Surveillance would be improved. Better case definitions and case report forms would be developed. Laboratory diagnosis would be strengthened to understand the kinetics of immune response, including cell-mediated immunity. The development of new

laboratory tests would be considered. Adequate guidelines for isolation in colleges would be created. The effectiveness of current vaccines and policy would be reviewed.

Update on the Vaccine Supply

Dr. Wallace reported that the most recent problems in the vaccine supply were due to influenza, tetanus-containing vaccines, MMR and varicella vaccines, Prevnar conjugate vaccine (PCV) I and II, Menactra®, outbreak responses, and adolescent, adult and niche vaccines. The most significant issues for influenza during the 2000-2001 to 2006-2007 seasons included production delays, greater supply than demand, late season demand, shortages, manufacturer uncertainties, and later than desired production and distribution.

Several approaches were taken to address problems with influenza vaccine, such as prioritizing high-risk populations; implementing a tiering strategy; producing less vaccine the following year; producing vaccine late in the season; prioritizing, redistributing and extending the vaccination season; planning for contingencies; and promoting use of the available supply. Several manufacturers are making significant investments to expand capacity of influenza vaccine production.

The vaccine supply was also challenged for routine vaccination with the tetanus and diphtheria/tetanus toxoid, DTaP, MMR, varicella, PCV I and II, and MCV4 vaccines. These resulted from problems which included updated GMP requirements, updates to the manufacturing process, fill line issues, abrupt departure from the market by manufacturers, and high demand.

Several approaches were taken to address problems with routine vaccination, such as prioritizing tetanus toxoid containing vaccine for wound care; prioritizing vaccine based on provider supply; deferring certain doses when the supply was inadequate; delaying timing of vaccine administration; and reinforcing recommendations to defer vaccination to certain populations. Current problems with the vaccine supply include the Hib, pediatric hepatitis A (HepA), adult HepA and HepB, and Tdap vaccines.

Four major issues are the source of vaccine supply problems. The current vaccine system has minimal redundancy due to sole-source vaccines and mergers of manufacturers. Most vaccines are produced at capacity with different timetables. The existing vaccine system is complicated, dynamic and constantly changes. Both real and perceived risks and benefits should be addressed. Several solutions have been applied over the past few years to address these problems.

The National Childhood Vaccine Injury Act (NCVIA) of 1986 was enacted to address the increasing threat of liabilities. NCVIA resulted in the establishment of the National Vaccine Injury Compensation Program in 1988, the Vaccine Adverse Event Reporting System (VAERS), the National Vaccine Program Office (NVPO), and Vaccine Information Statements (VIS). VAERS was created to mandate reporting of certain adverse events following vaccination. NVPO was created to coordinate immunization activities across HHS agencies. Vaccine information statements were created with a requirement that information would be provided to vaccine recipients or their parents or legal guardians prior to certain vaccinations.

The VFC program was established by the Omnibus Budget Reconciliation Act of 1993 as an entitlement for eligible children to receive certain vaccines free of charge. The VFC program increases coverage and access to vaccines to children in need. The VFC program accounts for ~40%-43% of the entire national childhood vaccine use. VFC legislation requires a six-month vaccine stockpile of all routinely recommended vaccines to be used for supply disruptions and disease outbreaks. A strategic reserve of an additional annual influenza vaccine stockpile was established in 2004.

NVPO coordinates incentives for influenza vaccine manufacturers to ensure year-round influenza vaccine capacity. The incentives are targeted to accelerated vaccine development, licensing and domestic production of cell-culture influenza.

Overall, the current vaccine system is growing, but is still fragile with increasing complexity. Dr. Wallace announced that the public could review up-to-date information on shortages of routine vaccines on the CDC web site.

Update on the Global Polio Eradication Initiative (GPEI)

Dr. Linda Venczel, of CDC, reported that the GPEI is based on four key strategies: (1) routine immunization with a polio-containing vaccine in all countries; (2) supplemental immunization activities; (3) surveillance with >157 accredited or specialized laboratories throughout the world to monitor and distinguish between virus transmission patterns; and (4) mop-up activities for outbreak control and rapid response in limited geographical areas. The World Health Assembly (WHA) adopted the GPEI in 1998 due to 125 polio endemic countries with >350,000 polio cases. Substantial progress has been made since that time based on four polio endemic countries in 2006 with 1,441 cases.

Data from June 4-October 4, 2006 showed that northern Nigeria, the Pakistan/Afghanistan border, and two states in northern India were the districts most infected with polio. From 2003-2006, 82% of the poliovirus spread was of Nigerian origin and 18% was of Indian origin. A one-year halt of vaccination activities in Nigeria caused poliovirus spread to other countries that had weak routine immunization programs. From 2005-2006, the contribution of outbreaks to overall cases dramatically shifted from importation of outbreaks to indigenous cases in endemic countries.

Based on the 2003-2004 outbreaks, WHA adopted new standards for polio outbreak response in May 2006 with five components: (1) a “fast” response started within four weeks; (2) a “very large” response covering 2-5 million children; (3) a “high quality” response implemented house-to-house to reach all children; (4) a “sustained” response for a minimum of three rounds to cover missing transmission; and (5) use of the licensed monovalent “optimal vaccine” for poliovirus types 1 and 3.

Complete and adequate implementation of the outbreak response strategy stopped or controlled all outbreaks that started in 2003-2005. The strategy was successfully implemented in Namibia, Nepal and Yemen, but the most significant risks remain in Somalia, Ethiopia, Angola, the Democratic and Republic of Congo due to hard-to-reach populations, poor surveillance and breakthrough cases.

A resurgence of cases was observed in Nigeria, India, Afghanistan and Pakistan from October 2005 to October 2006. Pakistan and Afghanistan accounted for 52 polio cases in 2006 due to a lack of security for healthcare workers and difficulties in reaching nomadic or tribal populations. However, large geographic areas and most densely populated areas in these countries are polio-free.

India accounted for 416 polio cases in 2006. The outbreak represents a decline in certain areas in quality of campaign implementation, fatigue among healthcare workers, community members who continually needed to be involved or exposed to polio vaccination, and quality and non-compliance issues in consistently reaching children in west Uttar Pradesh. However, Bihar has worked impressively to address quality issues and enhance government involvement. The spread of polio from the Western Uttar Pradesh outbreak was limited. Strategies are being explored to combine polio vaccination with other activities to address community needs.

Nigeria accounted for 920 polio cases in 2006. This outbreak was in part due to many children not receiving any doses of OPV (>30%). There has also been sub-optimal efforts to obtain ownership from local leaders. Many of the activities have revolved to ensure no additional spread into neighboring countries. However, southern states of Nigeria remain polio-free. International spread from Nigeria in 2006 is limited to Niger. "Immunization Plus Days" in which polio vaccination is integrated with bed nets, vitamin A and other community needs appear to have reached more children than polio-only campaigns.

The Horn of Africa accounted for 48 polio cases from April-October 2006 due to porous border areas, refugee camps, and nomadic and hard-to-reach populations. However, synchronized campaigns were launched that should help to halt further spread. Activities are being coordinated with local NGOs and GPEI partner funding for community mobilization strategies and vaccine. Quality campaign implementation was improved and efforts were made to vaccinate all persons in refugee camps.

Several new strategies are being implemented under the GPEI. Data from the monovalent polio vaccine type 1 (mOPV1) trial that was conducted in Egypt confirmed that a single mOPV1 dose resulted in ~75% seroconversion compared to ~30% seroconversion with trivalent OPV. Research with a birth dose of mOPV1 is being conducted in India to reach young children as quickly as possible. A combination of mOPV1 and IPV will be piloted in India next year to evaluate logistical challenges. Data will soon be available from mOPV1 licensing studies that were conducted in Punjab and Andra Pradesh. A fractional IPV dose study will be launched in Oman in November 2006. The results will be tracked over time and followed up with a challenge dose of mOPV1.

A study will be piloted in a large metropolitan area in Indonesia to evaluate the switch from an OPV to IPV routine schedule. Many countries are implementing an integrated approach in which polio vaccination is combined with other activities to respond to community requests. CDC and the global laboratory network developed a new algorithm to obtain laboratory results twice as fast to enable rapid outbreak response. The algorithm can be used to obtain results in <1 week to confirm wild poliovirus cases. New communications initiatives were implemented with national governments, religious leaders and local leaders in India and Nigeria to obtain input on community needs and ensure accurate and appropriate information is conveyed at the local level.

Efforts are being made to protect polio-free areas from importation. Brazil and Saudi Arabia are implementing vaccine requirements for OPV for certain country nationals to enter their respective countries. Persons entering these countries must provide complete documentation of OPV vaccination. WHO's *International Travel and Health Regulations* will be updated to recommend full polio immunization for all travelers to and from infected areas. Efforts are being made to incorporate a standing recommendation into the *International Health Regulations* beginning with the 2007 edition.

Overall, all outbreaks in polio-free areas since 2003 have been stopped or appropriate actions are being taken to reach this goal. Parts of Afghanistan, India, Nigeria and Pakistan have ongoing transmission that threatens the polio-free areas of these four countries and >190 additional countries in the world. The 2007 GPEI strategic approach will focus on stopping transmission in endemic areas and addressing any new outbreaks that occur.

Ms. Annelise Casano-Dickerson, of CDC, described activities that were conducted to respond to U.S.-bound East African refugees with possible exposure to poliovirus. The United States resettles 50,000-70,000 refugees each year. The percentage of African refugees increased from 9% in 1998 to 39% in 2005. The Immigration and Nationality Act was amended in 1996 to require vaccination of immigrants admitted as legal permanent residents or "green card holders." Because this law only applies to immigrants, U.S.-bound refugees are not required to have any vaccination before or after arrival unless school entry or other U.S. requirements apply.

Implementation of WHO vaccine recommendation is variable in refugee camps and typically depends on non-governmental organizations providing health care. Moreover, refugees are frequently excluded from national vaccination campaigns. Resettled refugee children are generally vaccinated under the VFC program, but vaccination of resettled adult refugees varies among states. Of 45 states that responded to a survey on routine polio vaccination policies for adult refugees, none would routinely vaccinate adult refugees from Kenya against polio due to adherence to ACIP recommendations. Refugee Medical Assistance funds cover state costs of providing some adult vaccinations after refugees arrive in the United States. Refugees are eligible to adjust their status to a legal permanent resident one year after arrival, but those who elect to take this action are required to be vaccinated as recommended by ACIP.

Dadaab refugee camp in Kenya includes three refugee camps with ~140,000 Somali refugees and was the source of the type 1 poliomyelitis case reported to CDC. U.S.-bound refugees from Dadaab and Kakuma refugee camps in Kenya and also from Tanzanian refugee camps spend at least three days in a transit center in Nairobi. Somalia had a reintroduction of polio in 2004 and ongoing transmission since 2005 with 216 reported cases. Four polio vaccination campaigns for children <5 years of age were launched in Dadaab in 2006.

In October 2006, CDC was notified of the first case of polio in Kenya in 22 years. The wild poliovirus type 1 case occurred in a female Somali refugee 3 years of age with an onset of paralysis in September 2006. The genetic sequence of the virus was linked to recent poliovirus isolates imported from Kismayo, Somalia and wild poliovirus type 1 imported from Nigeria. A joint response with national and international teams was initiated. From September 1-October 20, 2006, ~1,347 refugees had resettled in the United States, were en route from Dadaab, or were scheduled to arrive from the Nairobi transit center. An additional 1,000 refugees in the Dadaab camp are being considered for U.S. resettlement within the next two months.

CDC made the following recommendations to state and local health departments based on the poliomyelitis case in the Dadaab camp: (1) administer one IPV dose to resettled and en route refugees; (2) administer one OPV dose to refugees in the Dadaab camp; (3) obtain one stool sample from en route refugees; and (4) perform active surveillance once per week for four weeks of all refugees. The movement of refugees who were still in the Dadaab camps was temporarily halted pending an investigation and vaccination before departure.

An emergency regional campaign with mOPV1 is scheduled to be launched in Kenya on November 3, 2006. The campaign will cover ~250,000 children <15 years of age and will be coordinated with Somalia and Ethiopia. The next vaccination round is scheduled for December 2006 and might be expanded to included Nairobi and other high-risk areas. A clinical and epidemiological investigation in the refugee camp is ongoing.

Two different perspectives were provided on the GPEI. On the one hand, Dr. Stanley Plotkin, of sanofi pasteur, noted that consideration should be given to refocusing GPEI resources to address other needs in endemic areas. For example, the GPEI has resulted in an investment of >$4 billion to date, but was scheduled to end in 2000. Moreover, eradication of polio is an extremely complex problem. On the other hand, Dr. Hull pointed out that the GPEI should be continued due to its contributions to several non-polio areas. For example, the GPEI served as the foundation for the dramatic decline in measles in Africa, worldwide introduction of vitamin A supplementation, and elimination of rubella and measles in the United States.

In response to both comments, Dr. Venczel agreed that countries must be realistic about the challenges in eradicating polio. However, her position was that this goal could be achieved. She emphasized that a resurgence of polio cases would most likely occur if routine polio immunization and other GPEI activities were discontinued.

CDC/NCIRP [proposed]. Dr. Anne Schuchat reported that after the June 2006 ACIP meeting, CDC published an update in the *MMWR* on routine vaccination coverage in children 19-35 months of age with the 4:3:1:3:3:1 series. Racial disparities were eliminated in the series. Prevnar coverage in this age group dramatically increased from the 2004 period. Substantial variability among states continued. The newest vaccines still need to be improved. CDC also published updates in the *MMWR* on influenza vaccine coverage in young children and for school entry.

FDA. Dr. Norman Baylor reported that FDA approved the ID Biomedical influenza vaccine. FDA will continue to collaborate with manufacturers to facilitate involvement of even more influenza vaccine manufacturers and also to develop pandemic vaccine.

HRSA. Dr. Indira Jevaji reported that the extensive discovery process in phase 1 of the Omnibus Autism Proceeding is coming to an end. The deadline for submission of expert reports by petitioners is February 16, 2007. One of the Special Masters assigned to the case will determine causality between the MMR vaccine or thimerosal-containing vaccines. The court will apply the determination to individual cases after the hearing. To date, ~4,700 thimerosal cases have been filed under the National Vaccine Injury Compensation Program (VICP).

Several bills were introduced in the current Congressional session. The House passed a bill in July 2006 that would add an excise tax to meningococcal and HPV vaccines, but the Senate has not passed similar legislation. Two requirements must be met to add vaccines to VICP. First, the vaccine must be evidence-based, recommended by CDC for routine immunization of children and published in the *MMWR*. Second, Congress must pass an excise tax.

VICP coverage begins on the effective date the excise tax was enacted. Petitioners have a two-year window to file a claim for injuries that occurred up to eight years before the effective date of coverage for the newly added vaccine. VICP currently covers 14 vaccines that represent ~95% of vaccines distributed in the United States.

NVPO. Dr. Angela Shannon reported that NVPO is the lead office for ~10 of 199 tasks in the HHS implementation plan for the National Strategy for Pandemic Influenza. NVPO's responsibilities include vaccine production capacity, prioritization of vaccine, antiviral drugs and other countermeasures, and communication of research activities.

NVPO is the co-lead for the establishment of a new HHS-wide influenza risk management group that will provide a senior-level forum to (1) identify and assess risk management issues related to the development, acquisition, deployment and utilization of medical and public health countermeasures for pandemic and seasonal influenza; (2) monitor program milestones and timelines; (3) decide responsibilities for addressing issues; (4) track and follow-up activities for assigned tasks; and (5) facilitate interagency coordination and decision-making on key cross-cutting issues.

NVPO developed and submitted two documents to the HHS Secretary: "Ensuring the Optimal Safety of Vaccines" report and "The National Vaccine Safety Plan Priority Goals and Objectives" vaccine safety strategic plan. Both documents are undergoing the final review process at HHS. NVPO's FY'07 unmet needs and priorities include the vaccine supply and financial support for vaccine economic studies. NVPO is interested in receiving proposals for its FY'07 priorities to optimize funding. NVAC, its four standing subcommittees and two workgroups met in September 2006. The public can access the NVPO

web site to review slides and summaries of the meetings. The next NVAC meeting will be held on February 6-7, 2007.

Public Comment Period

Ms. Lyn Redwood, of SafeMinds, applauded CDC's efforts to investigate vaccine safety issues. However, she pointed out that this effort was undertaken only because CDC was reprimanded in the 2005 IOM report on vaccine safety research, public access and public trust. She expressed strong concerns about CDC's ability to conduct vaccine safety investigations due to its inherent ideological and financial conflicts of interest. Most notably, a recent investigative report revealed CDC's close ties to vaccine manufacturers. As a result, an independent entity with no inherent conflicts would be needed to oversee vaccine safety monitoring. Ms. Redwood advised CDC to recuse itself from vaccine safety monitoring and support the establishment of an independent entity.

Closing Session

Dr. Abramson thanked the participants for attending the meeting. With no further discussion or business brought before ACIP, Dr. Abramson adjourned the meeting at 3:08 p.m. on October 26, 2006.

I hereby certify that to the best of my knowledge, the foregoing Minutes of the October 25-26, 2006 ACIP Meeting are accurate and complete.

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Date

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Jon S. Abramson, M.D., Chair,
Advisory Committee on Immunization Practices