DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
NATIONAL IMMUNIZATION PROGRAM

CENTERS FOR DISEASE CONTROL AND PREVENTION

Advisory Committee on Immunization Practices
June 29-30, 2006
Atlanta, Georgia

Record of the Proceedings

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ATTACHMENT 2

Acronyms Used In This Report

AA	—	African American
AAFP	—	American Academy of Family Physicians
AAP	—	American Academy of Pediatrics
ACHA	—	American College Health Association
ACIP	—	Advisory Committee on Immunization Practices
ACP	—	American College of Physicians
AEs	—	Adverse Events
AIAC	—	Adult Immunization Advisory Committee
AIS	—	Adenocarcinoma *In Situ*
AIS	—	Adult Immunization Schedule
AMA	—	American Medical Association
Anti-PT	—	Anti-Pertussis Toxins
AS-CUS	—	Atypical Squamous Cells of Undetermined Significance
ASCO	—	American Society for Clinical Oncology
ASHA	—	American Social Health Association
BIG	—	The Balm in Gilead
BLS	—	Bureau of Labor Statistics
BRFSS	—	Behavioral Risk Factor Surveillance Survey
CAIS	—	Childhood/Adolescent Immunization Schedule
CDC	—	Centers for Disease Control and Prevention
CIN	—	Cervical Intraephithelial Neoplasia
CISA	—	Clinical Immunization Safety Assessment
CLF	—	Celebrate Life Foundation
CMI	—	Cell-Mediated Immunity
CMS	—	Centers for Medicare and Medicaid Services
COID	—	Committee on Infectious Diseases
CSTE	—	Council of State and Territorial Epidemiologists
CU	—	Columbia University
DOD	—	Department of Defense
DSMBs	—	Data Safety Monitoring Boards
EPA	—	U.S. Environmental Protection Agency
FAMA	—	Fluorescent Antibody to Membrane Antigen
FDA	—	Food and Drug Administration
FFF	—	Families Fighting Flu
GBS	—	Guillain Barré Syndrome
GMT	—	Geometric Mean Titer
GSK	—	GlaxoSmithKline
HCII	—	Hybrid Capture II
HCRU	—	Health Care Resource Utilization
HCWs	—	Healthcare Workers
HepA	—	Hepatitis A
HepB	—	Hepatitis B
HHS	—	Department of Health and Human Services
Hib	—	*Haemophilus influenzae B*
HICPAC	—	Healthcare Infection Control Practices Advisory Committee
HIV	—	Human Immunodeficiency Virus
HPV	—	Human Papillomavirus
HRSA	—	Health Resources and Services Administration
HZ	—	Herpes Zoster

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IgM	—	Immunoglobulin M
ILI	—	Influenza-Like Illness
IOM	—	Institute of Medicine
IPD	—	Invasive Pneumococcal Disease
ISA	—	Information, Support and Advocacy Center
ISO	—	Immunization Safety Office
LAIV	—	Live Attenuated Influenza Vaccine
MCO	—	Managed Care Organization
MCV4	—	Meningococcal Conjugate Vaccine
MMR	—	Measles, Mumps, Rubella
MMRV	—	Measles, Mumps, Rubella, Varicella
MMWR	—	*Morbidity and Mortality Weekly Report*
NCCS	—	National Coalition for Cancer Survivorship
NCPP	—	National Commission on Preventive Practices
NCRS	—	Nordic Cancer Registry Studies
NHANES	—	National Health and Nutrition Examination Survey
NIH	—	National Institutes of Health
NIP	—	National Immunization Program
NIS	—	National Immunization Survey
NNDSS	—	National Notifiable Disease Surveillance System
NSFG	—	National Survey of Family Growth
NVAC	—	National Vaccine Advisory Committee
NVPO	—	National Vaccine Program Office
OB-7	—	7 Outbreak-Related States
PCR	—	Polymerase Chain Reaction
PCV23	—	Pneumococcal Polysaccharide Vaccine
PCV7	—	Pneumococcal Conjugate Vaccine
PHN	—	Post-Herpetic Neuralgia
PPFA	—	Planned Parenthood Federation of America
PV	—	Pharmacovigilance
QALY	—	Quality-Adjusted Life Year
RCA	—	Rapid Cycle Analysis
RMP	—	Risk Management Plan
RRP	—	Recurrent Respiratory Papillomatosis
SAM	—	Society for Adolescent Medicine
SPS	—	Shingles Prevention Study
SSP	—	Sentinel Surveillance Project
Td	—	Tetanus and Diphtheria
Tdap	—	Tetanus, Diphtheria and Pertussis
TIV	—	Trivalent Inactivated Vaccine
TT	—	Tetanus Toxoid
VA	—	Department of Veterans Affairs
VAERS	—	Vaccine Adverse Event Reporting System
VASP	—	Varicella Active Surveillance Project
VFC	—	Vaccines for Children
VRBAC	—	Vaccines and Related Biologics Advisory Committee
VSD	—	Vaccine Safety Datalink
VVP	—	Varicella Vaccination Program
VZV	—	Varicella-Zoster Virus
WHO	—	World Health Organization
WIG	—	Women in Government
ZUE	—	Zoster Utility Evaluation

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
NATIONAL IMMUNIZATION PROGRAM

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
June 29-30, 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 Immunization Program (NIP) convened a meeting of the Advisory Committee on Immunization Practices (ACIP). The proceedings were held on June 29-30, 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.

Opening Session

Dr. Jon Abramson, the ACIP Chair, called the meeting to order at 8:02 a.m. on June 29, 2006 and welcomed the participants to the proceedings. He presented certificates and tokens of appreciation to four members whose terms have expired: Drs. Judith Campbell, Reginald Finger, Edgar Marcuse and Gregory Poland. The participants applauded the valuable and outstanding contributions the outgoing members made to ACIP and CDC during their service.

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 is regularly reserved on ACIP agendas for public comments, but formal comment periods are also scheduled during the deliberations of specific agenda items in limited circumstances. The next ACIP meeting will be held on October 25-26, 2006.

Dr. Pickering noted the following changes in ACIP representation or participation for the current meeting. Dr. Gary Freed would begin serving as the new ACIP liaison to the National Vaccine Advisory Committee (NVAC) due to his recent appointment as the NVAC Chair. *Ex- officio* representatives for the Department of Defense (DOD), Food and Drug Administration (FDA), and Department of Veterans Affairs (VA) were absent. Replacements for the DOD and FDA *ex- officio* representatives were in attendance.

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 issued limited conflict of interest waivers for certain other interests that may enhance the expertise of members while serving on ACIP. The following conditions apply to members with limited waivers. First, members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs)

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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 is not available or qualified to vote due to financial conflicts of interest. *Ex- officio* representatives who are formally requested to vote during these circumstances will be asked to disclose any potential conflicts of interest.

Dr. Abramson added that ACIP's charter requires members to vote only on the safety, efficacy and cost-effectiveness of vaccines. The members should not consider the existence or non-existence of federal or state dollars to pay for vaccines while voting.

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

- Dr. Janet Gilsdorf is an uncompensated independent safety monitor for an influenza vaccine trial sponsored by the National Institutes of Health (NIH).
- Dr. Gregory Poland chairs a Merck DSMB; serves as a consultant to Dyncorp and Vaxgen; and has engaged in preliminary discussions on clinical trials with Protein Sciences and PowderMed.
- Ms. Patricia Stinchfield was a stockholder in VIRA Pharma prior to her appointment on ACIP.
- Dr. John Treanor is a clinical investigator in influenza vaccine trials conducted by Merck, ID Biomedical, Protein Sciences and AlphaVax.

HUMAN PAPILLOMAVIRUS (HPV) VACCINE

The series of presentations, ACIP's discussion and vote, and the public comments on the HPV vaccine are set forth below.

Overview

Dr. Janet Gilsdorf, the HPV Vaccine Workgroup Chair, announced that the workgroup was formed in February 2004 with representation by ACIP, several federal agencies and professional organizations. Over this time, the workgroup listened to presentations from industry, academia and other experts; convened monthly conference calls to review trial data; and held biweekly conference calls to formulate recommendations.

FDA licensed the first HPV vaccine on June 8, 2006 for females 9-26 years of age to prevent cervical cancer, precancerous genital lesions and genital warts caused by HPV 6/11/16/18. Dr. Gilsdorf conveyed that the workgroup would now make a series of presentations, propose recommendations, and present the Vaccines for Children (VFC) Program resolution to facilitate ACIP's discussions and votes on the HPV vaccine.

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GARDASIL® Efficacy and Safety Data

Dr. Eliav Barr heads Merck's HPV Vaccine Clinical Program. He presented efficacy and safety data on GARDASIL®. GARDASIL® is a quadrivalent HPV vaccine that targets HPV types responsible for the majority of clinical HPV disease in the United States. The vaccine is available both as a vial and a syringe and is administered as a 0.5-mL intramuscular injection at 0, 2 and 6 months.

The GARDASIL® clinical program involved 27,000 subjects in 33 countries throughout the world. The program enrolled two distinct cohorts: 16- to 26-year-old women and children 9- to 15-year old children. Subjects were enrolled regardless of baseline HPV status because the vaccine will be used without pre-screening. This design was based on the recommendation by FDA's Vaccines and Related Biologics Advisory Committee (VRBAC) in 2001. The primary evaluation of the vaccine focused on prophylactic efficacy in baseline HPV-naïve subjects, while the supplemental evaluation focused on the general population impact in all subjects regardless of baseline HPV status.

The key efficacy endpoints for studies of GARDASIL® in women were: cervical, vulvar, and vaginal cancers via surrogates; the overall incidence of cervical intraephithelial neoplasia (CIN) of any grade or adenocarcinoma *in situ* (AIS); and external genital lesions caused by HPV 6/11/16/18. Immunobridging studies were also included in the clinical program because the vaccine will be administered to pre-adolescents.

Of the Phase II/III efficacy population, the mean age was 20 years, 94% were sexually active, and 73% were naïve to all four HPV vaccine types. Of women with abnormal Pap test results, 58% were naïve to both HPV 16/18. Women with abnormal Pap test results may still benefit from protection with the vaccine. The vast majority of the cohort was positive to one HPV vaccine type and susceptible to the other three types. The percentage of the cohort that was naïve to at least three of four HPV vaccine types was 93% overall and 94% in North America. Merck's clinical trial cohort and the National Survey of Family Growth (NSFG) showed a generally comparable distribution of sexual partners and sexual behavior.

The prophylactic efficacy rates of GARDASIL® in preventing clinical HPV disease in the pre-protocol efficacy population are as follows: (1) 100% effective against HPV 16/18-related cervical cancer by CIN 2/3 and AIS; (2) 100% effective against HPV 16/18-related vulvar and vaginal cancers by precancerous lesions; (3) 95% effective against HPV 6/11/16/18-related CIN or AIS; and (4) 99% effective against HPV 6/11/16/18-related external genital lesions. None of the cases that occurred among subjects who received GARDASIL® were due to waning immunity because all of the cases occurred shortly after the completion of the vaccine regimen.

GARDASIL® is best used prior to sexual debut and exposure to HPV. Impact studies of the vaccine were conducted in pre-adolescents, but efficacy studies were not feasible due to the difficulty in performing genital sampling on young girls and boys. Merck and FDA agreed that immunobridging studies could be conducted to extrapolate findings from females 16-26 years of age to those 9-15 years of age. The immunobridging studies would be used to demonstrate that anti-HPV levels induced in females 9-15 years of age were non-inferior to those observed in the population for which efficacy was demonstrated.

Anti-HPV responses were measured using competitive Luminex Immunoassays. These assays detect the subset of anti-HPV responses generated by GARDASIL® that compete against an antibody that is known to be neutralizing. The ratio of anti-HPV geometric mean titers (GMTs) between boys versus women and girls versus women was >1.0. These results achieved statistical criteria for non-inferiority and allowed an inference to be made that GARDASIL® is efficacious in 9- to 15-year-old individuals. In the adolescent population, anti-HPV levels at Month 7 and in the persistence phase were substantially

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higher than in adults (the population in which 100% efficacy was shown). These findings provided strong reassurance about the magnitude and durability of efficacy of GARDASIL® in young adolescents.

Population impact analyses were conducted to examine the effects of GARDASIL® in the general U.S. population of both infected and naïve women. Most older adolescents and young adult women in the general U.S. population are naïve to all HPV vaccine types on Day 1, but some females are infected with at least one HPV vaccine type on Day 1. Some females may develop disease due to HPV infection after Day 1. As a prophylactic vaccine, GARDASIL® has minimal impact on the course of infection present on Day 1. The efficacy of the vaccine in the general population greatly depends on baseline prevalence and will be reduced relative to prophylactic efficacy.

GARDASIL® will prevent new HPV infections and the diseases that such infections cause. However, as compared to infections present at Day 1, disease caused by new HPV infections would occur later in the clinical trial (subjects must first acquire infection and then develop disease). GARDASIL® will have limited impact on the course of an infection present on Day 1. However, even among women who are infected with one HPV type, the vaccine will be highly effective in protecting against disease caused HPV vaccine types that are not present at Day 1.

The population impact of GARDASIL® will be masked by the prevalent load of HPV infection and disease in the early course of the study, but efficacy will become more apparent over time. A preliminary analysis of prophylactic efficacy showed extremely high efficacy for each endpoint. The general population impact was lower, although readily apparent. The lower impact in the general population was due to cases of disease caused by infections present at baseline. An equal number of disease endpoints caused by infections present at baseline occurred in subjects who received GARDASIL® and subjects who received placebo. A shorter duration of follow-up will increase the impact of prevalent disease on the overall benefit of the vaccine.

Time to event analyses showed that event rates were comparable between the GARDASIL® and placebo groups early in the first 12 months, but rates of HPV 16/18-related CIN 2/3 disease increased in the placebo group over time. The impact of prevalent disease was found to be less significant for genital warts because women with known genital warts were excluded from the clinical trial. Overall, GARDASIL® reduced the general population burden of HPV 6/11/16/18-related disease after a median of two years of follow-up on average. Efficacy will become more apparent and represent a more substantial reduction in the general load of disease over time.

Protocol 007 was a Phase IIB quadrivalent dose ranging study and long-term efficacy evaluation. Because the minimal protective anti-HPV level has not been defined to date, the duration of protection afforded by GARDASIL® was measured through long-term efficacy evaluations. At five years of follow-up post-enrollment, prophylactic efficacy of the vaccine was high and no breakthroughs due to waning immunity were documented. In that study, the primary endpoint was the combined incidence of persistent infection, CIN, and external genital lesions caused by HPV 6/11/16/18. The persistent infection endpoint included detection of HPV on the last visit on record without confirmed persistence. Two cases were seen in the vaccine group. Subject 1 had an HPV 18 infection that occurred at months 12 and 18 and then resolved. Subject 2 had a positive HPV 16 test result at the last visit on record (Month 36), but without confirmed persistence.

Anti-HPV levels were stable over the 60-month observation period. As a reference for vaccine induced anti-HPV responses, anti-HPV levels were measured in placebo subjects who were seropositive and had negative polymerase chain reaction (PCR) test results on Day 1. These women developed an infection some time after sexual debut, mounted an immune response to the infection, and cleared the infection. Anti-HPV levels detected at Day 1 represented residual markers of previous successful clearances of infection. In these previously infected women, anti-HPV levels slowly decayed over the 5-year

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observation period. GARDASIL® induces high anti-HPV levels that reach a plateau. The plateau remains stable through month 60 and shows strong promise in terms of long-term protective efficacy of the vaccine. Vaccine efficacy of 96% through five years of follow-up was found to be highly statistically significant.

An immune challenge study was conducted to determine the presence of immune memory responses. The presence of immune memory is the hallmark of hepatitis B and other long-term protective vaccines. An immune memory response will allow women with low, negligible or non-detectable anti-HPV levels to mount an extremely robust anti-HPV response and abort infections. In the immune challenge study, a dose of GARDASIL® was given to ~240 subjects in the vaccine and placebo groups who had been followed for five years. The results demonstrated that administration of GARDASIL® induced robust immune memory and a strong anamnestic response to HPV 6/11/16/18.

The GARDASIL® clinical program will evaluate vaccine efficacy much longer than five years to mirror the long-term risk of women for HPV infection and disease. Many clinical study participants were enrolled in the Nordic region because this area has an extraordinary public healthcare infrastructure that allows for all Pap tests and biopsy results to be reported to the national database by identification number. Pap tests and biopsy results can be retrieved, followed and tested for HPV types. Sera will be available to evaluate anti-HPV levels because pregnant women are asked to donate a vial of sera to the registry.

At this time, 5,500 subjects have been enrolled in the CIN 2/3 efficacy study in the Nordic region and will be followed over time. These subjects were vaccinated in 2002 and have been entered in a follow-up registry. Registry results will be reported to ACIP, CDC and regulatory agencies to determine and evaluate the presence of waning immunity. Merck will be in a position to provide results on the potential for waning immunity well in advance of the need to consider a booster strategy. A booster strategy does not appear to be needed based on five-year data.

A long-term follow-up study is being conducted in adolescents to better understand the immune response in this population. Based on data through month 18, the levels have remained above those seen in adults. This population will also be followed over a long period of time. Protocol 18 includes ~1,800 subjects 9-15 years of age who were vaccinated in 2003 with a mean age of 12 years at enrollment. Beginning in 2007, subjects in this cohort who reach age 16 will enter an efficacy phase and undergo genital sampling. Protocol 18 results will be periodically reported to CDC, FDA and other regulatory agencies to demonstrate the long-term immunity and effectiveness of the vaccine in both adolescent boys and girls in this cohort.

The clinical trial program places strong emphasis on evaluating the safety profile of GARDASIL®. Of ~21,464 subjects, ~11,000 received detailed safety follow-up and the remainder received serious adverse experiences in medical history and pregnancy follow-up. The incidence of overall adverse events (AEs), injection-site AEs, and low-grade fevers >100°F was slightly higher in the GARDASIL® group compared to the placebo group. Systemic AEs were comparable between the two groups. Serious AEs and discontinuation due to adverse experiences were extremely rare.

GARDASIL® is a unique vaccine due to its administration to girls and women of child-bearing age. An extremely careful pregnancy evaluation was incorporated into the clinical trials program to monitor pregnancies. In the overall clinical database, 11% of the population became pregnant during the course of follow-up and some subjects had multiple pregnancies.

As of November 11, 2005, ~500 pregnancies were still ongoing and outcomes were known for ~2,000 pregnancies. Live births and fetal losses were comparable between the 1,244 pregnancies in the GARDASIL® group and the 1,272 pregnancies in the placebo group. The GARDASIL® group had a lower incidence of spontaneous miscarriage, lower incidence of elective termination, and higher incidence of

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live births. However, these differences compared to the placebo group were small. The overall rates of congenital anomalies were also comparable among the vaccination groups.

Further analyses were conducted in two strata of pregnancies: pregnancies whose estimated onset occurred within 30 days of administration of GARDASIL® and those pregnancies whose estimated onset occurred beyond 30 days of administration of GARDASIL®. In pregnancies whose estimated onset occurred within 30 days of administration of a dose of GARDASIL®/placebo, five cases of congenital anomalies were observed all in the group that received GARDASIL®. On the other hand, among pregnancies whose estimated onset occurred beyond 30 days of administration of a dose of GARDASIL®/placebo, fewer congenital anomaly cases were observed in subjects who received GARDASIL® compared to placebo subjects.

A panel of four teratologists from around the world examined these data in a blinded fashion and unanimously agreed that the congenital anomalies were highly unlikely to be associated with the administration of GARDASIL®. The opinions of the teratologists are further supported by pre-clinical developmental and reproductive toxicology studies that showed high doses of GARDASIL® had no impact on pregnancy outcomes and fertility. GARDASIL® is one of the first vaccines to have been granted a category B designation from FDA.

The key highlights and findings of the GARDASIL® clinical program are as follows. Prophylactic administration of GARDASIL® is highly effective in preventing cervical and genital disease caused by four HPV vaccine types based on a clinical trial of 27,000 women and five-year follow-up data. A long-term program was established to specifically focus on the duration of efficacy. Efficacy without breakthrough infections due to waning immunity has been demonstrated through year 5. Anti-HPV levels are stable at year 5 with extremely strong immune memory responses present. These data are solid indicators for the long-term protective efficacy of GARDASIL®.

Sentinel cohorts were established to examine the long-term efficacy of the vaccine. Data on waning immunity will be produced well in advance of the need to consider a vaccination policy. GARDASIL® is generally well-tolerated in females 9-26 years of age. The vaccine contains certain components that are well known and understood to be safe and effective long term. GARDASIL® demonstrated slight increases in injection-site AEs and low-grade fevers compared to placebo, but the rates of serious AEs and discontinuation were extremely low.

GARDASIL® will significantly impact a major public health problem in the United States and the burden of disease caused by HPV that results in precancerous lesions for cervical, vulvar and vaginal cancers. The vaccine has an excellent safety profile and demonstrated a population-based reduction in cervical pre-cancers and external genital lesions. Merck believes that GARDASIL® has a strong public health impact.

Dr. Barr provided additional details about the safety and efficacy of GARDASIL® in response to ACIP's questions.

- The most common AEs reported in the clinical trial were headache, dysmenorrhea and related symptoms, sore throat, and nasopharyngitis and other influenza-like conditions. These AEs were comparable between the GARDASIL® and placebo groups based on the subject's individual perception of a "mild," "moderate" or "severe systemic" AE. The overall AE rates were lower in the younger age group because dysmenorrhea and other types of symptoms were less frequent in this population.
- Of the 27,000 subjects, ~4,072 9-17 years of age received GARDASIL®.
- Similar to GARDASIL®, an age versus peak anti-HBs response was also seen with the hepatitis B (HepB) vaccine.

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- Merck conducted a co-administration study of GARDASIL® with the HepB vaccine. The adverse experience profile and immune response to both vaccines were found to be generally comparable. Merck is planning to conduct new co-administration studies of GARDASIL® with ADACEL™ and Menactra®. These data are expected to be available in late 2007.
- Merck completed two analyses to evaluate whether removal of common HPV types will result in replacement with non-vaccine HPV types. An HPV 16 vaccine trial showed 100% efficacy. Incidence rates for HPV 6/11/18 infections were comparable between vaccination groups over four years. Similarly, the incidence of CIN caused by HPV types other than 6/11/16/18 was analyzed in the general population in Phase III studies. No difference was seen between the vaccination groups. Thus, there is no evidence for replacement. Merck will continue this study in long-term surveillance.
- Merck is collaborating with the government of Norway in the establishment of a vaccination registry of each subject in the country. Merck will use these data in its pharmacovigilance (PV) activities to analyze trends in attack rates over time for HPV types not included in GARDASIL®. HPV biology does not indicate that replacement will occur because the rate of infection is higher with a second type if infection is already present with one type.

GARDASIL® Risk Management Plan (RMP)

Dr. Adrian Dana, of Merck & Co, Inc., presented the GARDASIL® RMP. The RMP will be structured in three major areas. First, the safety specification will summarize the safety database, safety knowledge, data gaps and known risks for the product. Second, the PV plan will outline approaches that will be taken to follow the safety of the product in the future; describe routine PV practices; and delineate action plans for specific safety concerns of the product. Third, a risk minimization plan will be developed if necessary, but is not expected to be needed for GARDASIL®.

Of >21,464 subjects enrolled in the clinical development program, >11,700 received GARDASIL®. No significant signals were identified, but adverse experiences not seen in clinical trials may become evident as the product is used more widely in the post-marketing setting. The RMP includes a post-marketing safety surveillance study and the Nordic Cancer Registry Studies (NCRS). The four components of the routine PV and action plans in the GARDASIL® RMP are detailed below.

First, exposures during pregnancy will be monitored. FDA gave GARDASIL® a category B product labeling because animal reproductive toxicology studies revealed no adverse effects, but no controlled trials have been performed on pregnant women. No signal was seen with respect to pregnancy outcomes in the clinical development program. Merck recommends deferral of vaccination if pregnancy occurs.

Pregnancy exposures serve as a rationale for intensified efforts to obtain outcome information and other safety data. Spontaneously reported pregnancy exposures will be routinely analyzed (routine PV). Additionally, Merck subscribes to the Swedish birth register of pregnant women for the entire country of Sweden. Merck obtains drug exposure data from the registry and annual information on women who were exposed during pregnancy in Sweden.

Merck is currently developing a pregnancy registry for the United States, France and Canada for enhanced surveillance of spontaneously reported pregnancy exposures. Data from the registries will be continuously reviewed. Reports will be prepared and submitted annually to regulatory and public health

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agencies and healthcare practitioners who report exposures to the registry. The cumulative annual reports can serve as a foundation for exposed women to receive counseling.

Merck will conduct an observational post-marketing safety surveillance trial in a managed care organization (MCO) setting. The study will focus on pregnancy exposures that occur during the trial to provide a descriptive epidemiology of exposures. The government of Norway committed to establishing an HPV vaccine registry for the entire country. Merck will use data from the HPV vaccine registry and existing birth registers in Norway to analyze pregnancy exposures and outcomes (this is part of the NCRS).

Second, replacement with non-vaccine viral types will be monitored due to the theoretical concern that vaccination against some types will leave a niche for other types to emerge. This theory is influenced by the pathogenicity of the organism and the virulence of the specific types. No biologic data have been produced to support this theory and no evidence of replacement has been seen in clinical trials to date. Infection with one HPV type is actually a risk factor for infection with other types.

The NCRS will be designed to monitor replacement in the future. The Protocol 15 cohort has been vaccinated and will be followed in the future to determine if these subjects tend to develop higher rates of infection with other types. The HPV vaccine registry in Norway will also be analyzed to monitor population trends over time and determine whether replacement becomes an issue.

Third, long-term effectiveness and immunogenicity will be monitored. The five-year data on GARDASIL® do not show breakthroughs due to waning immunity and demonstrate that the vaccine has the ability to induce long-lasting immune memory. However, the duration of protection and the need for a booster are unknown at this time. The action plan for this component includes reviews of NCRS data; long-term follow-up of the Protocol 15 cohort to monitor effectiveness and immunogenicity; and a similar follow-up study with the adolescent Protocol 18 cohort.

Fourth, unanticipated safety signals will be detected. For short-term safety, an observational post-marketing safety surveillance study will be conducted in an MCO setting in the United States among 44,000 vaccinees. Safety issues that occur 60 days following a dose will be analyzed. Thyroiditis, rheumatoid arthritis and other autoimmune disorders will be analyzed six months following a dose.

For long-term safety, NCRS data will be reviewed. The Protocol 15 cohort will be followed over a long period of time to monitor long-term effectiveness, immunogenicity and safety. The incidence of major diseases and other trends will be compared between the study cohort and the general population using existing disease registries in the Nordic region. Overall, Merck is committed to analyzing GARDASIL® and following its impact long term.

Drs. Dana and Barr provided additional details about the GARDASIL® RMP in response to ACIP's questions.

- Merck has several reasons to be confident about its ability to make comparisons between the Nordic and U.S. populations. The large population-based registries in the Nordic region provide a unique opportunity to obtain much more complete data for improved evaluation and follow-up. Epidemiologic studies in the Nordic region indicate that the distribution of HPV types and disease progression is similar to other areas in Europe and the United States. The Nordic population has HPV demographics, attack rates and sexual behavior patterns that are comparable to the U.S. population. The Nordic region will serve as an excellent area to analyze and follow any signals that are generated.

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- Merck will not solely rely on data from the Nordic region. The adolescent cohort that will be followed long-term represents 50% of subjects from the United States. The short-term safety study with 44,000 subjects will be conducted in the United States.
- The clinical trial database includes data that strongly support the use of GARDASIL® in various ethnic groups. Large Hispanic and African American (AA) cohorts were evaluated. The five-year efficacy data were primarily from subjects in Brazil and Scandinavia. Merck is committed to analyzing the data with respect to racial/ethnic and country-specific differences.
- The GARDASIL® clinical trial program did not demonstrate ethnic differences in the efficacy of anti-HPV levels. Populations in the Nordic region are more homogeneous than those in the United States, but the Nordic cohort was stratified by disease rates, co-morbidities, behavior patterns and other non-ethnic factors.

GARDASIL® Post-Marketing Safety Surveillance

Dr. John Iskander, of the CDC Immunization Safety Office (ISO), described CDC's vaccine safety monitoring plan for the quadrivalent HPV vaccine. ISO partners with FDA, MCOs and other private-sector companies, academic medical centers and international collaborators in conducting post-marketing safety surveillance activities for newly licensed vaccines. The Vaccine Adverse Event Reporting System (VAERS) is a national passive surveillance system for reporting AEs and is co-managed by CDC and the FDA. VAERS has under-reported data and an inability to determine causal relationships between vaccines in most reports. Despite these limitations, VAERS maintains a solid track record as a hypothesis-generating system.

VAERS is designed to detect rare or previously unknown AEs that may warrant further detailed study and identify potential risk factors for adverse reactions. The rationale for the VAERS design is because pre-licensure trials are of limited size and typically exclude special populations that may subsequently receive the vaccine following licensure. Federal regulations define "serious AEs" as those involving hospitalization, death, life-threatening illness, disability, and congenital anomalies or certain other serious medical conditions. CDC, FDA and subject-matter experts review serious AEs reported to VAERS and follow-up these reports after obtaining additional medical records.

The Vaccine Safety Datalink (VSD) is a network of MCOs that participates in a large linked database. VSD conducts vaccine safety hypothesis testing studies and performs active surveillance of AEs for newly licensed and other vaccines. Rapid cycle analysis (RCA) is a new VSD component that involves reviewing VSD data at selected sites on a weekly basis, identifying AEs of interest, and determining whether predetermined statistical thresholds were exceeded.

For the quadrivalent HPV vaccine, the RCA will focus on cardiovascular, allergic and clinical issues identified pre- or post-licensure. Women who received the vaccine will be followed for up to 30 days using automated linked data. Chart review for diagnosis verification will be conducted as needed. Sequential probability ratio testing will be used to compare expected and actual outcome rates.

The development of an analytic data file of pregnancy outcomes for VSD is underway to compliment data from VAERS and Merck's pregnancy registry. Women who are vaccinated during pregnancy or become pregnant following HPV vaccine or other vaccines of interest will be actively monitored. The pregnancy outcomes of interest include spontaneous and elective pregnancy terminations, stillbirths, live births and congenital anomalies.

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Potential Cost-Effectiveness of HPV Vaccination in the United States

Dr. Harrell Chesson, of the CDC Division of STD Prevention, presented data to demonstrate the potential cost-effectiveness of HPV vaccination in the United States. Two types of models have been used in the HPV vaccine cost-effectiveness literature. Markov models are typically used to model the natural history of HPV infection, but may understate the benefits and cost-effectiveness of vaccination. These models do not include transmission effects or herd immunity. Dynamic models may be more realistic because HPV transmission is modeled. However, these models may introduce additional uncertainty due to the inclusion of transmission probabilities, sexual mixing patterns and other factors.

Of three published studies that utilized Markov models to estimate the cost-effectiveness of HPV vaccination in the United States, two included current cancer screening in the United States and focused on cost-effectiveness in terms of cost per quality-adjusted life years (QALY) gained. The Goldie study was published in 2004 with the following base case assumptions. The vaccine would have 90% efficacy against HPV 16/18. Females would be vaccinated at 12 years of age with 100% vaccination coverage. The duration of the vaccine would be lifetime and the cost would be $377 per series. Under these base case assumptions, the cost per QALY for female-only vaccination would be $24,300 in the Goldie study.

The Sanders model was published in 2003 with the following base case assumptions. The vaccine would have 75% efficacy against all high-risk HPV types. Females would be vaccinated at 12 years of age with 70% vaccination coverage. The duration of the vaccine would be ten years plus an additional ten years with a booster. The cost would be $300 per series and an additional $100 for the booster. Under these base case assumptions, the cost per QALY for female-only vaccination would be $22,800 in the Sanders study.

In sensitivity analyses of published Markov models, cost-effectiveness estimates were sensitive to the duration of vaccine efficacy and cervical cancer screening factors, such as the frequency and age of initiation of screening. The cost-effectiveness estimates were less sensitive to reasonable changes in natural history parameters and screening test characteristics.

Two studies utilized dynamic models to estimate the cost-effectiveness of HPV vaccination. The Taira study was published in 2004 with the following base case assumptions. The vaccine would have 90% efficacy against HPV 16/18. Females would be vaccinated at 12 years of age with 70% vaccination coverage. The duration of the vaccine would be ten years plus an additional ten years with a booster. The cost would be $300 per series and an additional $100 for the booster. Under these base case assumptions in the Taira study, the vaccination of females 12 years of age would cost $14,600 per QALY compared to no vaccination.

The ongoing Merck study has the following base case assumptions. The vaccine would have 90% efficacy against infection and 100% efficacy against disease for HPV 6/11/16/18. Females would be vaccinated $\leq$12 years of age with a catch-up scenario at 12-24 years of age. Vaccination coverage would be 70%, the duration of the vaccine would be lifetime, and the cost would be $300 per series. Under these base case assumptions, the vaccination of females 12 years of age and the addition of a catch-up strategy for females 12-24 years of age compared to screening without vaccination would both be cost-saving (<$0 per QALY) in the Merck study.

The approach of adding a catch-up strategy dominated the vaccination-only strategy of females 12 years of age in the Merck study. Unpublished Merck data show that in the long run, the reduction in cervical cancer incidence attributable to HPV 16/18 would be the same regardless of catch-up vaccination. However, reductions in cervical cancer incidence would be seen ~10 years sooner with a catch-up vaccination. Merck also designed an alternative scenario to conduct a sensitivity analysis of its model.

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Under these assumptions, the vaccine would cost $360 per series and have a ten-year duration of protection with 50% coverage. The utility loss from HPV-related health outcomes would be reduced by 33%. A time horizon of 25-100 years would be used to calculate the cost and benefits of vaccination.

Compared to screening and no vaccination, the cost per QALY associated with the vaccination-only strategy of females 12 years of age increased from ~$27,000->$70,000 as the time horizon decreased from 100-25 years. The cost for the catch-up strategy increased from ~$12,000-~$25,000 over the same time horizons. The approach of adding a catch-up strategy dominated the vaccination-only strategy. Cost-effectiveness estimates for the catch-up strategy were less sensitive to changes in the time horizon as those for the strategy of vaccinating only females 12 years of age. The findings demonstrate that the HPV vaccine will be a long-term investment with benefits increasing over time.

Merck also changed its assumptions to mirror Markov models. The impact of the vaccine on HPV 6/11 and transmission effects resulting in herd immunity were removed. Efficacy of 90% against HPV infection and disease was assumed. The outcomes of this analysis were similar to the Markov model estimates. The cost-effectiveness of vaccinating females 12 years of age compared to no vaccination was $21,400 per QALY at a vaccine series cost of $400.

CDC developed a detailed spreadsheet to estimate the cost and benefits of vaccination over a 50-year time period. HPV outcomes were estimated based on age-specific incidence rates in the United States. The calculations were made with the following assumptions. Females 12 years of age would be vaccinated each year with 70% coverage. Efficacy of the vaccine would be 100% with lifetime duration of protection against the four HPV types. CDC's base case assumptions were modified to compare with the other models and a 50-year time horizon was used. Cost and QALY estimates for HPV-related health outcomes were obtained from the literature.

No transmission effects were assumed in the base case analysis, but a transmission scenario was developed. The reduction in disease burden among unvaccinated females was assumed to be a function of the percentage of those vaccinated in a five-year age group. The reduction in genital warts among males was assumed to be 75% of the decrease in females.

A small reduction in the HPV burden was seen in year 5 compared to year 50. The reduction in disease burden was greater in each of the 50 years when transmission effects were included to represent herd immunity impacts. CDC modified the spreadsheet to mirror vaccine efficacy rates and vaccine costs of the Goldie, Sanders, Merck and Taira studies. CDC's estimates of the cost per QALY of routine vaccination were similar to these models when the base case assumptions were changed.

CDC acknowledges the substantial variations in cost-effectiveness that can occur when base case parameter values and assumptions are modified. For example, the vaccine was not found to be cost-saving when base case assumptions were slightly modified with a 50-year time horizon. CDC also realizes that the limitations of models must be considered when making cost-effectiveness estimates. Substantial uncertainty exists about the transmission dynamics of HPV, duration of immunity, role of natural immunity and other factors. Models cannot address all potential effects of vaccination, such as the decreased positive predictive value of the Pap test; AEs following vaccination; sexual, health-seeking and other behaviors; and other HPV-related cancers.

CDC reached the following conclusions in reviewing cost-effectiveness studies of HPV and estimating the cost and benefits of vaccination. The vaccination of females 12 years of age was estimated to cost ~$23,000 per QALY compared to screening and no vaccination based on a Markov model of a bivalent vaccine. Cost-effectiveness estimates were more favorable toward vaccination when protection against HPV 6/11 and herd immunity impacts were considered.

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Preliminary results from the Merck study suggest that catch-up vaccination of females 12-20 years of age would be more cost-effective than a vaccination-only strategy of females 12 years of age. Cost-effectiveness estimates would be more favorable toward vaccination as the time horizon increases and fairly consistent across different models when key assumptions are similar. Cost-effectiveness estimates would substantially vary as model assumptions are modified. The vaccination of females can be cost-saving under certain assumptions.

Drs. Abramson and Lieu emphasized the critical need to apply lessons learned with the HepB vaccine to HPV. Based on experiences with the HepB vaccine, the failure of many adolescents to present for all three doses of the HPV vaccine should be explicitly incorporated into cost-effectiveness models. Dr. Lieu found the herd immunity models to be impressive, but she noted that the ability to achieve high coverage rates to obtain herd immunity is unknown. The cost-effectiveness of catch-up vaccination is also uncertain due to unanswered questions related to herd immunity.

Drs. Chesson, Barr and Erik Dasbach of Merck provided additional details about the potential cost-effectiveness of HPV vaccination in the United States in response to ACIP's comments and questions.

- Lower vaccine efficacy and decreased cost-effectiveness can be assumed if only one or two doses of the three-dose HPV vaccine series are administered.
- Merck modelers reported that the cost-effectiveness of catch-up vaccination was under $50,000 per QALY even when excluding the benefits of herd immunity and the benefits of protection against HPV 6/11.
- It was noted that a set of replacement handouts for the cost-effectiveness summary had been distributed to ACIP.
- Merck has not analyzed the cost-effectiveness of catch-up vaccination followed by a vaccination strategy of females 11-12 years of age.
- Merck plans to conduct studies on infants in the future, but administering GARDISIL® to babies is premature at this point. Merck is extremely confident about the long-term efficacy of the vaccine in adolescents based on five-year data, but a much longer duration of efficacy is needed between the time an infant is vaccinated and reaches the risk period.
- All of the cost-effectiveness models accounted for age-specific event rates and the duration of efficacy because HPV is a common infection and sexually active women remain at risk regardless of age. Event rates in the United States continue to be substantial for women ≥30 years of age. A new peak is now being seen among women in older age groups.
- The transmission models account for fewer males acquiring HPV if the prevalence of HPV is lower in female sex partners. In this scenario, both male-to-female and female-to-male transmission would be reduced.

Public Comment Period

Dr. Mark Gorman, of the National Coalition for Cancer Survivorship (NCCS), made the following comments for ACIP's consideration. NCCS urges ACIP to recommend optimal usage of the HPV vaccine. The NCCS President attended the May 2006 VRBPAC meeting to endorse FDA approval of the HPV vaccine with coverage to as many young persons as possible consistent with available data.

NCCS looks forward to the imminent coverage of the vaccine to young males to more efficiently interrupt transmission of the HPV virus. The vaccine can prevent thousands of cases of cervical, vaginal, vulvar, anal, penile, and head and neck cancers. NCCS encourages ACIP to take advantage of a special and

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unique opportunity to make available a preventive and cost-effective intervention that will bypass suffering associated with current cancer treatment. ACIP should also recommend inclusion of the HPV vaccine in the VFC Program to ensure that the greatest number of at-risk young persons receive the vaccine at the earliest possible time.

Ms. Emily Stewart, the Regulatory and Policy Analyst for Planned Parenthood Federation of America (PPFA), made the following comments for ACIP's consideration. The combination of the HPV vaccine, cervical cancer screening programs, and early detection and treatment has an enormous potential to impact public health. Lessons learned from successful immunization strategies should be reviewed and access to the HPV vaccine should be a public health priority.

ACIP should recommend routine immunization and inclusion of the vaccine in the VFC Program to ensure the widest possible access and coverage. ACIP should also recommend administration of the vaccine to females 11-12 years of age; all females up to 26 years of age who missed vaccination; and a complimentary vaccination strategy for males as more evidence is generated.

The public health impact of the HPV vaccine must not be derailed by false ideological propaganda. PPFA is counting on ACIP to make rational decisions based upon science and public health. The inability of prevention to promote sexual activity is well established. Moreover, cancer prevention is preferable to cancer treatment.

Dr. Denise Ross, the Chief Medical Officer of AmeriChoice, made the following comments for ACIP's consideration. AmeriChoice serves >1.3 million government beneficiaries in the healthcare system in 13 states. Of all AmeriChoice clients, ~50% are children who would benefit from the HPV vaccine. Cervical cancer is the leading cause of morbidity and mortality among women in the United States. Cervical cancer caused by HPV disproportionately affects AA and Hispanic women at rates that are roughly double than the general population.

Data indicate that widespread immunization of the HPV vaccine could prevent 70% of cervical cancers associated with HPV 16/18, a substantial proportion of vaginal and vulvar cancers, and genital warts. AmeriChoice places tremendous emphasis on immunization, promotes other prevention strategies, and strongly supports the use of the HPV vaccine in its health plans. ACIP's recommendations for coverage should be as broad as FDA's recent approval of the vaccine.

AmeriChoice's position is that emphasis on the importance of the HPV vaccine by health plans, physicians and parents may increase the number of adolescents who are immunized with other recommended vaccines. This approach may also expand the number of adolescents who present for preventive care visits. AmeriChoice is committed to strengthening its efforts to reach at-risk adolescents as this population reaches an age when sexual activity may commence. The HPV vaccine represents a notable advance in preventing disease through immunization, particularly cancers that cause a tremendous amount of suffering among minority and other women in the United States. AmeriChoice urges ACIP to recommend widespread use of the HPV vaccine.

Dr. Anafidelia Tavares, Director of Women's Health at The Balm in Gilead (BIG), made the following comments for ACIP's consideration. AA women have the highest rate of cervical cancer mortality of any group of women in the United States. BIG makes sustained and concerted efforts to address these disparities through the following activities. The health status of persons of African descent is improved by building capacity of the AA faith community to address life-threatening diseases. A cervical cancer initiative was developed to educate AA women about cervical cancer, HPV and the need for screening. A partnership was formed with three AA religious denominations with a combined reach of >6 million women.

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Research has shown that uninsured and vulnerable women have the highest burden of disease from cervical cancer. FDA data have demonstrated that the HPV vaccine is safe and efficacious. The prevention of cervical cancer cases in the future will depend on access to the HPV vaccine for all women. BIG urges ACIP to recommend the most comprehensive indications for use of the vaccine. ACIP's recommendations will drive access to the vaccine through private insurers and the VFC Program. ACIP's recommendations will also influence outcomes to the most privileged and vulnerable women. BIG encourages ACIP to recommend wide use of the HPV vaccine to stem the tide of cervical cancer and ensure that the life-saving promise of the vaccine reaches all women.

Ms. Deborah Arrindell, Vice President of Health Policy for the American Social Health Association (ASHA), made the following comments for ACIP's consideration. ASHA has a 92-year history of attempting to eliminate sexually transmitted diseases and associated outcomes for individuals, families and communities. ASHA is confident that ACIP has thoroughly considered the science and public health advantages of the HPV vaccine. The vaccine is an exciting and critically important tool to prevent cervical cancer in the United States and throughout the world.

ASHA urges ACIP to take three critical actions in its decision-making process. First, the HPV vaccine should be recommended for as broad an age group as permitted by FDA. Second, providers should be strongly encouraged to inform all patients that comprehensive cervical cancer screening and follow-up programs must be continued even with the HPV vaccine. GARDASIL® has proven to be >99% effective against HPV types that cause 70% of cervical cancers. Continued screening and HPV testing will be essential to detect the remaining 30% of cancers from other high-risk types. Third, national outreach should be promoted to ensure that underserved women have access to the HPV vaccine through VFC and other federally funded public health programs.

ASHA is particularly concerned about access to the vaccine among at-risk females. HHS has acknowledged that cervical cancer rates are sentinel markers for larger systemic healthcare concerns. Access of the vaccine among groups with the highest burden of cervical cancer must be a public health priority.

ASHA is a member of a newly formed partnership of >30 national organizations. The mission of the network is to end cervical cancer and ensure the immediate inclusion of vaccines that prevent cervical cancer into routine health care for women. To fulfill its mission, the network will focus on HPV and cervical cancer education; health disparities that impede access to vaccines and other routine preventive care; coverage and reimbursement; and the need for an infrastructure for adult immunization programs. ASHA is prepared to support widespread availability and acceptability of cervical cancer vaccines.

Dr. Otis Brawley is a Professor of Medical Oncology and Epidemiology at the Emory University Cancer Center. He represented the American Society for Clinical Oncology (ASCO) and made the following comments for ACIP's consideration. Data have shown that the HPV vaccine prevents cervical cancer and is 100% effective in preventing vaginal and vulvar cancers associated with certain HPV types.

ASCO strongly believes that ACIP's general and VFC recommendations should provide for the widest possible coverage of immunization with the HPV vaccine among at-risk young persons. The disproportionate impact of cervical cancer on AA and Hispanic women provides ACIP with a strong rationale to issue a generous recommendation on comprehensive VFC coverage. At a minimum, recommended coverage should be as broad as the FDA-approved labeling of females 9-26 years of age. ASCO acknowledges the need to continue screening.

ASCO strongly supports the immunization of males because this strategy will optimize the potential of the vaccine and promote a strong message of shared male-female responsibility for prevention. Lessons learned with the rubella vaccine demonstrate that female-only immunization is not a successful approach.

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Data on males should be expeditiously reviewed and recommendations for male immunization should be adopted accordingly. ASCO believes recommendations on the use of the HPV vaccine should be expanded beyond the current FDA approval to include immunizations of males if the data support this approach.

Ms. Michelle Hannah, founder of Celebrate Life Foundation (CLF), made the following comments for ACIP's consideration. Ms. Hannah's mis-diagnoses and three surgeries led to her personal mission, purpose, commitment and passion to provide education, promote awareness about HPV and eliminate cervical cancer. She is also making these efforts to ensure her young daughter does not face the same struggle in the future.

CLF is concerned that the HPV vaccine will not be available to low-income, inner-city and uninsured populations. CLF is partnering with Howard University and the Washington Hospital Center to address these issues and identify solutions. However, ACIP should also consider these concerns in formulating recommendations on the HPV vaccine.

Ms. Gloria Lawlah is the State Senator for Maryland. She represented Women in Government (WIG) and made the following comments for ACIP's consideration. The elimination of cervical cancer is one of WIG's top priorities. WIG's "Challenge to Eliminate Cervical Cancer Campaign" has resulted in state legislators introducing bills and resolutions targeting cervical cancer prevention in 45 states. Since 2004, 39 of these measures have been enacted. FDA's recent approval of the HPV vaccine is a tremendous milestone and an important step in ensuring that no more women die of cervical cancer.

WIG acknowledges the critical need for the HPV vaccine to be made available to all recommended age groups regardless of socioeconomic status. WIG urges ACIP to recommend coverage for all FDA-approved age groups and include the vaccine in the VFC Program. WIG's network of state legislators around the country is ready to support a public health effort to ensure that all age-appropriate females receive the HPV vaccine regardless of race, ethnicity or socioeconomic status.

WIG's position is that HPV vaccines should be included in comprehensive cervical cancer prevention programs with advanced and medically appropriate screening and testing methods. WIG's network of state legislators will await ACIP's recommendations on the HPV vaccine and make efforts to reach the mutual goal of eliminating cervical cancer for all women in the United States.

Mr. Michael Green is the founder and Executive Director of the International Recurrent Respiratory Papillomatosis (RRP) Information, Support and Advocacy Center (ISA). He made the following comments for ACIP's consideration. HPV 6/11/16/18 cause RRP in addition to genital warts and cervical cancer. RRP is a disease in which tumor-like lesions grow on the larynx, trachea and lungs. Untreated lesions can convert to cancer, cause suffocation and eventually result in death. The burden of RRP can equal tens of millions of cases in the United States alone.

RRP can be passed from pregnant women with HPV to their children, but the disease can also affect adults. RRP is associated with a tremendous emotional burden and unrelenting guilt of mothers who pass the disease to their children. These children must undergo hundreds of surgeries to maintain open airways. Dr. Keerti Shah is a world-renowned expert on HPV and RRP and recently stated that GARDASIL® will prevent RRP. During its decision-making process, ACIP should consider that GARDASIL® prevents RRP, head and neck cancers, and cervical cancer.

ACIP should recommend wide use of the vaccine for females 9-29 years of age and uninsured children in the VFC Program. This recommendation will increase access to the vaccine through both public health programs and private health plans. ISA is also requesting that ACIP's broad-based recommendations

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include males in addition to females. The immunization of adolescent males with the HPV vaccine will prevent the development of RRP in this population.

Mr. Green described the impact of non-cervical HPV disease on Ms. Kathy Blankenship, ISA's research investigator. Ms. Blakenship can only speak through a computer and electronic larynx. The quality of her life was severely affected in 2001 by a series of HPV-related tumors and cancers. HPV affects males and females of all ages. The disease causes RRP and 25% of all head and neck cancers in addition to cervical cancer.

The World Health Organization (WHO) identified HPV vaccination as one of four public health strategies that could reduce the world cancer burden by up to 33%. ACIP should consider this powerful message when formulating its recommendations on the HPV vaccine. ACIP's recommendations will have a strong influence on insurance companies. The cost of prevention is minuscule compared to the expenses associated with cancer treatment.

Proposed Recommendations for the Quadrivalent HPV Vaccine

Dr. Lauri Markowitz is the CDC lead on the HPV Vaccine Workgroup. She presented the workgroup's proposed language, supporting data and rationale in formulating recommendations for the quadrivalent HPV vaccine. FDA licensed the quadrivalent HPV vaccine on June 8, 2006 for use in females 9-26 years of age for prevention of certain diseases caused by HPV 6/11/16/18. The workgroup is soliciting ACIP's votes on four recommendations.

Recommendation 1 is for routine vaccination. "ACIP recommends routine vaccination of females 11-12 years of age, with three doses of the quadrivalent HPV vaccine. The vaccine series can be started as young as nine years of age at the discretion of the provider." The workgroup's rationale and data to support routine vaccination are outlined below.

The incidence of infection with one or more serotypes of HPV is high, and the risk to the individual of infection increases rapidly following onset of sexual debut among members of the population. Targeting high-risk groups is not possible. Modeling shows greater impact with a routine rather than a risk-based strategy. The target age of 11-12 years will allow vaccination of most females before sexual debut. Delivery of a three-dose series will be challenging in this age group, but the implementation advantages include the opportunity provided by the young adolescent healthcare visit recommended by a variety of professional organizations, when other vaccines are provided.

Data from bridging immunogenicity studies show high antibody titers after vaccination in this age group. The duration of protection is not known at this time, but five-year data do not show evidence of waning immunity. Studies will be conducted on an ongoing basis to monitor duration. A 2005 published study of 2002 NSFG data showed that 26% of females had vaginal sex by 15 years of age and 77% by 19 years of age (Mosher, *et al.*). A 2003 published study showed that 40% of females had acquired HPV infection by two years after sexual debut and >50% had acquired infection by four years after sexual debut (Winer, *et al.*).

Recommendation 2 is for catch-up vaccination. "ACIP recommends vaccination for females 13-26 years of age who have not been previously vaccinated. Ideally, vaccine should be administered before onset of sexual activity, but females who are sexually active should still be vaccinated." The workgroup's rationale and data to support catch-up vaccination are outlined below.

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Females 13-26 years of age who are not yet sexually active can be expected to fully benefit from vaccination due to non-exposure to HPV vaccine types. Sexually active females in this age group may not fully benefit from the vaccine due to pre-existing infection with HPV vaccine types. However, only a small percentage of females are likely to have been infected with all four HPV vaccine types. The vaccine would provide protection against disease caused by other HPV vaccine types for women already infected with ≥one HPV vaccine types. The overall effectiveness of the vaccine would be lower in a population of sexually active women, but most females will still derive benefit from vaccination.

The benefit of vaccination will decrease with increasing age because more females will have been infected with HPV vaccine types. Minimal data have been generated on the cumulative incidence of HPV infection by specific type. Serologic studies underestimate cumulative incidence for HPV because not all persons with HPV develop an antibody response after natural infection. Some studies show that ~60% of females with HPV 16 develop antibody. Detection of HPV DNA underestimates cumulative incidence because only a point prevalence estimate is provided and most infections clear within one year.

Unpublished data from Merck's quadrivalent HPV vaccine trials showed that >90% of North American subjects were sexually active at the time of enrollment. PCR or serology results showed that 24.4% of women 16-26 years of age had evidence of past or present infection with at least one HPV vaccine type; 76% were naïve to all types based on methods used in the study; and <1% had evidence of infection with all four types. These data also showed that the percentage of women with evidence of past or present infection increased with increasing age. Of this cohort, 14% had evidence of infection with HPV 16/18 at 16 years of age and 24% had evidence of infection at ≥23 years of age.

Data from CDC's 1991-1994 National Health and Nutrition Examination Survey (NHANES) were also reviewed to ensure the sample was representative of the general U.S. non-institutionalized population. Seroprevalence of HPV 16 was 6.8% in females 12-19 years of age and 24.7% in females 20-29 years of age. These data underestimate cumulative incidence and estimates were made based on some assumptions. The cumulative HPV 16 infection by 20-29 years of age would be ~41% with the assumption that only 60% of women develop antibody after natural infection. Even with assumptions for underestimates, the majority of women 20-29 years of age would still benefit from a vaccine that protected against HPV 16.

The workgroup proposes to include the following statement about cervical cancer screening in the *ACIPRecommendation*. "There is no change in the recommendations for cervical cancer screening. Vaccinated females could be subsequently infected with non-HPV vaccine types. Sexually active females could have been infected prior to vaccination. The decision to vaccinate should not be based on Pap testing, HPV DNA testing or HPV serologic testing."

The workgroup proposes the following language for simultaneous administration of the quadrivalent HPV vaccine. "The quadrivalent HPV vaccine can be administered with other age-appropriate vaccinations, such as Tdap, MCV4 or HepB vaccine. The immune response to both HepB and quadrivalent HPV vaccines is not inferior when administered at the same or a different visit. No data have been produced for co-administration with Tdap or MCV4, but the quadrivalent HPV vaccine is not a live vaccine. No components have been found to adversely impact safety or efficacy of other vaccinations." The proposed language is consistent with ACIP's general recommendations for other non-live vaccines.

The workgroup considered the implications of the routine and catch-up recommendations on price and supply. Merck's private-sector price of the vaccine is $120/dose or $360/series. The workgroup calculated the potential doses that would be needed in the first year based on the broad proposed recommendations. Based on an optimistic uptake of 20% and full administration of all three doses, 2.4 million doses would be needed for females 11-12 years of age and 19.2 million doses would be needed

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for females 11-26 years of age. Merck has given assurances that its vaccine supply is adequate to meet these estimates in the first year.

Recommendation 3 is for five special situations. The quadrivalent HPV vaccine can be administered in all of these situations. One: females with "an equivocal or abnormal Pap test. However, providers should advise patients of the potential to already have been infected with an HPV vaccine type. Data do not indicate that the vaccine will have any therapeutic effect on existing cervical lesions or HPV infection." The workgroup's rationale and data to support special situation 1 are outlined below.

Infection with any of the 40 high- or low-risk genital HPV types is possible. The likelihood of infection with HPV 16/18 increases with the severity of Pap test results. Infection with all four types would be unlikely. The patient may not be infected with any vaccine type. Vaccination would provide protection against infection with HPV vaccine types not already acquired. Data from CDC's HPV Sentinel Surveillance Project (SSP) show that most women with an abnormal Pap test have no evidence of HPV 16/18 infection.

Two: females with "a positive HPV tests using the Digene Hybrid Capture II® (HCII) assay. However, providers should advise patients of the potential to already have been infected with an HPV vaccine type. Data do not indicate that the vaccine will have any therapeutic effect on existing cervical lesions or HPV infection." The workgroup's rationale and data to support special situation 2 are outlined below.

FDA approved the use of the HCII test for women <30 years of age with atypical squamous cells of undetermined significance (ASC-US) on Pap tests. A positive test indicates infection with any of 13 high-risk types, but the test does not identify specific HPV types. Testing for specific types is not currently available in routine clinical practice. Vaccination would provide protection against infection with HPV vaccine types not already acquired. Unpublished data from CDC's HPV SSP showed that among 118 females 14-26 years of age with positive DHCII results, 37% were positive for HPV 16/18.

Three, females with "genital warts or a history of genital warts. However, data do not indicate the vaccine will have any therapeutic effect on existing genital warts or HPV infection." The workgroup's rationale to support special situation 3 is outlined as follows. A history or clinical examination of genital warts indicates HPV infection, primarily with HPV 6/11. Individuals may not have had infection with both HPV 6/11 or 16/18. Vaccination in this situation would provide protection against the vaccine HPV types not already acquired. Four, "immunosuppressed patients. Immune response and vaccine efficacy may be less than in immunocompetent persons." Five, "lactating women."

Recommendation 4 is for precautions and contraindications. "Vaccination should be deferred until after moderate or severe acute illnesses improve. A history of hypersensitivity or severe allergic reaction to yeast or any other vaccine component should be classified as a contraindication. Initiation of the vaccine series should be delayed until after completion of the pregnancy. Completion of the vaccine series should be delayed until after the pregnancy if a pregnancy is identified after initiating the vaccine series. There is no indication for intervention if a vaccine dose has been administered during pregnancy. Cases of vaccination during pregnancy should be reported to the registry. FDA gave the quadrivalent HPV vaccine a category B designation. The quadrivalent HPV vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events to the developing fetus. More safety data are needed on vaccination in pregnancy."

ACIP Vote on the HPV Vaccine

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Recommendation 1. ACIP made several suggestions to strengthen the proposed recommendation on routine vaccination.

- Add language to emphasize the adolescent platform and the rationale of targeting the recommendation to females 11-12 years of age.
- Add language to explicitly state that ACIP's intention is for health plans to cover administration of the vaccine in females as young as 9 years of age.
- Add language to clearly delineate the minimum interval between the three doses.

Drs. Markowitz and Barr provided additional details on the proposed recommendation for routine vaccination.

- "Naïve" means an individual had no antibody with PCR testing based on measurements that have been used to date. However, whether an individual is truly naïve cannot be fully determined because some persons do not develop antibody.
- Data from Merck's clinical trial of ~1,200 subjects who were seropositive and PCR-negative at baseline showed that women who were infected and cleared the infection were partially rather than fully protected. Administration of the vaccine in this population was 100% effective in preventing recurrent disease, but event rates were low.
- Merck has given assurances that the vaccine can be readily supplied across all the proposed recommended age cohorts.

Dr. Abramson called for a motion on the proposed recommendation for routine vaccination. Dr. Gilsdorf moved as follows: "ACIP recommends routine vaccination of females 11-12 years of age with three doses of quadrivalent HPV vaccine. The vaccine series can be initiated in females as young as 9 years of age at the discretion of the provider." Ms. Stinchfield seconded the motion and Dr. Abramson proposed a friendly amendment for the recommendation to emphasize the adolescent platform.

The motion passed by a majority vote. The disposition of the vote is as follows:

- **13 in favor:** Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Stinchfield, Womeodu.
- **2 with conflicts:** Poland, Treanor.
- **0 opposed**.

Recommendation 2. Dr. Allos pointed out that ACIP previously voted to make the HepB vaccine recommendation risk-based rather than age-based. For internal consistency with the HPV recommendation, she strongly urged ACIP to revisit the HepB vaccine language and include an age-based recommendation for adults. Dr. Abramson confirmed that the Hepatitis B Workgroup has already been charged to address this issue.

Drs. James Turner and Stanley Gall, the ACIP liaisons for the American College Health Association (ACHA) and American College of Obstetricians and Gynecologists, respectively, expressed strong support for the proposed recommendation on catch-up vaccination.

Dr. Abramson called for a motion on the proposed recommendation for catch-up vaccination. Dr. Gilsdorf moved as follows: "ACIP recommends vaccination for females 13-26 years of age who have not been previously vaccinated. Ideally, vaccine should be administered before onset of sexual activity, but females who are sexually active should still be vaccinated." The motion was seconded by Dr. Womeodu and **passed by a majority vote.** The disposition of the vote is as follows:

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- **13 in favor:** Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Stinchfield, Womeodu.
- **2 with conflicts:** Poland, Treanor.
- **0 opposed**.

Recommendation 3. Dr. Abramson called for a motion on the proposed recommendation for special situations. Dr. Gilsdorf moved as follows: "ACIP accepts the proposed recommendations for the five special situations of an equivocal or abnormal Pap test, positive HPV test, genital warts, immunosuppression, and lactating women." The motion was seconded by Ms. Stinchfield and **passed by a majority vote.** The disposition of the vote is as follows:

- **13 in favor:** Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Stinchfield, Womeodu.
- **2 with conflicts:** Poland, Treanor.
- **0 opposed**.

Recommendation 4. Dr. Markowitz provided clarification on the proposed recommendation for precautions and contraindications. The workgroup proposes to classify moderate or severe acute illness as a precaution; hypersensitivity as a contraindication; and pregnancy as a contraindication.

ACIP made several suggestions to strengthen the proposed recommendation.

- Make the pregnancy recommendation a precaution rather than a contraindication to avoid the need to include language on pregnancy tests and similar issues.
- Include the pregnancy recommendation in a separate "vaccination in pregnancy" section or under "special circumstances" rather than in the precautions and contraindications section.
- Include an explicit statement that pregnancy testing before vaccination is not necessary.
- Replicate language on pregnancy from ACIP's previous statements. For example, advise providers to ask patients about their pregnancy status, record the response in the chart and proceed with immunization.
- Change "hypersensitivity" to "immediate hypersensitivity."
- Do not include a statement about pregnancy testing because this language will complicate the recommendation.
- Add "should not be based on pregnancy testing" to the pregnancy language that states "the decision to vaccinate should not be based on screening."

Dr. Abramson acknowledged that ACIP would continue to be challenged in addressing the use of vaccines in pregnancy. As a result, he announced the ACIP's intention to form a new Vaccines in Pregnancy Workgroup to address questions related to administration of vaccines during pregnancy. In the interim, however, he called for a motion on the proposed recommendation for precautions and indications.

Dr. Gilsdorf moved as follows: "ACIP recommends deferring vaccination in females with moderate or severe acute illnesses until after the illness improves. ACIP recommends classifying a history of hypersensitivity or severe allergic reaction to yeast or any vaccine component as a contraindication. ACIP recommends moving pregnancy to the special situations section and adding new language to the screening section to clarify that vaccination should not be based on pregnancy testing." Dr. Womeodu seconded the motion.

Drs. Abramson and Campbell proposed two friendly amendments to the motion. "Hypersensitivity" should be changed to "immediate hypersensitivity." The following language should be moved with the revised

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pregnancy statement to the special situations section. "Initiation of the vaccine series should be delayed until after completion of the pregnancy. Completion of the vaccine series should be delayed until after the pregnancy if a pregnancy is identified after initiating the vaccine series. No indication for intervention has been established if a vaccine dose has been administered during pregnancy. Cases of vaccine in pregnancy should be reported to the registry. FDA gave the quadrivalent HPV vaccine a category B designation during pregnancy. The quadrivalent HPV vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events to the developing fetus. More safety data are needed on vaccination in pregnancy."

The motion passed by a majority vote. The disposition of the vote is as follows:

- **13 in favor:** Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Stinchfield, Womeodu.
- **2 with conflicts:** Poland, Treanor.
- **0 opposed**.

Proposed VFC Resolution

Dr. Angela Calugar, of CDC, proposed the following language to add the quadrivalent HPV vaccine to the VFC Program. ACIP's VFC resolution on February 1, 2006 would be updated with "add HPV vaccines." "HPV" would be added to the existing list of 15 diseases covered by vaccines in the VFC Program and would be administered as described in other VFC resolutions.

Eligible groups include females 9-18 years of age. A three-dose series for the quadrivalent HPV vaccine is recommended for females 11-12 years of age with the following schedule: dose one at an elected date; dose two at 2 months after dose one; and dose three at 6 months after dose one. The minimum age of vaccination is 9 years. The minimum interval from dose one to two is 4 weeks. The minimum interval from dose two to three should not be less than 12 weeks. Catch-up vaccination is recommended for females 13-18 years of age who have not been previously vaccinated or have not completed the full series. Eligible females as young as 9 years of age can be vaccinated.

Proposed statements for an interrupted vaccine schedule, recommended dosage, and special situations for immunocompromised persons and lactating women are in coordination with ACIP's HPV recommendations. Based on ACIP's previous vote, pregnancy will be included under special situations. In the precautions and contraindications section, acute illnesses will remain; vaccination during pregnancy will be deleted; and hypersensitivity or allergy to vaccine components will remain and be changed to "immediate hypersensitivity."

ACIP Vote on the Proposed VFC Resolution

Mr. Beck expressed concern about the ability to achieve the projected levels of vaccine delivery, particularly with application of an estimated 70% coverage rate among adolescents. These estimates will tremendously impact and may substantially increase cost-effectiveness. Mr. Beck acknowledged ACIP's responsibility to be prudent in its VFC resolution. Most notably, a statement should be made for the record if ACIP's position is that the estimates are not realistic. This type of language could encourage financial analysts to obtain more reliable data.

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Drs. Abramson and Pickering responded to Mr. Beck's concerns. Issues related to vaccine financing are beyond the scope of ACIP's charter. However, NVAC recently announced its new role of addressing financing for HPV and all other vaccines. Moreover, VFC is an entitlement program of vaccine coverage to eligible children through 18 years of age. Issues related to vaccine cost-effectiveness and financing are outside of the VFC Program.

Drs. Lieu and Finger also made comments on the cost-effectiveness of the HPV vaccine. CDC's data clearly demonstrate that the vaccine is a solid investment regardless of the specific coverage rate achieved. The data also showed an acceptable range for cost-effectiveness in both the catch-up and vaccination-only strategies. The base case scenario assumed a vaccination-only strategy of females 12 years of age, a 50-year time horizon, and no herd immunity. However, the data clearly demonstrated that cost-effectiveness would be improved with a higher coverage rate.

Dr. Mark Feinberg, of the Merck Vaccine Division, expressed Merck's strong interest in monitoring the utilization rates of the HPV vaccine over time and documenting the value of this investment to the healthcare community. Merck has established a program to provide the vaccine free of charge to clinics and private physicians' offices; eligibility criteria include ineligibility for the VFC program, low socioeconomic status, appropriate age range (19 years and above), uninsured and <200% of the federal poverty limit. Merck's program will be available for HPV and all of its other vaccines. Dr. Feinberg emphasized that the strength of ACIP's recommendations will play an important role in reaching high immunization coverage levels.

Ms. Linda Murphy, the ACIP *ex- officio* representative for the Centers for Medicare and Medicaid Services (CMS), clarified that Medicaid recipients who initiate the HPV vaccine series under the VFC Program at 18 years of age can complete the series after 18 years of age under Medicaid. This option is not available under the VFC program because the legislation specifically covers vaccines in children up to 18 years of age only.

Drs. Poland and Campos-Outcalt suggested two changes to the proposed resolution. "HPV vaccine" should be changed to "quadrivalent HPV vaccine." Eligible groups should be changed to females 9 "through" 18 years of age rather than "to."

Dr. Abramson called for a motion on the proposed VFC resolution. Dr. Gilsdorf moved as follows: "ACIP approves the VFC resolution for the HPV vaccine." The motion was seconded by Dr. Morse and **passed by a majority vote.** The disposition of the vote is as follows:

- **13 in favor:** Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Stinchfield, Womeodu.
- **2 with conflicts:** Poland, Treanor.
- **0 opposed**.

The participants applauded the outstanding leadership of Drs. Gilsdorf and Markowitz in guiding the HPV Vaccine Workgroup in developing recommendations for an extremely complex vaccine.

VARICELLA VACCINE

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

Update on Varicella Epidemiology

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Dr. Dalya Guris, of CDC, reported data on varicella vaccination coverage in the United States, disease trends and outbreaks, the accumulation of susceptible persons, and one and two doses of varicella vaccine. National Immunization Survey (NIS) data show that the varicella vaccination program (VVP) has resulted in a steady increase in vaccination coverage from 1997-2004. Coverage among children 19-35 months of age was 88% in 2004. Vaccination coverage ranged from 70%-94% among states. The District of Columbia and 45 states have implemented childcare or school entry requirements.

Two studies published in 2005 demonstrated that the VVP has also resulted in a substantial reduction in morbidity and mortality (Zhou and Nguyen, respectively). Hospitalizations decreased by 88% and ambulatory visits decreased by 59% in 2002 compared to 1994-1995. Hospitalizations due to varicella decreased in all age groups with the largest reduction among children <10 years of age. The average number of varicella deaths in 1999-2001 compared to 1990-1994 decreased in all age groups with a 92% reduction among children 1-4 years of age.

Data from two of CDC's Varicella Active Surveillance Project (VASP) sites showed that varicella cases quickly decreased in the early years of the program due to a rapid increase in vaccination coverage. However, a plateau has been observed in the number of varicella cases at the VASP sites over the past few years despite high vaccination coverage.

A similar trend was seen in Texas in which varicella vaccination coverage reached 85% in 2004, but the decreasing trend in the number of cases did not persist. Provisional surveillance data reported by Texas in 2005 showed that most varicella cases were among children 5-9 years of age. The number of cases among children 10-14 years of age has steadily increased over the past four years. In 2005, the vaccination status was known for ~70% of the reported cases; 82% of children 1-4 years of age and 92% of children 5-9 years of age were vaccinated.

Varicella in vaccinated persons is less severe compared to disease among unvaccinated persons. VASP data from 2002-2004 showed that ~30% of vaccinated cases had ≥250 lesions compared to ~65% of unvaccinated cases. Although hospitalizations and deaths rarely occur among vaccinated varicella cases, breakthrough disease is infectious and poses a risk for persons at risk for severe disease. An adult death was reported in Florida in 2005 following exposure to chickenpox from his vaccinated child.

Several varicella outbreaks have been reported among highly vaccinated schoolchildren with coverage ranging from 96%-100% and overall attack rates ranging from 11%-17%. Attack rates were up to 41% in some classrooms. These outcomes demonstrate that a one-dose vaccination policy does not provide sufficient herd immunity levels to prevent school outbreaks. Moreover, the accumulation of susceptible persons may result in larger epidemics in the future because children are entering into adolescence and adulthood without exposure to varicella. A shift of cases toward older ages has already been observed at one VASP site. The peak age of cases was 3-6 years in 1995 compared to 9-11 years in 2004.

The risk of exposure to varicella-zoster virus (VZV) decreases as the overall disease incidence declines. In a population with 100% coverage, 20% of persons will remain susceptible because vaccine effectiveness is ~80%. Both vaccinated and unvaccinated susceptible persons are accumulating and will be at risk for disease and outbreaks later in life when disease can be severe. CDC calculated the accumulation of susceptible persons with a one-dose vaccination program based on the following assumptions: a 4 million birth cohort, 95% coverage rate, 80% vaccine effectiveness, and 30% of vaccinated persons susceptible to typical disease. The findings showed that ~40% of susceptible persons would have the potential to develop typical disease with ≥250 or more lesions if exposed to VZV.

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Most field studies indicate that one dose of varicella vaccine is 80%-85% effective. Several risk factors for vaccine failure were assessed, including time since and age at vaccination, asthma, use of steroids, eczema, and cold chain problems. However, the literature is not consistent on identifying risk factors for vaccine failure. A recent ten-year prospective study showed that the cumulative rate of breakthrough disease after one dose increased throughout the follow-up period. The rate did not increase after year 6 among children in the two-dose group.

No additional cases were observed among children in the two-dose group during the remainder of the follow-up period, but breakthrough disease continued to occur among children in the one-dose group (Kuter, *et al.*). The study used historical population incidence rates to compare the efficacy of two versus one dose. The estimated two-dose vaccine efficacy of 98.3% was significantly higher than the estimated one-dose vaccine efficacy of 94.4%. The attack rate among children in the one-dose group was 3.3-fold higher than the attack rate among children in the two-dose group.

Overall, the VVP has resulted in substantial disease reduction in the first ten years, but challenges still exist. One-dose vaccination is 80%-85% effective. Breakthrough cases are infectious and disease among vaccinated children can be severe. Outbreaks continue to occur even among highly vaccinated schoolchildren and their investigations are placing an increasing demand on state and local health departments and school staff.

Varicella incidence is not continuing to decline. The age of varicella cases is shifting to adolescents. Persons susceptible to varicella are accumulating due to reduced incidence. Adults will be at higher risk for disease at times when disease can be severe, such as infection during pregnancy. The potential exists for large outbreaks in high schools and colleges. One-dose vaccination will not provide adequate protection.

Immune Responses to One and Two Doses of Varicella Vaccine

Dr. Anne Gershon, of Columbia University (CU), serves as a consultant to the Varicella Workgroup. She presented data to support the workgroup's proposed recommendation for a routine two-dose regimen of varicella vaccine to children. The VVP should reduce the varicella burden in childhood, but if breakthrough disease develops, there is potential transmission of wild type VZV, potential for development of latent infection, and possible zoster. The VVP should also prevent accumulation of fully or partially susceptible young adults who would be at risk for developing severe chickenpox. However, primary immune failure of even 5% after a single dose could result in 200,000 non-immune children annually.

A 1991 published study on seroconversion among 2,442 children after one dose of VARIVAX suggested that primary immune failure was unusual (4%) (White, *et al.*). The study methods included a gp ELISA test, a cutoff for immunity of >3 units, and a low GMT of 1:12. It was projected that children with no detectable antibodies might have cell-mediated immunity (CMI) against VZV and children with $\geq$5 units by gp ELISA six weeks post-vaccination were less likely to develop breakthrough infections over time than those with lower titers six weeks post-vaccination.

New unpublished data suggest that primary vaccine failure may be more common after one dose than previously reported in the literature (Michalik, *et al.*). The following methods were used in this study. A cohort of 80 healthy susceptible children with a mean age of 16 months was given one dose of VARIVAX. Sera were obtained from the cohort both before and 16 weeks after vaccination. The fluorescent antibody to membrane antigen (FAMA) test was used to measure seroconversion rates. The FAMA test

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has been validated and published in the literature. The percentage of children who achieved a titer ≥1:4 was 76%. In this study, the primary vaccine failure rate was 23%.

Other recent unpublished data also show a high primary vaccine failure rate using similar methods (LaRussa, *et al.*). A cohort of 56 healthy susceptible children with a mean age of 25 months was given one dose of VARIVAX. Sera were obtained from the cohort both before and six weeks after vaccination. The FAMA test was used to measure seroconversion rates. The percentage of children who achieved a titer ≥1:4 was 88%. In this study, the primary vaccine failure rate was 12%.

Unpublished data from a ten-year study at a VASP site over the 1995-2004 time period suggest that the incidence of breakthrough varicella may be increasing (Chaves, *et al.*). A substantial decrease was seen in circulation of wild type VZV, but a slow increase in the breakthrough rate was observed up until year 9. Although these results should be validated in other settings, the data demonstrate an accumulation of children with primary vaccine failure and an inadequate initial response that falls below the threshold for protection.

Four studies published in 2002 and 2004 demonstrated an increase in breakthrough varicella over time that suggests some degree of waning immunity (Galil, Lee, Tugwell, Vazquez). More breakthrough cases of varicella were observed in children vaccinated 3-5 years previously than in those vaccinated within a shorter interval. However, these data are confounded by different ages and forces of infection.

Data from CU revealed that a two-dose regimen of varicella vaccine would provide a boost of immunity. These calculations support the immunologic concept of the importance of an initial burst of the host response to establish long-term anti-viral immunity. CU's calculations are also consistent with an actual case of a physician who was immunized in experimental studies in 1979 and never developed chickenpox or zoster despite exposure to chickenpox in an emergency room and from his two children.

Unpublished data showed an increase in gp ELISA titers in children who received two doses of varicella vaccine (Levin). The data showed that the seroconversion rate of 87.3% six weeks after dose one increased to 99.5% following dose 2. The GMT also dramatically increased from 12.8 after dose 1 to 141.5 following dose 2. Other unpublished data also showed a marked increase after two doses of measles, mumps, rubella and varicella (MMRV) (Kuter). Seroconversion rates and GMTs to VZV increased from 87% and 12, respectively, after dose 1 to 99% and 478, respectively, following dose two.

Laboratory data showed that two doses of varicella vaccine can increase CMI in children and provide a significant boost for at least one year (Arvin). The mean CMI in the one-dose group of 39 children was 9.3 at 1 year post-vaccination compared to 22.2 in the two-dose group of 39 children. A 1995 published study showed that a second dose of varicella vaccine can provide an effective boost in immunity 6 years following primary vaccination (Watson). During the time period before and 3 months after the booster, the mean GMT increased from 25.7 to 119 and CMI increased from 40.3 to 61.4.

A 2004 published study showed that the efficacy of two doses of varicella vaccine over 10 years was greater than one dose (Kuter, *et al.*). Varicella was 3.3-fold lower in children after two doses than after one dose. Breakthrough disease was significantly decreased in children who received two doses. The 10-year efficacy of 94.3% after dose one versus 98.3% after dose two was significant. The modified severity of varicella even with one dose suggests evidence of priming of the immune response in some children.

The Varicella Workgroup reached the following conclusions based on its review of the literature. Available evidence suggests that two doses of varicella vaccine are superior to one. Dramatic boosts in humoral and cellular immunity and better protection against disease were seen after two doses. Breakthrough varicella is probably due mostly to partial or incomplete primary vaccine failure after one

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dose rather than waning immunity. The evidence suggests that primary priming of the immune response occurs in many vaccinees after one dose, but the initial burst is insufficient for protection after normal decline.

The single dose regimen was expected to require reassessment after successful introduction of routine varicella vaccination. Introduction of MMRV provides a solid opportunity to introduce a two-dose regimen. A shift in varicella disease burden to young adults can be predicted without a change to a two-dose regimen. This trend would be based on an accumulation of young adults with complete or partial primary vaccine failure; an inadequate initial immune response that declines to below protective levels; and a reduction of opportunities for boosting from varicella exposures. Outbreak control is problematic, expensive and will not prevent the shift of infection to young adults.

Projected Benefits and Costs of a Second Dose of Varicella Vaccine

Dr. Tracy Lieu is a member of the Varicella Workgroup. She presented data prepared and analyzed by Dr. Fangjun Zhou, of CDC, on the projected benefits and costs of a second dose of varicella vaccine. As presented in 2005, the ~$1 million cost per life-year saved appeared to be high and the cost of MMRV was unknown. In 2006, outbreak costs have been studied and the previous data analysis has been updated to credit the vaccine with preventing varicella morbidity.

The data analysis was based on several assumptions. Varicella incidence rates were obtained from VASP. A second dose of vaccine would reduce varicella by 79%. Immunity would be life-long from the second dose. An outbreak costs $5,900. The benefits of the vaccine in preventing Group A Streptococcus and averting zoster were not included. The data analysis showed the following results based on these assumptions.

Incremental annual health benefits for the U.S. population using MMRV vaccine for the second dose would include the prevention of 400,000 varicella cases (10% of potential cases) and the saving of five lives. The cost of varicella vaccine (using MMRV vaccine) is $58 per child for one dose and $116 per child for two doses. Assuming that 63% of the MMRV vaccine would be given in the public sector, the incremental national cost would be $218 million; savings from varicella prevented would be $124 million; and the net incremental cost would be $93 million. The net costs (savings) would be $967 million with the one-dose program compared to $874 million with the two-dose program. The two-dose program would also be cost-saving compared with no intervention.

The second dose of varicella vaccine would save few lives, but the vaccine should be credited for preventing disease cases in addition to deaths. Two studies published in 1998 and 2003 that interviewed parents and older persons about the value in preventing varicella and zoster were used to estimate QALYs saved (Bala and Brisson, respectively). Using these estimates, the workgroup's analysis showed that the second dose saved an additional 1,365 QALYs and resulted in an incremental $96,000 cost per QALY saved from a societal perspective.

The data analysis included a comparison to other vaccines. The Zhou data showed that the second dose of varicella vaccine would prevent 400,000 disease cases; save 1,400 QALYs; cost $311 million for the direct cost of vaccination and net societal cost; and result in $96,000 per QALY saved. The Lee data showed that pertussis vaccination of adolescents would prevent 31,000 disease cases; save 1,600 QALYs; cost $77 million for the direct cost of vaccination and net societal cost; and result in $20,000 per QALY saved. The Shepard data showed that meningococcal vaccination would prevent 270 disease cases; save 1,800 QALYs; cost $432 million for the direct cost of vaccination and net societal cost; and result in $138,000 per QALY saved.

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Secondary analyses to credit MMRV with preventing related conditions would improve the base case cost-effectiveness. Savings from averting Group A Streptococcus would add an incremental cost per QALY saved of $91,000. Benefits from preventing zoster would add an incremental cost per QALY saved of $17,000. However, uncertainties must also be considered in decisions to add a second dose of varicella vaccine. The duration of immunity after the second dose is unknown. Catch-up vaccination and its cost-effectiveness have not been analyzed to date.

Overall, the data analysis showed that the cost-effectiveness of a second dose of varicella vaccine is likely to fall in the reasonable range. Important factors along with cost-effectiveness should be weighed, such as the social disruption from school outbreaks and burden to public health agencies.

State Health Department Perspective on Varicella Outbreak Response

Dr. Dale Morse is a member of the Varicella Workgroup. He presented a state health department's perspective on a two-dose varicella vaccination schedule. The failure of the one-dose measles vaccination program should be reviewed to avoid making the same mistakes with varicella. Measles cases and outbreaks continued to occur in the United States despite the one-dose measles elimination program to end indigenous measles in October 1982. New York had a 99% reduction in measles cases, but cases and outbreaks continued to occur in high schools.

In the late 1980s, New York and other states began to actively exclude any child from school entry without a history of measles immunization. States continued to control outbreaks and monitor rates while the debate continued over the need for a second dose of measles vaccine. New York adopted a state policy of two-dose measles vaccine following outbreaks in college settings. In a four-month period, 21 outbreaks occurred and 90% of college students were immunized for measles. New York's administration of >50,000 doses cost >$850,000 for the vaccine and ~$3 million for outbreak control. ACIP soon developed a national policy of two-dose measles vaccine following the New York State policy.

CDC administered a survey in 2004 to 57 state immunization grantees to determine the extent of varicella outbreaks in the United States. Of 93% of states that responded to the survey, 85% reported being contacted about varicella cases or outbreaks; 15% estimated being contacted for 75%-100% of local outbreaks; and 87% responded to outbreaks at the state or local level. CDC used a standard tool to collect information and learned that seven grantees reported "personnel" as the majority of costs for outbreak investigations. The grantees also reported that a typical response to a school outbreak cost $3,000. An active outbreak response in which an immunization clinic was established cost $6,000. A hospital outbreak investigation cost $7,700.

Of CDC's immunization grantees, Connecticut has maintained more active surveillance of varicella cases and outbreaks than other states in its population of ~3.5 million persons. Of 1,038 cases detected in schools from September 2003-June 2004, 44% were outbreak-related. Of 41 outbreaks that occurred in 41 schools, 93% were in elementary schools. The mean age of cases was nine years. The duration of outbreaks in the schools among well immunized children ranged from 15-93 days.

ACIP responded to these outbreaks in June 2005 by recommending a second dose of varicella vaccine during an outbreak for persons who had received one dose, if resources permitted. Several states have attempted to comply with the ACIP guidance. For example, an outbreak continued over ~3 months in a Maine elementary school with ~350 students despite an immunization rate of 98% with one dose. An immunization campaign ultimately ended the outbreak.

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Maine identified several challenges in responding to the outbreak of October 2005-January 2006. A tremendous burden of 382 extra hours was placed on school and health personnel. School and work days were missed and the outbreak response cost $26,761. Recognition of the outbreak was delayed. Public and private providers were reluctant to accept an immunization clinic and exclude non-vaccinated children. Difficulties were encountered with the clinical case definition and confirmatory laboratory tests. State law currently requires one dose of varicella vaccine and does not cover school exclusion. The second dose of the vaccine was not covered by insurers.

Similar to the one-dose measles vaccine program, the one-dose varicella vaccination policy is failing to eliminate a childhood disease. The outbreak control policy is not effective in controlling varicella outbreaks. Susceptible persons are accumulating and will be at risk later in life when disease can be more severe. Efforts are underway by professional organizations to address these concerns.

The American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID) voted to recommend universal administration of a second dose of varicella-containing vaccine. The Council of State and Territorial Epidemiologists (CSTE) adopted a position statement during its June 2006 meeting recommending that ACIP consider a universal two-dose varicella vaccination policy with catch-up provisions. CSTE adopted the position statement due to the endemic occurrence of varicella cases, outbreaks among well-immunized children who received a single dose of varicella vaccine, and the demonstrated futility of outbreak follow-up and control measures.

Dr. Jane Seward, of CDC, and Dr. Barbara Kuter, of Merck, provided additional details related to the proposed catch-up strategy for varicella vaccination. The age limit for catch-up vaccination could potentially range from children 6-12 years of age to adults 22 years of age who were 12 years of age in 1995 and received one dose. Merck's studies show that the second dose of vaccine will provide a solid boost regardless of the level of antibody or time since the first dose.

Consideration of a Universal Two-Dose Recommendation for Varicella Immunization

Dr. Judith Campbell, the Varicella Workgroup Chair, covered several topics to facilitate ACIP's discussion and vote on a routine two-dose policy for varicella vaccination. The workgroup is soliciting ACIP's vote in two areas. Recommendation 1 proposes a change in the current varicella vaccination policy. Children would be routinely vaccinated with two doses at 12-15 months of age for dose one and 4-6 years of age for dose two with a caveat regarding the minimum interval between the two doses.

Recommendation 2 proposes catch-up vaccination for children, adolescents and young adults who previously received one dose, to improve individual protection against varicella and for more rapid impact on school outbreaks. Catch-up vaccination could be implemented during routine healthcare visits and through school and college entry requirements.

The workgroup extensively reviewed the varicella immunization science in formulating the recommendations. Initial implementation of the varicella immunization policy in 1995 has resulted in successful reductions in varicella incidence, morbidity and mortality. However, the reduction in varicella incidence has reached a plateau over the past 4-5 years in states with high immunization coverage rates. Although high immunization rates have been achieved in active surveillance sites and many states, breakthrough infections and outbreaks in school settings continue to occur. Breakthrough infections are contagious and frequently serve as the source of outbreaks or ongoing transmission to persons who are susceptible or at high risk for severe disease.

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Varicella vaccine effectiveness was estimated at 80%-85% post-licensure. Of all varicella vaccine recipients, 15%-20% are non-responders or partial responders after one dose. The incidence of breakthrough infection in children who received one dose has increased with time since vaccination. The susceptible population is accumulating due to the decreased overall incidence of wild type varicella. The higher risk for more serious disease among adolescents and adults will pose a risk for large outbreaks in high schools and colleges.

Two doses of varicella vaccine parallel the immune response to natural infection with higher antibodies levels measured by FAMA or gp ELISA and cellular immune response measured by stimulation index. The number of breakthrough infections is significantly lower in two-dose recipients compared to one-dose recipients. The workgroup acknowledges that the varicella immunization science is limited because the duration of two doses is not known beyond 10 years.

The workgroup discussed and considered the varicella immunization standard of care from diverse sources in formulating the recommendations. Surveys administered to providers show that most pediatricians and family practitioners have experience with breakthrough infections and will give a second dose of varicella vaccine if recommended by ACIP. The availability of MMRV increases the willingness of providers to administer a second dose. The AAP COID has approved the drafting of a revised varicella immunization statement that recommends a universal second-dose policy.

State and local health departments have emphasized that an interim strategy of a second dose for outbreak control is not efficient. A tremendous amount of resources and time are required to respond to outbreaks and breakthrough infections. The increasing prevalence of breakthrough infections has affected public confidence in varicella immunization and vaccination programs in general.

In addition to considering the perspectives of providers, health departments and public, the workgroup also made strong efforts to address issues raised during the June 2005 ACIP meeting. In response to ACIP's concerns about cost-effectiveness, the workgroup updated the data analysis. The more recent data show that both one- and two-dose varicella vaccination programs would be cost-saving from a societal perspective compared to no vaccination. The incremental cost-effectiveness of the second dose of varicella vaccine likely falls within the reasonable range.

In response to ACIP's concerns about programmatic issues and suggestions to delay the second dose until the availability of MMRV, the workgroup notes that MMRV was licensed in the fall of 2005. The cost of the vaccine is now known and was factored into the updated cost-effectiveness analysis. In response to ACIP's concerns about the purpose and outcomes of a second dose, the workgroup acknowledges several key factors. The immune response is more like that of natural infection. Population-based immunity will be increased. The decrease in breakthrough infections will lead to reducing outbreaks and transmission to other individuals in schools and families with susceptible adolescents, young adults and adults.

In response to ACIP's concerns about the priority of a two-dose varicella vaccination program relative to other new vaccines under consideration, the workgroup acknowledges several key factors. Hepatitis A (HepA) vaccine and other vaccines with successful initial programs were approved for routine administration to maintain the success of the program. The proposed two-dose varicella vaccination program is a priority due to the accumulation of susceptible high school students, college students and young adults into adulthood. The proposed intervention is timely.

The workgroup identified the advantages and disadvantages of two policy options. Policy 1 would be to continue the routine one-dose policy with no changes. On the one hand, no additional costs would be incurred. However, modifications to the current policy would need to be considered to determine whether two doses should continue to be recommended in outbreaks. CSTE informed the workgroup that efforts

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to implement ACIP's 2005 recommendation were not effective at state and territorial levels. CSTE would be in a position of reconsidering the feasibility and purpose of case-based surveillance.

On the other hand, ongoing outbreaks require a tremendous amount of resources from state and local health departments. Two doses are not effective for outbreak control. The 2010 goal of a 90% reduction in varicella disease may not be achieved or maintained. The accumulation of susceptible persons may result in increased disease among adolescents and adults. Confidence in the vaccination program may be lost.

Policy 2 would be to change the recommendation to include a routine second dose. On the one hand, data show a 3.3-fold reduction in attack rates among children who received two doses. Cellular and humoral immunity would be improved, providing immunity similar to that obtained through natural infection. Studies have demonstrated that two-dose effectiveness remains stable and high over 10 years. The two-dose program is cost-saving compared to no vaccination. On the other hand, the incremental cost is high and the duration of vaccine-induced immunity after two doses is still unknown. Data are available for up to 10 years, but lifetime immunity in the absence of external boosting is unknown.

The workgroup reached consensus on a policy change for a routine two-dose varicella vaccination program with catch-up provisions. The advantages of catch-up vaccination are the ability to target the current disease burden (schoolchildren with the highest incidence of outbreaks) and capacity to immunize susceptible children prior to adulthood. The disadvantage would be the incremental cost of catch-up vaccination. However, the workgroup noted that catch-up vaccination can be implemented during routine healthcare visits and through school and college entry requirements.

Dr. Guris described the rationale and data to support the workgroup's consensus on three programmatic issues. One, the workgroup reached consensus on changing the age of the first dose of varicella vaccine to 12-15 months. A discrepancy exists between the current recommended ages of the first dose of MMR at 12-15 months and varicella at 12-18 months. The proposed change will harmonize the schedule with that of measles, mumps and rubella (MMR) and will ease the use of MMRV vaccine. Some studies found that vaccination at a young age was a risk factor for vaccine failure, but this limitation will be compensated by administration of the routine second dose.

The workgroup reviewed data from five studies published in 2002-2005 that found early age at vaccination to be a significant risk factor for vaccine failure (Dworkin, Haddad, Lee, Vasqyez Verstraeten). The 2003 Verstraeten retrospective cohort showed that children vaccinated <15 months of age were 1.4 times more likely to develop varicella compared to those vaccinated at ≥15 months of age. The 2005 Haddad outbreak investigation showed that among children vaccinated >5 years before the outbreak, those vaccinated at ≤18 months of age were 9.3 times more likely to develop varicella than those vaccinated at >18 months of age.

The workgroup also reviewed data from an unpublished prospective cohort study that followed 7,585 vaccinated children (Black, *et al.*). Age at vaccination was not found to be associated with a risk for developing breakthrough disease. Most outbreak investigations that studied whether age at vaccination was associated with an increased risk for vaccine failure did not find age at vaccination to be a risk factor for vaccine failure.

Two, the workgroup reached consensus on routine second-dose administration of varicella vaccine at 4-6 years of age and permissive use of dose two at an earlier age provided that 3 months have elapsed after the first dose. The early second-dose schedule will provide better protection for preschool-aged children. However, the proposed schedule is not harmonized with MMR, will not maximize use of the combination MMRV vaccine, and may result in lower two-dose coverage until school entry. The schedule would

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require extra injections (two VARIVAX or one ProQuad). The impact on current disease burden would be delayed.

The later second-dose schedule will not require an extra injection if ProQuad is used. School entry vaccination for measles will provide an opportunity for high vaccination coverage. The impact on the high incidence in schools will be seen more rapidly and protection will be provided to younger children through impact on school outbreaks and herd immunity. However, some children will have a delay in achieving a protective immune response due to the delay in second-dose administration.

The workgroup reviewed VARIVAX immunogenicity data of an early second-dose schedule (Ngai, Kuter) and a later second-dose schedule (Watson). In the early second-dose schedule with 1,647 participants, the GMT and mean stimulation increased from 12.5 and 44.72, respectively, after dose one to 142.6 and 67.69, respectively, after dose two. In the later second-dose schedule with 419 participants, the GMT and mean stimulation increased from 25.7 and 40.3, respectively, after dose 1 to 218.8 and 58.6, respectively, after dose 2.

The workgroup also reviewed unpublished Merck data on ProQuad immunogenicity that compared early and later two-dose schedules and demonstrated high antibody levels. In both schedules, 99% of children had ≥5 gp ELISA units after dose two and GMTs were high after dose two as well. The data review showed no substantial differences regarding immune response. The major issues seen were programmatic, such as coverage, extra injections and the impact on disease burden.

Three, the workgroup reached consensus on maintaining a three-month minimum interval for routine administration of two varicella-containing vaccine doses. However, dose two does not need to be repeated if dose two was administered after at least 28 days following dose two. Several issues were discussed related to this decision.

Despite the availability of a combination MMRV vaccine, minimum intervals between two doses of MMR and varicella vaccines are different for persons <13 years of age. The discrepancy between a four-week minimum interval for MMR and a three-month minimum interval for varicella will create confusion in the field. This discrepancy also facilitates waste because administration of the second dose of varicella-containing vaccine four weeks after dose one will not be considered a valid second dose and the child will be re-vaccinated. Moreover, children may need two MMR-containing vaccines with as short an interval as possible in certain situations, such as measles, rubella or mumps outbreaks, prior to travel or before school entry. These special situations would also create confusion, limit the use of MMRV or lead to unnecessary repeat doses.

The 4-week interval is currently used for persons ≥13 years of age. Data from a 1995 study that compared adults 13-19 years of age vaccinated at 4- versus 8-week intervals showed that GMTs were 23 in the 4-week interval group and 30.1 in the 8-week interval group (Kuter, *et al.*). However, the vaccine dose used in the study is lower than the currently licensed dose. A recommendation with a 4-week interval between the two doses will be harmonized with MMR, prevent unnecessary repeat doses and reduce vaccine waste. ACIP's general recommendations currently allow vaccination with two parenteral live vaccines at least 28 days apart. The shorter interval will also facilitate rapid immunization of children for school entry and travel. Studies were conducted for children with a 3-month interval to fit the routine well child visit schedule and not for other reasons. However, the 4-week interval is an off-label recommendation. No data have been evaluated on an interval <3 months in children.

ACIP members made several comments on the workgroup's proposed changes to the varicella vaccination policy. Dr. Lieu was hesitant about the catch-up strategy because catch-up vaccination is typically less cost-effective than the overall program. Catch-up vaccination will most likely be implemented with varicella as a stand-alone dose rather than MMRV. However, she was unsure of the

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rationale in recommending a routine second dose and then allowing the unvaccinated group to become older without the protection of a second dose. Moreover, the extra number of injections for the target age groups will require more nursing administration time. However, Dr. Lieu's overall position was that catch-up vaccination would most likely be beneficial even if the strategy is less cost-effective.

Dr. Hull conveyed that a recommendation of a two-dose policy without catch-up vaccination would not be beneficial from a state public health perspective. State epidemiologists are charged with controlling outbreaks, responding to criticism and concerns by anxious parents, and addressing the long-term potential of children who will be hospitalized with varicella pneumonia as adults. His position was that ACIP should not recommend a two-dose policy without catch-up vaccination.

Dr. Hull also urged ACIP to harmonize the schedule with MMR to reduce the burden on parents, physicians and public health clinics. If ACIP recommends a 3-month interval, studies should be rapidly conducted to decrease the interval to one month. Dr. Kuter confirmed that Merck is planning to initiate studies on a one-month interval in the fall of 2006. She also pointed out that the varicella vaccine has been recommended for routine use in Europe as MMRV with administration of two doses as early as possible, with a minimum interval of one month, and a maximum interval of three months. Merck will use the European data on all four components of the MMRV vaccine to support its upcoming studies.

Dr. Cody Meissner, the AAP liaison, announced that COID is currently revising AAP's varicella statement. A recommendation will be made for universal administration of a second dose of varicella-containing vaccine for children 12 months-12 years of age. A second dose will also be recommended for adolescents and young adults who previously received one dose before 13 years of age.

AAP's updated statement will focus on four key points. One, the first dose of a varicella-containing vaccine should be routinely administered at 12-15 months of age. This recommendation represents a change from 12-18 months and is being made to facilitate use of MMRV at the age presently recommended for administration of MMR. Two, the second dose of a varicella-containing vaccine should be routinely administered at 4-6 years of age or at least three months after dose 1. The interval may be as short as 28 days if administration of dose 2 is necessary at an earlier interval, such as during a measles or mumps outbreak.

Three, catch-up immunization will be addressed by recommending that all children entering elementary, middle, and high school, and college should have received two doses of varicella-containing vaccine unless other evidence of immunity to varicella is presented. Four, the preference for use of the MMRV combination vaccine whenever possible will be encouraged.

In 2005, COID concluded that a second dose is critical for improved control of the burden of disease due to varicella and unanimously voted in favor of a recommendation for a second dose. COID is now awaiting ACIP's decision on a second dose for the target age group because disparate recommendations among professional organizations will lead to confusion. Dr. Meissner emphasized that AAP hopes ACIP will now endorse routine and catch-up recommendations for a second dose to facilitate the implementation of uniform recommendations by AAP, ACIP and the American Academy of Family Physicians (AAFP).

Dr. Samuel Katz, the Infectious Disease Society of America liaison, strongly supported a second dose of varicella vaccine. However, he cautioned ACIP against comparing measles and varicella because the immunopathogenesis of the two diseases is entirely different. He also advised ACIP to convey clearly to the public that unlike measles, varicella will not be eliminated in the United States by a two-dose schedule.

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Dr. Abramson added that a two-dose schedule will decrease rather than eliminate breakthrough disease. This understanding will avoid a false sense of failure when breakthrough disease is still present in the future. Dr. Philip Brunell, of NIH, agreed with these comments based on the existing data. He asked ACIP to consider recommending a 4-in-1 dose for children 12-15 months of age and a second dose for children and adults who previously received only one dose.

Dr. Doug Campos-Outcalt, the AAFP liaison, was uncertain of the advantages in recommending a second dose of varicella vaccine at an earlier age than MMR. This change will complicate several issues, such as an increased number of injections, vaccine storage and the overall schedule. If ACIP recommends an earlier age for the second dose of varicella vaccine, however, he supported harmonization with the second dose of MMR. Dr. Campos-Outcalt expressed an interest in reviewing mathematical modeling data on children <4 years of age.

Drs. Kuter and Florian Schödel of Merck provided additional details in response to ACIP's questions.

- Merck reviewed studies on the second dose of varicella vaccine to distinguish between persons who did and did not respond to the first dose. The data showed the following results. Some persons were primary vaccine failures. GMTs showed that persons who failed to respond after dose 1 clearly responded after dose 2. This trend occurred in 99% of persons with titers $\leq$5, but GMTs of this cohort were not as high as the group that obtained a take after dose 1. Merck committed to sharing these data with ACIP.
- The potency of the vaccine has remained the same since licensure. Merck has conducted numerous studies and found that seroprotection is slightly lower than seroconversion after a single dose. Seroprotection (a threshold $\geq$5 gp ELISA) was relatively lower than the high seroconversion rate of 90%. However, seroconversion rates do not correlate as well with the absence of breakthrough disease compared to seroprotection. More breakthrough disease is seen with seroconversion alone, but at a very low titer.

ACIP Vote on the Varicella Vaccination Policy

Recommendation 1 proposes a change in the current varicella vaccination policy. Children would be routinely vaccinated with two doses at 12-15 months of age for dose 1 and 4-6 years of age for dose 2 with the following caveat: "The second dose can be administered at an earlier age provided the interval between the first and second dose is at least three months. However, the second dose does not need to be repeated if the second dose was administered after at least 28 days following the first dose."

Dr. Abramson called for a motion on the proposed recommendation. Dr. Campbell moved as follows: "ACIP adopts a routine two-dose varicella vaccination policy as outlined by the workgroup." The motion was seconded by Dr. Finger and **passed by a majority vote.** The disposition of the vote is as follows:

- **13 in favor:** Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Stinchfield, Womeodu.
- **2 with conflicts:** Poland, Treanor.
- **0 opposed**.

Recommendation 2 is on catch-up vaccination. "To improve individual protection against varicella and for more rapid impact on school outbreaks, second-dose catch-up varicella vaccination is recommended for children, adolescents and young adults who previously received one dose. Catch-up vaccination can be

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implemented during routine healthcare provider visits and through school and college entry requirements."

In response to Dr. Turner's questions, Dr. Seward pointed out that issues related to varicella vaccination of healthcare workers (HCWs) and pregnant women are covered in ACIP's varicella prevention statement. The workgroup would address vaccination of HCWs during its update on the evidence of immunity to varicella. With respect to pregnancy, the current recommendation is for providers to question patients about pregnancy. CDC and Merck have been jointly operating a varicella vaccine in pregnancy registry for the past ten years. No congenital varicella syndrome or adverse outcomes have been reported to date based on ~600 notifications to the registry on women who inadvertently received the vaccine during pregnancy. However, varicella vaccine is contraindicated during pregnancy.

ACIP suggested that recommendation 2 be changed to "young adults through 22 years of age" or "adults" rather than "young adults."

Dr. Abramson called for a motion on the proposed recommendation. Dr. Campbell moved as follows: "ACIP adopts the policy for catch-up varicella vaccination with the revision of deleting 'young' and stating '...for children, adolescents and adults who previously had one dose.'" The motion was seconded by Ms. Stinchfield and **passed by a majority vote.** The disposition of the vote is as follows:

- **13 in favor:** Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Stinchfield, Womeodu.
- **2 with conflicts:** Poland, Treanor.
- **0 opposed**.

Dr. Guris reported that the workgroup reviewed comments from state health departments to make the following revisions to the evidence of immunity in the ACIP varicella prevention statement. The following are criteria for evidence of immunity: (1) documentation of age-appropriate vaccination: one dose for preschool-aged children ≥12 months and two doses for school-aged children, adolescents and adults; (2) laboratory evidence of immunity or laboratory confirmation of disease; (3) born in the United States before 1980; (4) a healthcare provider diagnosis of varicella or verification of history of varicella disease; and (5) history of herpes zoster based on healthcare provider diagnosis.

The workgroup changed the previous cutoff point of 1965 to "born in the United States before 1980" based on new national seroprevalence data that suggest persons born between 1965-1980 have a susceptibility rate between 2.6%-2.8%. The following footnote was added to the new cutoff. "Healthcare facilities should consider recommending varicella vaccine for HCWs born before 1980 and without evidence of immunity."

The workgroup clarified "verification" by adding the following footnote to "a healthcare provider diagnosis of varicella or verification of history of varicella disease." "Verification can be done by a clinician (e.g., a school or occupational clinic nurse, physician assistant or physician). For atypical and/or mild disease history, epi-link to a typical varicella case or evidence of laboratory confirmation at the time of acute disease should be sought." This language is intended to increase specificity about breakthrough disease and give clearer guidance to providers who will assess children for evidence of immunity.

The workgroup clarified the previous language on vaccination of human immunodeficiency virus- (HIV) positive children. ACIP's previous vote on the vaccination of HIV-infected children with CD4 T-lymphocytes >15% did not specify the clinical classification. The revised language states that "single antigen varicella vaccine should be considered for HIV-infected children in CDC class N2, A2 or B2 with CD4+ T-lymphocytes ≥15%."

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Dr. Kathleen Neuzil, the American College of Physicians (ACP) liaison, reiterated her previous concern that varicella vaccine is contraindicated in HIV-positive adults, as per guidance provided inthe adult immunization schedule. Dr. Seward confirmed that CDC is attempting to gather data from correctional facilities and other settings to address this issue. In response to Dr. Campos-Outcalt's question, Dr. Seward and Dr. Schödel clarified that "single antigen varicella vaccine" is recommended due to the absence of data on MMRV. Merck has not produced data to support the use of ProQuad in immunocompromised children.

The following suggestions were made to refine the language on vaccination of HIV-positive children. A footnote should be added to clarify that single antigen varicella is recommended due to higher titers of VZV in MMRV and the absence of any data on MMRV. The language should be revised to "N2, A2, B2 or better."

Dr. Abramson called for a motion on the proposed recommendation. Dr. Campbell moved as follows: "ACIP adopts the revised varicella prevention statement with the following additional edits. A footnote will be added to clarify that single antigen varicella is recommended due to higher titers of VZV in MMRV and the absence of any data on MMRV. The language will be changed to 'N2, A2, B2 or better.'" The motion was seconded by Dr. Gilsdorf and **passed by a majority vote.** The disposition of the vote is as follows:

- **13 in favor:** Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Stinchfield, Womeodu.
- **2 with conflicts:** Poland, Treanor.
- **0 opposed**.

Proposed VFC Resolution

Dr. Gregory Wallace, of CDC, reported that the purpose of the resolution is to incorporate changes for the use of measles, mumps, rubella and varicella-containing vaccines. A two-dose schedule is being recommended for varicella-containing vaccine and the indication for the MMRV formulation is being updated. The workgroup agreed to cite the immune globulin table published in the *Morbidity and Mortality Weekly Report* (*MMWR*) rather than reproduce the table in the VFC resolution.

The first dose of varicella vaccine would be administered at 12-15 months of age and the second dose at 4-6 years of age. A footnote was added to the minimum interval to clarify that for persons <13 years of age, the second dose does not need to be repeated if the second dose was administered after at least 28 days following the first dose. ACIP's recommended language on immune status and children with a CD4 count ≥15% was incorporated. Administration of MMRV is not recommended as a substitute for the component vaccine when vaccinating HIV-infected children. The recommended ages for MMRV will be changed to 12 months "through" 12 years rather than "to" 12 years.

The following language is being incorporated to reflect ACIP's discussion on catch-up vaccination. "MMRV may be administered when a dose of MMR or varicella vaccine is indicated (first dose or second dose). MMRV should not be administered for the second dose of MMR or varicella except when both are indicated or if no MMR or varicella vaccine is available at the time the dose is indicated."

ACIP Vote on the Proposed VFC Resolution

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The following suggestions were made to refine the VFC resolution. A caveat should be added to the recommendation to use a single component. The language should clarify the higher varicella antigen content and the absence of data on MMRV. The general recommendations should be cited for the antibody table because this information includes more recent data in 2002.

Dr. Abramson called for a motion on the proposed VFC resolution. Dr. Campbell moved as follows: "ACIP approves the proposed VFC resolution. The motion was seconded by Ms. Stinchfield and **passed by a majority vote.** The disposition of the vote is as follows:

- **13 in favor:** Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Stinchfield, Womeodu.
- **2 with conflicts:** Poland, Treanor.
- **0 opposed**.

INFLUENZA VACCINE

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

Next Steps in Decreasing Influenza-Associated Morbidity and Mortality Through Annual Vaccination

Dr. Ban Allos, the Influenza Workgroup Chair, reviewed the current burden of influenza disease; summarized the existing influenza vaccination target groups; and described future options to expand the annual recommendations for influenza vaccination. Of the U.S. population, 5%-20% is infected with influenza each year with the highest rates of infection among children. Of >200,000 hospitalizations annually, most occur in persons >64 years of age. Hospitalization rates in children <2 years of age are similar to those among adults >65 years of age.

Influenza is the number one cause of vaccine-preventable disease in the United States. Of >36,000 deaths caused by influenza each year, >90% occur in adults >65 years of age. A study published in 1996 showed that the highest illness rates occur in children 5-14 years of age (Sullivan). A study published in 2004 showed that the greatest rates of hospitalization per 100,000 person years occur in persons >65 years of age and children <5 years of age (Thompson). The large majority of influenza-associated deaths occur in persons >65 years of age.

ACIP currently recommends annual vaccination for persons at increased risk of severe complications from influenza and those who live with or care for these persons. Routine vaccination is also permissive for the general population. The groups recommended for annual influenza vaccination increased from ~80 million persons in 1964 to 218 million persons in 2006. The influenza vaccination target groups now represent 73% of the total U.S. population and include:

- Children aged 24–59 months;
- Children and adolescents (aged 6 months-18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reye's syndrome after influenza virus infection;
- Women who will be pregnant during the influenza season;
- Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma (hypertension is not considered a high-risk condition);
- Adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus),

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renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by HIV);

- Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- Persons aged 50-64 years;
- Persons aged ≥65 years;
- Healthy household contacts and caregivers of children 0-59 months of age and persons at high risk for severe complications from influenza; and
- HCWs.

The limitations of the current risk-based strategy include confusing recommendations. The 12 different influenza vaccination target groups are difficult for both healthcare providers and patients to remember. The complicated system may play a role in low coverage levels among the target groups. NIS data showed that 7.4% of children 6-23 months of age received ≥1 influenza vaccine doses and 4.4% were fully vaccinated during the 2002-2003 influenza season. Vaccination levels in this population during the 2003-2004 influenza season were 17.5% with ≥1 influenza vaccine doses and 8.4% with full vaccination (the second year of ACIP encouragement). Self-reported data from the National Health Interview Survey showed that coverage levels in most adult target groups between 1989-2004 were far below the *Healthy People 2010* goal for influenza vaccination.

Several options can be considered to further reduce the burden of influenza. Vaccination levels can be increased in the existing target groups by improving public awareness, provider education and practices. A universal vaccination policy could be incrementally established with children and more generally with adults. Participants of an October 2005 workshop agreed that incremental steps should be taken toward an annual universal influenza vaccination policy beginning with children first because this population accounts for the highest infection and transmission rates. Moreover, vaccination of children is likely to be easier and more feasible compared to other target groups.

A study published in 1969 showed that the influenza infection rate did not peak in adults in a town with vaccinated schoolchildren in grades K-12 compared to a nearby town with no vaccination of the same population (Monto, *et al.*). However, several critical factors must be assessed before changing the current recommendations and advancing toward a universal policy. New surveillance systems should be developed or existing systems should be enhanced to better evaluate influenza illness. Vaccine effectiveness and safety should be monitored. The feasibility of annually vaccinating school-aged children and working adults should be assessed. An adequate vaccine supply must be assured.

The ACIP Influenza Working Group has developed a potential time frame to modify the annual influenza vaccine recommendations. Critical issues could be assessed and addressed from 2006-2008. An expansion of the recommendation to include all school-aged children 5-18 years could be considered in 2008-2009. The recommendations could be broadened to include household contacts and caregivers of school-aged children from 2010-2011. Universal vaccination could be recommended if necessary and the recommendations could be extended to persons 18-49 years of age from 2012-2013.

During the discussion following the presentation, Dr. Allos noted that efforts are also underway to increase influenza vaccination of HCWs. HCWs are now required specifically to decline vaccination. The Joint Commission on the Accreditation of Healthcare Organizations reached agreement on a new policy for hospitals to collect, report and publish rates of HCW vaccination in local newspapers.

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Several ACIP members provided input on the workgroup's proposed timeline for universal vaccination. Dr. Morse's position was that the interval to the target date of 2013 date could be shortened if the seasonal strategy was linked to the pandemic influenza plan. He did not believe a universal policy would place a tremendous burden on the vaccine supply because the current recommendations now cover 73% of the total U.S. population. Dr. Hull pointed out that universal vaccination would essentially be reached in 2011 after the recommendations were expanded to include household contacts and caregivers of school-aged children.

Dr. Poland's position was that the proposed timeline would not decrease confusion among providers and the public about influenza vaccination. He also found the interval to the 2013 target date to be unacceptably lengthy, because a large segment of the U.S. population will continue to become infected with and die from influenza before that time. Dr. Poland expressed concern that the influenza morbidity and mortality would result in billions of dollars in direct and indirect costs prior to 2013. Moreover, the workgroup's proposed timeline is risk-based and no evidence has been produced to support these types of programs. A faster timeline to a universal policy would actually contribute to an expansion in vaccine supply.

Dr. Poland urged the ACIP to minimize the focus on vaccine safety because this approach decreases confidence in and unnecessarily raises concerns about the influenza vaccine. He noted that a five-year pilot study of a universal policy in Ontario, Canada resulted in a doubling of vaccination levels in high-risk groups and the development of vaccine distribution and administration programs to increase pandemic preparedness. Dr. Poland supported a universal policy at this time with an incremental approach to emphasize special risk groups.

Dr. Bruce Gellin, the ACIP *ex officio* representative for the National Vaccine Program Office (NVPO), announced that the HHS Secretary recently awarded >$1 billion to five companies to accelerate the development of a cell culture vaccine, licensure of additional seasonal influenza vaccines in the United States, and construction of additional manufacturing facilities in the United States. The companies are in various stages of development, but HHS expects to see initial progress in 2008. HHS also recently awarded ~$100 million a year to sanofi pasteur to accelerate cell culture vaccine production. The ultimate goal of these awards is to provide sufficient pandemic vaccine for the entire country. Consideration can then be given to an adequate seasonal vaccine supply for the entire country after pandemic needs are addressed.

Dr. Carol Baker, the AAP liaison, supported universal implementation for all existing target groups because a universal immunization policy still would not assure vaccination of pregnant women and other high-risk populations. She encouraged the ACIP to deliver strong messages about universal implementation. Moreover, the public, physicians and all other components of the healthcare community should be informed that solid data have been produced that support the administration of annual vaccination to the target populations. Dr. Kristin Nichol, the VA *ex officio* representative, joined the meeting by conference call and pointed out that four key strategies have demonstrated effectiveness in enhancing immunization levels among HCWs: convenient access, free vaccine, education, and leadership by healthcare institution management.

Mr. Steve Allred, of Get A Flu Shot.com, listed several reasons for ACIP to quickly advance toward universal immunization. Manufacturers will reduce production if vaccine is not utilized. The longest period of time that has passed between pandemics in the last century has been 39 years. The 1968 Hong Kong influenza outbreak was the last pandemic. Restrictions placed on vaccine during a shortage result in persons in high-risk groups declining vaccination. Mr. Allred emphasized that influenza morbidity and mortality rates will remain high if ACIP delays recommending universal vaccination.

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Mr. John Vittas and Mr. Gary Stein, of Families Fighting Flu (FFF), lost a grandchild and child, respectively, to influenza. Both children were >23 months of age and were outside of ACIP's influenza vaccination target group of children 6-23 months of age. FFF deeply thanks ACIP for its February 2006 recommendation to expand the influenza vaccination target groups to include children 24-59 months of age. This recommendation will play a critical role in protecting children and supporting FFF's mission to reduce childhood influenza deaths and raise awareness about the importance of all children receiving influenza vaccine. FFF hopes that ACIP will further expand the influenza vaccination target groups to include all children in the near future.

Dr. Abramson announced that ACIP would not vote on the workgroup's proposed timeline. He advised the members to provide Dr. Allos with additional comments and feedback by e-mail.

One Versus Two Doses of Trivalent Inactivated Influenza Vaccine (TIV) in Influenza Vaccine-Naïve Children

Dr. Neuzil summarized recent data on one versus two TIV doses in influenza vaccine-naïve children. Immunogenicity data on children <2 years of age are limited, but data on children 2-6 years of age with no detectable hemagglutination inhibiting antibody levels show that this population has lower responses than children with detectable levels. As a result, pre-existing immunity is significant. Data also demonstrate that antibody responses to influenza type B strains resulting from vaccination or infection can be substantially lower compared to responses after exposure to influenza type A strains due to vaccination or infection.

A study was published in 2005 to gather more immunogenicity data (Englund). In year 1 of the study, children were enrolled in the spring of 2003 and randomized to either receive the 2002-2003 TIV or defer vaccination until the fall. The cohort was given one dose with the new season's vaccine in the fall, but the antigen content was the same as the previous year. Antibody responses after two spring/fall doses and two fall doses were compared. The year 1 results showed that immunogenicity after two doses was superior to one dose. Early administration of the first dose was not inferior to routine administration of the first dose in years when antigens do not change.

The 2003-2004 TIV formulation was not changed in year 2 of the study, but new H3N2 and B antigens were added to the 2004-2005 TIV formulation. Three studies were conducted in year 2 with the change in vaccine antigens. Study 1 is in press and randomized children 6-23 months of age to receive the first dose in the spring versus the first dose in the fall (Walter, *et al.*). Antibody responses were assessed after two doses. The conclusions of study 1 in year 2 are as follows: Immunogenicity after two doses was superior to one dose. Post-dose 2 antibody responses were similar between early and standard dose schedules when the antigen did not change. Priming was less robust with the drifted H3N2 antigen, but ~70% of children still had protective antibody levels. The major change in the B antigen resulted in a markedly decreased response after two doses of vaccine.

Study 2 is in press and was an observational, non-randomized and open-label trial comparing children 6-23 months of age who received one dose in both the prior and current fall seasons and children who received two doses in the current fall season (Englund). The group 1 children were significantly older than those in group 2. The conclusions of study 2 in year 2 are as follows. Post-dose 2 antibody responses were similar regardless of whether the child received one dose in the prior and current fall seasons or two doses in the current fall season when the antigen did not change. The drifted H3N2 priming made no difference. The major change in the B antigen resulted in a markedly decreased response among children who received one dose in the prior and current fall seasons versus those who received two doses in the current fall season.

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Study 3 is in press and was a prospective open-label trial of one versus two TIV doses in the fall among vaccine-naïve children 5-8 years of age (Neuzil). All children in the study received two doses of vaccine. Blood was drawn pre-dose 1, post-dose 1 and post-dose 2. The conclusions of study 3 in year 2 are as follows. A two-dose regimen in children 5-8 years of age was superior to a one-dose regimen when the response to all antigens was considered. Pre-existing antibody was the strongest predictor of antibody response. Even after two doses, >33% of children in the study did not have protective responses to the B antigen.

Two published studies showed limited correlation between antibody response data and clinical data in children. A 1990 study administered a single TIV dose to children 6-9 years of age and demonstrated protection against subsequent laboratory-confirmed influenza B infection (Gruber, *et al.*). The protection was correlated with influenza B neutralizing antibody response. A 2005 retrospective study with 5,000 children 6-23 months of age estimated vaccine effectiveness of 49% against clinical pneumonia and influenza-like illness (ILI) among children who received two TIV doses (Ritzwoller). No effectiveness was seen among children who received one dose. The study did not produce immunogenicity data.

A recent study that analyzed influenza vaccine effectiveness in the 2003-2004 season is in press (Allison, *et al.*). The cohort of children 6-21 months was stratified by those unvaccinated, partially vaccinated with one dose, and fully vaccinated with two doses in the same season or one dose in each season. Outpatient visits for ILI and pneumonia or influenza served as the primary outcomes. The stratified analysis indicated effectiveness against ILI of 82% for children who received two doses in the same year and 62% for children who received two doses in different years.

Overall, one year of data from the recent studies suggest that the current recommendation for children to receive one dose in the current year if one dose was obtained the previous year provides adequate protection for influenza A and inferior protection for influenza B. However, protection for influenza B may be inferior even after two doses and in older age groups. A determination has still not been made on whether current efforts to measure influenza B are adequate.

In response to a question raised by Dr. Treanor, Dr. Neuzil said she would follow-up to determine whether a sufficient number of children 6-23 months of age were enrolled in the studies to identify the role of pre-existing immunity in this age group. She acknowledged that this analysis was made only in older children 5-8 years of age.

Options for Children Who Were Not Fully Vaccinated Initially

Dr. Nicole Smith, of CDC, presented options for ACIP to consider in vaccinating children <9 years of age who received only one dose of influenza vaccine in the first season that they are vaccinated. ACIP's current recommendation of two doses of influenza vaccine for children <9 years of age who have not been previously vaccinated is consistent with the evidence. However, compliance with this guidance is a continual challenge. COID is considering changing AAP's guidance to recommend two influenza vaccine doses during the subsequent season for children who should have received two doses during an initial season, but received only one dose.

The Influenza Working Group proposed that ACIP consider whether the data are sufficient to justify a change in ACIP's recommendation. The workgroup also requested feedback on strategies to address the potential discrepancy between the ACIP and AAP recommendations if ACIP does not approve a change in its current guidance and AAP changes its recommendations. CDC's influenza statement for the 2006-2007 season recommends only one TIV dose the following season if a child 6 months-<9 years of age

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who received influenza vaccine the first time did not receive a second dose of vaccine within the same season. CDC's new influenza statement, which provides information for both TIV and the live attenuated influenza vaccine (LAIV), can be viewed at www.cdc.gov/flu.

The workgroup identified the advantages and disadvantages of two options to facilitate ACIP's discussion and vote. Option 1 would not change the current recommendation. On the one hand, the limitations of existing data would be acknowledged, the complexity would be decreased, and the challenges of providing two doses to an additional group of vaccine-naïve children would not need to be addressed. On the other hand, the current recommendation may result in lost opportunities to better protect children against influenza. ACIP and AAP guidance may be inconsistent.

Option 2 would change the recommendation for children <9 years of age who were not fully vaccinated initially to receive two doses in the subsequent season. On the one hand, an opportunity would be provided to better protect children against influenza. The potential for inconsistency between ACIP and AAP recommendations would be minimized. On the other hand, the change would not fully acknowledge the limitations of existing data, particularly the absence of direct evidence on the need to provide two doses in the subsequent vaccination season. There was also a concern that providers may be less inclined to ensure provision of two doses during the initial vaccination season. The demand on the currently limited vaccine supply for young children may increase depending upon the timing of implementation.

ACIP Vote on Options for Children Who Were Not Fully Vaccinated Initially

Dr. Allos listed several reasons for her opposition to changing the current recommendation at this time. Complexities and difficulties associated with influenza vaccination may increase for pediatricians and parents. ACIP has not had an opportunity to review, evaluate and identify potential flaws in the unpublished studies. AAP has not yet reached a definite decision on its influenza vaccination recommendations for the target population.

Dr. Hull was concerned that a change in the current recommendation would worsen the scheduled vaccine shortage for young children in upcoming influenza season. Moreover, no evidence has been produced to demonstrate adequate levels of protection for children who received two doses in one year and one dose the following year if a major change in the vaccine occurred. Dr. Treanor supported a conservative approach in which the current recommendation would be maintained while more data are collected to support a change.

In response to a question raised by Dr. Pickering, Dr. Neuzil clarified that the major difference between children 6-23 months and 5-8 years of age in the recent studies was that one dose was sufficient by the age of five years with a single antigen vaccine and the H3N2 strain. However, both age groups appeared to need two doses to obtain adequate immunogenicity.

Dr. Keith Powell, the AAP liaison, summarized COID's conclusions based on its review of the recent studies. Two doses are superior to one dose for children. The administration of one dose in two different seasons is not optimal with changes in antigen. "Fully vaccinated" should be simply defined as two doses in one year due to the different variables that must be considered. COID agreed that children will be fully vaccinated by changing the AAP recommendation to two doses in the same season and one dose the following season. Dr. Powell expected AAP to adopt COID's consensus opinion during its meeting in the fall of 2006.

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Dr. Michael Decker, of sanofi pasteur, pointed out that neither of the two options addresses the relevant question of being primed for the currently circulating strain. He supported a year- and strain-specific recommendation, but he realized that this strategy would be virtually impossible to implement. Dr. Jonathan Temte, the AAFP liaison, emphasized the critical need for ACIP to issue solid guidance that balances vaccine supply issues and the feasibility of clinicians to implement the recommendation. He noted that compliance with ACIP's recommendations would decrease among family physicians if the guidance changes each year.

Dr. Melinda Wharton, of CDC, reminded ACIP that the pre-booking process typically occurs before decisions are made about the strain selection. An unfeasible situation would occur if pediatricians and family physicians who vaccinate children need to place vaccine orders that would depend on knowing what strain selection changes were going to occur without that knowledge being available. Dr. Kathy Coelingh, of MedImmune, announced that MedImmune published LAIV data on children <9 years of age. Children 5-7 years of age in a pediatric trial were randomized to a single dose to address the issue of whether one or two doses are actually needed in the same season. The MedImmune data showed 100% efficacy with a single dose. The efficacy rate was also 100% when the same cohort was randomized to the same treatment regimen of a single dose the following year and the strain drifted.

Dr. Abramson called for a motion on the options for children who were not fully vaccinated initially. Dr. Hull moved as follows: "ACIP accepts option 1 to not change the current recommendation due to the lack of data to make a decision at this time." The motion was seconded by Dr. Allos and **unanimously approved by all 15 voting members**: Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Poland, Stinchfield, Treanor, Womeodu.

Dr. Abramson committed to obtaining a ruling on Dr. Treanor's potential conflict in which the University of Rochester is conducting a study for ID Biomedical and this company is owned by GlaxoSmithKline (GSK). He also confirmed that ACIP would revisit its vote if AAP issues a different recommendation.

Options for Tiered Use of TIV

Dr. Smith presented options for ACIP to consider in the tiered use of TIV in the event of a vaccine shortage or delay. Disruptions in vaccine production or distribution have occurred during recent seasons. The total influenza vaccine supply for the 2006-2007 season is expected to be ~100 million doses. CDC's new influenza statement advises providers to take advantage of the additional doses by developing plans to expand outreach, enhance infrastructure and vaccinate more individuals than the previous year. Providers are also encouraged to create contingency plans for the timing and prioritization of influenza vaccine in the event of a delay or reduction in supply.

In February 2006, ACIP approved annual vaccination for children 24-59 months of age, their household contacts and out-of-home caregivers. Due to the timing of this recommendation, some providers may not have sufficient vaccine for patients <4 years of age. The ACIP/CDC 2005-2006 influenza vaccine prioritization statement recommended that state and local health officials and vaccination providers prioritize persons in group 1A before all other groups on rare occasions when local vaccine supply is extremely limited. The statement also recommended that persons in groups 1A, 1B and 1C be considered equivalent and simultaneously vaccinated in all other vaccine shortfall situations.

Priority groups for influenza vaccine were established to protect high-risk and healthy persons and prevent deaths, hospitalizations and other serious complications associated with influenza. The current prioritization scheme was published in the summer of 2005 and includes two tiers and three sub-tiers for the influenza vaccination target groups. Tiers 1A and 1B are designed to prevent deaths and

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hospitalizations, respectively. Tier 1C is designed to protect high-risk populations with a "cocooning" approach by vaccinating household contacts and caregivers of high-risk persons. Tier 2 is designed to further implement the cocooning approach and also protect healthy persons. Tier 3 is designed to protect healthy persons.

The Influenza Working Group identified the advantages and disadvantages of four key questions to facilitate ACIP's discussion. First, should the tiers be renumbered with a new prioritization scheme of tiers only and no sub-tiers? On the one hand, elimination of the sub-tiers would more clearly express prioritization across different groups. On the other hand, the number of tiers would increase to five.

Second, should prioritization be established between tiers if the sub-tiers are retained? The following language could replace the current text if ACIP reaches agreement on this option: "Providers should consider prioritizing group 1A before group 1B and group 1B before group 1C on rare occasions when local vaccine supply is extremely limited." On the one hand, "should consider" would allow for discretion at the local level. Prioritization between sub-tiers would also acknowledge that a limited supply may not permit equal vaccination of groups 1B and 1C. On the other hand, vaccination of group 1B would be given a higher priority than group 1C.

Third, should healthy persons 5-64 years of age be included as one priority group or should adults 50-64 years of age continue to serve as a separate group? The alternative tier 3 could be "persons 2-64 years of age without high-risk conditions" if ACIP reaches agreement on this option. On the one hand, the creation of one priority group of adults 50-64 years of age would recognize that healthy persons should have a lower priority for receiving vaccine in the event of a shortage. The priority groups would be simplified by eliminating the need to distinguish between healthy persons in different age groups with the exception of children <5 years of age. On the other hand, the current focus on the need to vaccinate adults 50-64 years of age would be eliminated.

Fourth, what approaches should be taken to include children 24-59 months of age in the priority group table? CDC's new influenza statement for the 2006-2007 season emphasizes the need to prevent emergency department and outpatient visits in addition to deaths and hospitalizations.

The Working Group suggested four specific options for ACIP's consideration. Option 1 would change tier 1B with the addition of "children 6-59 months of age" and change tier 3 to "persons 5-64 years of age without high-risk conditions." On the one hand, option 1 would be consistent with the paradigm shift that the burden of illness includes emergency department and outpatient visits in addition to deaths and hospitalizations. Healthy persons 5-64 years of age would be grouped in one tier. On the other hand, the relative prioritization of children 6-23 months versus children 24-59 months of age would not be addressed.

Option 2 would change tier 1C with the addition of "children 24-59 months of age" and change tier 3 to "persons 5-64 years of age without high-risk conditions." On the one hand, option 2 would group healthy persons 5-64 years of age in one tier and address the relative prioritization of children 6-23 months versus children 24-59 months of age. On the other hand, a sub-tier would be created that combines direct prevention of the burden of disease and indirect protection through vaccination of caregivers.

Option 3 would place "children 24-59 months of age" in a separate tier 1C and change tier 3 to "persons 5-64 years of age without high-risk conditions." Household contacts and out-of-home caregivers of children <6 months of age and HCWs would be placed in a new tier 1D. On the one hand, option 3 would group healthy persons 5-64 years of age in one tier and address the relative prioritization of children 6-23 months versus children 24-59 months of age. On the other hand, an additional sub-tier would be established under tier 1.

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Option 4 would place "children 24-59 months of age" in a separate tier 1C. Household contacts and out-of-home caregivers of children <6 months of age and HCWs would be placed in a new tier 2A. Household contacts of children and adults at increased risk for influenza-related complications would be placed in a new tier 2B. Tier 3 would be changed to "persons 5-64 years of age without high-risk conditions." On the one hand, option 4 would clearly identify three distinct tiers based on the different rationale; group healthy persons 5-64 years of age in one tier; and address the relative prioritization of children 6-23 months versus children 24-59 months of age. On the other hand, an additional sub-tier would be established under tier 2.

ACIP Vote on Options for Tiered Use of TIV

Dr. Allos noted that the confusing and complicated tiering strategy does not contribute to reducing the burden of disease due to influenza. She hoped that ACIP would recommend elimination of the entire system in the near future. In the interim, however, she supported actions to simplify the priority group table and make the recommendations more feasible. Dr. Allos suggested that children 24-59 months and children 6-23 months of age be placed in the same tier. Prioritization between tiers should not be established.

Dr. Morita reminded ACIP of the importance of the tiering strategy because the priority group table was developed for vaccine shortages rather than routine use. She was in favor of separating children 6-23 months and those 24-59 months of age due to the critical need to distinguish among death, hospitalization, and emergency department and outpatient visits during a vaccine shortage. She also supported grouping healthy persons 5-64 years of age in one tier.

Drs. Campbell and Marcuse expressed concerns about the low prioritization of household contacts and caregivers of infants <6 months of age. Although solid evidence has not been produced to date to demonstrate that the cocooning approach actually protects this group, it was suggested that household contacts and out-of-home caregivers of this population also be placed in tier 1B with pregnant women. Infants <6 months of age are at risk for severe disease and should be prioritized.

Dr. Poland was in favor of simplifying the priority group table by maintaining tiers 2 and 3 and combining tiers 1A, 1B and 1C because a vaccine supply of <50 million doses is not likely. Sub-tiers could be developed and implemented for worst-case scenarios. He also pointed out the critical need for CDC to clearly define "shortage" because the term is interpreted differently at the local level by institutions, clinicians and cities.

Dr. Finger supported an all-numbered tiering system with no sub-tiers that would clearly indicate cutoffs. Dr. Lieu was also in favor of renumbering the tiers with no sub-tiers and placing children 24-59 months and 6-23 months of age in separate tiers. Dr. Treanor's position was that no changes should be made to the current tiering system other than placing the new influenza vaccination target group of children 24-59 months of age into a tier.

Dr. Temte reported that he converted the pandemic tiering system into electronic medical records for use in actual clinical practice and found the entire exercise to be simple, feasible and helpful. He acknowledged that the tiering system should depend on the epidemiology of influenza. Dr. Decker urged ACIP to prioritize children 6-59 months of age because the tiering system has the most relevance for this group.

Mr. Allred encouraged ACIP to place HCWs in tier 1A rather than 1C because a strong healthcare infrastructure is required to care for all patients with health issues. HCWs have the greatest number of contacts with high-risk persons and are the most likely group to spread infection. Dr. Poland agreed with

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this comment because data from two randomized trials showed a decrease in influenza morbidity and mortality when HCWs rather than residents of long-term care facilities were vaccinated. Dr. Wallace pointed out that regardless of ACIP's vote, CDC will need to issue guidance to providers who do not have an adequate vaccine supply for children three years of age.

Dr. Abramson called for a motion on the options for tiered use of TIV. Dr. Treanor moved as follows: "ACIP will retain the existing tiering system, but will add the new group of children 24-59 months of age to tier 1C." Dr. Gilsdorf seconded the motion. Dr. Abramson clarified that persons in tiers 1A, B and C would be treated equally unless a severe shortage occurs. Dr. Wharton requested a change to the language in tier 3 to be consistent with the motion, whereby the priority group in tier 3 would be persons 5-49 years of age without high-risk conditions. **The motion passed by a majority vote.** The disposition of the vote is as follows:

- **12 in favor:** Abramson, Allos, Beck, Campbell, Gilsdorf, Hull, Lieu, Morita, Morse, Stinchfield, Treanor, Womeodu.
- **3 opposed:** Finger, Marcuse, Poland.
- **0 abstentions**.

ISO Update

Dr. Robert Davis, the ISO Director, covered the following areas in his report. CDC is committed to building a robust vaccine safety activity to maintain pace with the increasing number, combinations and complexity of recommended immunizations. ISO was moved from NIP to the CDC Office of the Director, Office of the Chief Science Officer in 2005. Several reasons support this transition. Immunizations impact nearly all Americans. Public confidence in the benefit and safety of vaccinations is essential to the success of the life-saving immunization program. Confidence in immunizations can only be sustained through scientific quality, objective recommendations, and the absence of perceived conflicts within and outside of CDC.

CDC took several actions before relocating ISO from NIP. Internal and external input was obtained from health professionals, scientists, policymakers and parents. A Blue Ribbon Panel of health and safety science professionals was convened in 2004 to provide an independent assessment of ISO's activities. Listening meetings were held in communities throughout the country to obtain additional feedback from parents and concerned citizens. ISO is now committed to partnering with other HHS agencies to define priorities and an agenda for vaccine safety research and safety monitoring in the United States. ISO will continue to communicate with concerned parents, public officials and healthcare professionals to emphasize the transparency of CDC's science and research on immunization safety issues.

ISO is organized into four major components. First, VAERS is an early warning passive surveillance system that detects potential problems related to vaccines. ISO uses VAERS to identify signals and generate new hypotheses. Second, VSD is a collaborative network of eight MCOs that collect comprehensive medical and immunization histories on >7.5 million persons. ISO is currently conducting >24 vaccine safety studies under VSD and has completed >100 vaccine safety studies under the project to date. ISO uses VSD to test hypotheses.

Third, the Clinical Immunization Safety Assessment (CISA) Network is designed to conduct in-depth clinical investigations of persons with unusual or severe vaccine AEs. ISO uses the CISA Network to identify biological underpinnings of vaccine AEs and create re-vaccination protocols. Fourth, the Brighton Collaboration is a global initiative to standardize case definitions and provide a common vocabulary for vaccine safety research. ISO uses the Brighton Collaboration to support its other three components.

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Two new policy and communications functions were established in ISO to streamline the presentation of scientific data and ensure that consistent messages are delivered.

ISO's recent successes with vaccine AEs and vaccine safety are highlighted as follows. The large increased risk for intussusception following rotavirus vaccination was rapidly identified. The risk of AEs after the second MMR dose was found to be greater at 10-12 than 4-6 years of age. No increased risk for multiple sclerosis was seen after administration of the HepB vaccine. Acellular pertussis vaccine was found to be safer than whole cell pertussis vaccine. No increased risk for inflammatory bowel disease was found after administration of MMR vaccine. No increased risk for type 1 diabetes was seen after vaccination.

ISO will face significant challenges in the future. The rotavirus, HPV, MMRV, Menactra®, zoster, and tetanus, diphtheria and pertussis (Tdap) vaccines will strain capacity to provide active and complete surveillance, assure the safety of vaccines and respond to new signals. Coincidental or causal relationships will need to be systematically analyzed. The study of Guillain Barré Syndrome (GBS), anaphylaxis and other rare AEs will require a larger infrastructure.

Increased focus will be placed on adolescents and adults in the near future, particularly with meningococcal, varicella and HPV vaccines. These vaccines will be administered to groups with health profiles that are different than those of traditional populations of relatively healthy persons 0-6 years of age. Vaccines will be administered in large scale to adolescents, young adults and older adults with a higher increased risk of background disease. Ongoing efforts will need to be made to maintain and strengthen public perception regarding vaccine safety.

ISO will take advantage of key opportunities and fulfill certain obligations to address these challenges. NVPO will establish an external advisory panel with diverse stakeholders to obtain broad input on ISO's annual research agenda. Active surveillance of new vaccines will be performed through weekly VSD updates and real-time assessments of vaccine safety. The vaccine safety research agenda will be extended to the genomics field to increase capacity to identify persons at increased risk and obtain more knowledge on populations and subgroups at increased risk for vaccine AEs and vaccine failure.

GBS following Menactra® vaccination is one of ISO's most recent and high-profile challenges. The distribution of *Neisseria meningitidis* cases from 1991-2005 showed a recent decrease in overall incidence, but an increase in disease in adolescents and young adults. Menactra® was introduced in January 2005 and licensed for use in persons 11-15 years of age with the following expectations. Of all meningococcal disease among persons ≥11 years of age in the United States caused by serogroups C, Y or W-135, Menactra® would cover 75% of cases. The number of cases prevented would be 2.7-3/100,000 doses and 4.5-5/100,000 doses if freshmen and freshmen living in dormitories, respectively, were vaccinated.

An April 2006 *MMWR* article reported eight confirmed cases within six weeks post-vaccination and three additional cases with onset >100 days post-vaccination that were not believed to be associated with Menactra®. The total number of reported cases was equal to that expected by chance alone. The *MMWR* article reinforced the recommendations to administer the vaccine to indicated persons and report GBS cases that occurred in temporal proximity to vaccination. VAERS data as of May 31, 2006 detected ten GBS confirmed cases within six weeks after administration of Menactra®, including two new cases with onsets of two and ten days, respectively, post-vaccination.

ISO analyzed data from the 2000-2003 Healthcare Cost and Utilization Project national inpatient sample of GBS cases. A statistically increased risk for GBS following Menactra® vaccination was not seen with the ten new cases. The cluster was possibly due to a large number of vaccine doses administered within the United States during the summer of 2005, but a true causal relationship could not be ruled out. ISO

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will use the VSD RCA to analyze all children who are given Menactra® each week at eight health maintenance organizations and follow all vaccinated persons for 42 days to identify any potential GBS cases. As of June 2006, data from VSD and United Health Care did not detect any GBS cases from 140,000 total Menactra® doses administered.

ISO will conduct a new project under VSD to determine whether an association exists between GBS and Menactra® and quantify the vaccine attributable risk if a relationship is detected. The administration of Menactra® and the risk for GBS will be assessed in adolescents from the period March 1, 2005-August 31, 2008. The project will include a cohort study with data from all VSD sites and several MCOs to confirm all GBS cases and compare GBS rates between vaccinated and unvaccinated persons. A case-control study will be conducted with the same cases and controls as the cohort study if a signal is detected. Medical record reviews and patient interviews will be performed to identify potential confounding variables.

Public Comment Period

Ms. Lyn Redwood, President of Sensible Action for Ending Mercury-Induced Neurological Disorders, made the following comments for ACIP's consideration. She was deeply concerned about ACIP's recent recommendations for pregnant women, infants and children to receive influenza vaccine. She distributed a letter to ACIP in which 15 national organizations are asking ACIP to state a preference for thimerosal-free influenza vaccines to be administered to pregnant women, infants and children as recommended in the October 2001 Institute of Medicine (IOM) report.

Ms. Redwood cited several published studies and listed other reasons to support this request. Adequate safety studies were not conducted prior to marketing thimerosal as a vaccine preservative. The history of thimerosal as a preservative documents its toxicity and ineffectiveness. AEs from mercury exposure have been documented following administration of thimerosal-containing vaccines to infants. Exposure to vaccine-level thimerosal crosses the blood brain barrier and results in significant deposition of mercury in the brain.

ACIP's policy of not stating a preference for thimerosal-free vaccines is not current with international and state practices in which four countries and seven U.S. states have banned thimerosal-containing vaccines. ACIP's policy will also minimize provider and public confidence in NVPO. Ms. Redwood urged ACIP to place a discussion on thimerosal-free vaccines for pregnant women, infants and children on its October 2006 meeting agenda. She announced that her son received 237.5 µg of ethyl mercury in his infant vaccines.

Dr. Julia Whiting, a practicing emergency physician in Charlottesville, Virginia, made the following comments for ACIP's consideration. A large segment of the U.S. population does not trust the influenza vaccine for a variety of reasons. Patients are typically shocked upon learning that vaccines contain mercury. CDC is in jeopardy of losing the trust of the entire population as public awareness about mercury continues to increase. Most notably, CDC data show that only 34% of physicians and nurses receive annual influenza vaccination. Dr. Whiting urged ACIP to revisit the thimerosal issue in NVPO as a matter of public trust.

Ms. Lujene Clark made the following comments for ACIP's consideration. As the parent of a child who experienced severe neurological, neurodevelopmental and neurobehavioral symptoms after receiving two influenza shots in 2002, she expressed concern about mercury in vaccines. However, she continues to firmly believe in the importance of immunization. She described several recent events that are contributing to the reduction in public trust of NIP.

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During the current meeting, one ACIP member expressed a wish to "take the concern about vaccine safety off the table." Another member publicly disclosed a potential financial conflict of interest with the influenza vaccine, but still voted on this issue. Of seven missions outlined in NIP's policy, mission statement and strategic blueprint for success, "vaccine safety" is number 6 only ahead of a "happy work environment." Ms. Clark emphasized that NIP's mission should be to protect children from horrible diseases rather than protecting the program. Parents will not trust NIP until children and science are placed before profit and politics. NIP will fail unless ACIP objectively views its behavior and prioritizes children.

Ms. Karen Beauvais made the following comments for ACIP's consideration. She is the mother of a son six years of age who received 277 times more than the amount of mercury allowed by the U.S. Environmental Protection Agency (EPA) during his catch-up vaccinations. He virtually discontinued speaking after being immunized with double doses of mercury-containing vaccines at 15 months of age. Her son does not produce a sufficient amount of glutathione to excrete mercury contained in vaccines due to his extremely low cysteine level and deficient and improperly functioning immune system.

Ms. Beauvais is extremely proud that her son recently completed kindergarten and is now learning to read. On behalf of her son and other affected children, however, she implored ACIP to recommend the ban of mercury from vaccines because less harmful preservatives can be used.

Ms. Patti Hawkins made the following comments for ACIP's consideration. She is the mother of a son 21 years of age who was diagnosed with autism. The diagnosis is extremely perplexing because the medical literature states that autistic symptoms must manifest by three years of age, but her son showed no symptoms of autism until 15 years of age after receiving four different booster shots with thimerosal-containing vaccines on the same day. Prior to this time, her son met or exceeded developmental milestones for children in terms of academics, sports and social activities. After the booster shots, he virtually discontinued speaking and his academic performance deteriorated.

A recent brain scan and a battery of neurological, psychiatric and medical tests showed that Ms. Hawkins' son is mercury toxic and has a metabolic disorder and traumatic brain injury. She implored ACIP to recommend the ban of thimerosal from vaccines because no studies have been conducted to demonstrate the safety of this preservative.

With no further discussion or business brought before ACIP, Dr. Abramson recessed the meeting at 6:18 p.m. on June 29, 2006.

Update on Menactra® Supply and Prioritization

Dr. Abramson reconvened the ACIP meeting at 8:04 a.m. on June 30, 2006 and yielded the floor to the first presenter.

Dr. Wallace reported that from January-May 2005, FDA licensed Menactra®; ACIP adopted a recommendation and VFC resolution for use of the vaccine; CDC secured a contract to provide the vaccine to grantees; and recommendations were published in the *MMWR.* ACIP recommended vaccination for children 11-12 years of age during the routine visit, previously unvaccinated adolescents at high school entry, and college freshmen living in dorms and other populations at increased risk of disease.

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Due to the initial high demand placed on the vaccine by college freshmen in the summer of 2005, the manufacturers instituted order limits, back orders developed, and CDC emphasized the current recommendations. Sanofi pasteur compiled insurance claim data through August 20, 2005 that showed Menactra® was preferentially administered to persons 18 years of age compared to other adolescent age groups where vaccine use was equally distributed. Insurance claim data through March 26, 2006 showed that other age groups caught-up to persons 18 years of age, but emphasis was still not being placed on the target groups of children 11-12 years of age and adolescents at high school entry.

CDC data on the first year of Menactra® distribution showed the popularity of and tremendous interest in the vaccine because more doses were administered by the private sector than the public sector. In year 1, ~4.2 million doses were distributed and complaints and concerns decreased in the fall and winter. The manufacturer projects production of ~6 million doses in year 2. However, the summer demand is expected to be higher than year 1 and approximately an equal number of doses during the summer are projected.

CDC convened a workgroup with representation by AAP, AAFP, ACHA, ACIP, FDA, sanofi pasteur and the Society for Adolescent Medicine (SAM) that recommended temporary deferment of vaccination for children 11-12 years of age due to the limited supply expected during the summer. The recommendations continue to prioritize adolescents at high school entry and college freshmen living in dorms who are at higher risk for disease as well as other high-risk groups. The notice was published in the *MMWR* on May 19, 2006.

CDC's lessons learned from previous supply issues emphasized the importance of open communications with stakeholders to markedly improve interventions. However, CDC acknowledges that the implementation of new vaccines and recommendations is increasingly complicated. Supply and demand are often unpredictable and responses need to be dynamic and transparent. CDC will continue to hold biweekly calls with the stakeholder workgroup to monitor supply and demand. Routine recommendations will be re-instituted after supply and demand issues improve. The use of Menactra® will be reevaluated in response to the interim recommendations.

Dr. Finger commended CDC for maintaining control of the Menactra® supply and prioritization issues. He did not interpret the current situation with adolescents 11-18 years of age as non-compliance with the recommendations due to the variation in ages upon high school and college entry. He viewed CDC's actions in response to these issues as successful. Dr. Amy Middleman, the SAM liaison, urged CDC to enhance the adolescent immunization platforms. This approach will result in stronger capacity to effect changes in more discrete packages in the future.

Dr. Abramson described three issues ACIP will need to consider and address in the future. First, pediatricians have sent letters to ACIP and AAP expressing concerns about an "ethical quandary" because Menactra® is not available to immunize children in the recommended target groups. Second, the public has unfairly blamed sanofi pasteur due to a misunderstanding about events that actually caused the limited vaccine supply. Third, ACIP's recommendations must be revisited by the ACIP Meningococcal Workgroup because FDA will most likely approve use of the vaccine for a lower age range. Dr. Marcuse agreed that the discrepancy between supply and demand in ACIP's recommendations has created a tremendous amount of anguish among parents and damaged ACIP's credibility.

Dr. Philip Hosbach, of sanofi pasteur, confirmed that FDA is currently considering the recommendation for use of Menactra® in children 2-10 years of age. FDA will most likely make a decision in the summer of 2006. In response to Dr. Katz, representatives for Emergent BioSolutions, Novartis Vaccines, sanofi pasteur and Wyeth Vaccines all confirmed that these manufacturers have active meningococcal vaccine programs, including vaccines against meningococcal B.

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Tdap VACCINE IN PREGNANT WOMEN

The series of presentations and ACIP's discussion and vote on the use of Tdap vaccine in pregnant women are set forth below.

Pertussis Workgroup Report

Dr. Dale Morse, the Pertussis Workgroup Chair, highlighted the workgroup's recent activities. The workgroup initiated its deliberations in June 2004; two Tdap vaccines were licensed in 2005; and ACIP adopted recommendations for the use of Tdap in adolescents, routine use in adults, a cocooning approach to protect infants by vaccinating adults around the infants, and use of Tdap in HCWs. The workgroup was charged with evaluating the safety and efficacy of Tdap during pregnancy and is now presenting draft recommendations for ACIP's consideration. The workgroup specifically focused on whether the administration of Tdap would provide passive antibody protection to the infant or interfere with the infant's antibody response to Tdap immunization.

The workgroup fulfilled its charge by obtaining expertise from 25 members representing ACIP, various federal agencies, and 16 consultants representing state health departments, academia and a diverse group of professional organizations. The members and consultants reflect a wealth of clinical experience, extensive backgrounds, and a strong interest in protecting the lives and health of pediatric and obstetric clients.

The workgroup systematically and scientifically reviewed the major issues related to the safety and efficacy of Tdap during pregnancy, but was challenged in reaching consensus. The subject matter is tremendously complex and the scientific evidence is limited. Individual opinions among the workgroup members ranged from no immunization during pregnancy to no restriction and the promotion of Tdap during pregnancy. Of the entire workgroup, approximately two-thirds supported a conservative approach and emphasized the need to gather additional scientific data, while approximately one-third favored a pragmatic strategy based on existing clinical knowledge and experience.

The workgroup has continued to work toward consensus and toward providing the best document possible for ACIP's consideration given the current levels of clinical knowledge and scientific uncertainty. Due to existing gaps in the scientific literature, the workgroup strongly urges funding of necessary research to facilitate the development of definitive and evidence-based guidance in the future.

Considerations for Tdap in Pregnant Women

Dr. Trudy Murphy, of CDC, outlined the rationale for considering Tdap in pregnant women; described concerns about interference with the infant immune response to DTaP by maternal antibody; presented alternatives to Tdap during pregnancy; and summarized results of the Pertussis Workgroup survey. The primary reason to consider Tdap in pregnant women is to prevent the morbidity of pertussis during pregnancy. Although the morbidity from pertussis is substantial at any age, studies limited to 1981 and 1993 reported no increase in morbidity or adverse outcomes from pertussis in pregnant women (MacLean and Beiter, respectively).

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Secondary reasons to consider Tdap in pregnant women are to decrease mother-to-infant transmission of pertussis in early life and to protect infants from pertussis through maternal antibodies passively transferred via the placenta. Mothers are the identified source of pertussis in 15%-20% of reported infant cases <6 months of age; the source is unknown for >55% of cases (Bisgard, *et al.*). The ability of maternal antibodies induced by Tdap to protect infants from pertussis in early life is unknown.

A study published in 1946 raised the possibility that infants might receive passive protection from maternal antibody (Cohen). For one year, this study followed a cohort of unvaccinated infants whose mothers were hyper-immunized with six doses of crude *B. pertussis* vaccine administered during the second trimester of pregnancy. The infants appeared to be protected for ~6 months. When routine infant and childhood vaccination was recommended in the late 1940s, vaccination of pregnant women to protect infants was abandoned because of concerns that maternal antibody would interfere with the infant's active immune response to DTP vaccination.

Interference with the infant response to DTP vaccines has been demonstrated in several studies (e.g., Van Savage and Englund, published in 1990 and 1995, respectively). Interference was found to occur at relatively low maternal antibody titers in women not vaccinated since childhood and after the infant had been immunized with three DTP doses. Effects for some antigens were larger when infants were vaccinated with whole cell pertussis rather than acellular pertussis vaccine, but variations were seen based on the type of pertussis antigen and type of acellular pertussis vaccine.

The significance of interference on infant protection is unknown, but maternal antibody titers are likely to be substantially higher after Tdap during pregnancy than in most women who have not received booster pertussis vaccination. No information in pregnant women vaccinated with Tdap is available. The Adult Pertussis Trial (APERT) published in 2004 examined pertussis antibody titers among 200 non-pregnant subjects 15-65 years of age who received either HepA or acellular pertussis vaccine that did not contain tetanus and diphtheria toxoids (Le). In the HepA vaccine group, mean titers of anti-pertussis toxins (anti-PT) were low during the 18-month follow-up period. In the pertussis vaccine group, titers of anti-PT peaked in the one-month post-vaccination period, dropped at six months and remained relatively stable above baseline for over one year. If the response to Tdap in pregnant women is similar, early protection of the infant by passive maternal antibody and later interference with the infant immune response to DTaP are possible.

An article published in 2003 demonstrated the hypothetical influence of higher titer maternal antibody on the infant's response to DTaP (Siegrist). Maternal antibody at high titer might provide protection to infants, but the antibodies would likely mask the vaccine antigen binding sites so that the infant's B cells could not respond. At low titer, the binding sites would no longer be masked by maternal antibody and the infant's B cells would see the sites and mount a protective response to subsequent doses of DTaP vaccine antigens. Partial masking of binding sites would create a situation in which the infant might be without protection from maternal antibody or from DTaP vaccination and might be more susceptible to pertussis.

The proportion of reported infant pertussis deaths by month of age in the pre-vaccine era (7,125 U.S. infants from 1938-1945 [Sako]) showed that deaths peak in the second and third months, but continue throughout the first year of life. From the proportion of reported infant pertussis deaths by month of age during the last five years (92 U.S. infants from 2000-2004 [CDC unpublished data]) and from other studies, two doses of DTaP vaccine reduce deaths and hospitalizations from pertussis by as much as 80%. This protective response after one or two doses of infant DTaP is achieved in the setting of low maternal titers of antibody to pertussis.

No data have been collected to date on the safety, immunogenicity and efficacy of Tdap in pregnant women. Tetanus and diphtheria toxoids (Td) and tetanus toxoid (TT) vaccines are safe in pregnant

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women and effective in preventing maternal and neonatal tetanus based on many years of experience. No increase in pregnancy AEs is anticipated from adding pertussis antigens to Tdap. The immunogenicity and efficacy of Tdap in pregnant women are expected to be similar to what has been found for non-pregnant adolescents and adults.

Effective alternative strategies to prevent pertussis in early infancy are available. Antibiotic prophylaxis for the mother, infant and household contacts has demonstrated effectiveness in preventing infant pertussis when the mother is suspected of having pertussis at delivery (Granström, 1987). ACIP recommended a cocoon approach in October 2005 encouraging Tdap vaccination pre-conception; postpartum as soon as feasible in conjunction with vaccination of household contacts of infants <12 months of age; and for mothers with no previous vaccination. A rise in maternal antibodies is expected within seven days post-vaccination when Tdap is given in the immediate postpartum period (Halperin, 2003). On-time DTaP vaccination remains the most effective measure to decrease morbidity and prevent mortality from pertussis among infants.

In summary, data supporting use of TIV include evidence that pregnant women with influenza have increased fatality rates; the safety and immunogenicity of TIV have been studied in >2,000 women; and the age of first infant dose of TIV is six months after decline in maternal antibody. By contrast, pregnant women with pertussis are not known to have increased morbidity compared to non-pregnant women; the safety and immunogenicity of Tdap has not been studied in pregnant women; and the age of first infant dose of DTaP is six to eight weeks when maternal antibody conceivably could interfere with the infant response to the first two doses, critical for infant protection. Data on primary immune response to DTaP among infants born to vaccinated mothers is not available. Phase I studies of Tdap in pregnant women are planned.

The Pertussis Workgroup administered an internal survey as the basis for drafting the recommendations. Of 21 respondents, 19 were in favor of gathering more evidence in one or more area before making a routine recommendation and two supported a routine recommendation now for Tdap in pregnant women. If the risk of pertussis were increased, 11 supported postpartum Tdap as soon as feasible with flexibility for choice by the provider. The remaining five of the 16 respondents expressed a preference for or would recommend Tdap during pregnancy.

When a Td booster is due during pregnancy, 11 preferred or would recommend Td with flexibility for choice by the provider. The remaining five of the 16 respondents expressed a preference for or would recommend Tdap during pregnancy. Respondents who preferred or would recommend the Td booster during pregnancy favored deferring Td until delivery and administering Tdap as soon as feasible if sufficient Td protection was likely. The workgroup found evidence to support Td protection in most pregnant women.

The 2003 National Vital Statistics showed that 97% of live births in the United States occur among women 11-39 years of age. A study published in 2002 with 1988-1994 NHANES data found that among women <40 years of age, >80% have tetanus antitoxin titers $\geq$0.15 IU/ml above the protective level of 0.1 IU/ml and >60% of women <40 years of age had diphtheria antitoxin titers in the protective range (McQuillian). Although this rate is lower than for tetanus, diphtheria continues to be rare in the United States. Of four cases of neonatal tetanus reported in the United States since 1984, none of the mothers had a three-dose primary series of TT vaccine. Most women who received the ACIP recommended schedule of vaccination and are due for a decennial Td booster during pregnancy are likely to have sufficient tetanus protection until delivery.

Dr. Murphy provided additional details on the workgroup's deliberations in response to questions posed by Dr. Baker. First, safety and immunogenicity studies of Td in pregnant women were not conducted

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before the vaccines were licensed. Research has been performed since that time and show safety for Td and efficacy for protection against maternal and neonatal tetanus.

Second, diphtheria studies have been conducted to determine potential problems with interference of active infant immunization, but this research did not include the current vaccine. Third, the cocoon approach for Tdap was only recently recommended by ACIP and has not yet been analyzed. This strategy has been shown to be effective in other settings, such as influenza vaccination of HCWs to protect elderly persons. Fourth, studies on pertussis morbidity among pregnant women are being conducted at this time, but CDC recognizes the interest in and need for research in this area. CDC's national data do not show any pertussis deaths during pregnancy.

Dr. Campos-Outcalt raised the possibility of using an age-specific mortality rate as a basis of comparison for infant pertussis deaths. Dr. Plotkin urged ACIP to develop and issue a strong statement about data on the safety of vaccines in pregnancy. He emphasized that an official ACIP statement would have an extremely positive effect on vaccine manufacturers and would also offer legal protection.

Draft Recommendations for Tdap in Pregnant Women

Dr. Murphy highlighted key points from four sections of the workgroup's draft statement on the use of Tdap in pregnant women to facilitate ACIP's vote and discussion.

Introduction. Tdap is licensed for single dose use and encouraged during routine visits and before conception for adolescents 11-18 years and adults 19-64 years of age. Tdap replaces the next scheduled Td dose, protects women against pertussis, and may prevent exposure to infants who have an increased risk of severe and complicated disease. Pregnancy is not a contraindication for use of Tdap. The safety, immunogenicity and outcomes of pregnancy after Tdap administered during pregnancy are expected to be similar in pregnant and non-pregnant women, but these data are not available.

High maternal titers of pertussis antibodies after Tdap during pregnancy have implications for the infant. Tdap might provide protection against pertussis in early life, but might also interfere with the infant's ability to mount an adequate immune response to pertussis antigens in DTaP during infancy. The administration of Tdap may be warranted for pregnant women in certain situations. Providers who choose to administer Tdap during pregnancy should inform patients about the lack of data in pregnant women and both the potential benefits and potential adverse effect for the infant. ACIP evaluated data and found the evidence to be insufficient to support a recommendation for routine vaccination with Tdap in pregnant women at this time and is providing guidance to clinicians until more information is available.

Section1: Routine Recommendations. Section 1A recommends Tdap for postpartum women as soon as feasible, but ideally before discharge from a hospital or birthing center. Breast-feeding mothers are included in this recommendation. Peak levels of pertussis antibodies in the mother are expected within 1-2 weeks after vaccination. An interval of $\geq$2 years is suggested between the last Td dose and administration of Tdap to postpartum women. Safety of a one-time short interval since the last Td dose is supported by a Canadian study and is consistent with the adult Tdap recommendation, but a shorter interval can be used. Providers are referred to Section 2F of the statement for additional guidance.

Section 1B outlines the dosage and route of administration for Tdap and Td. Section 1C recommends simultaneous vaccination with Tdap and other indicated vaccines during the same visit using separate syringes at different sites. Section 1D cautions providers to prevent AEs by focusing on the age-appropriate vaccine formulation and using proper technique. Section 1E informs providers that records are required to be maintained for vaccines covered under the National Childhood Vaccine Injury

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Compensation Act. Adolescents and adults are also encouraged to maintain a personal vaccine record to prevent unnecessary immunizations. The guidance for "vaccine providers to record the type of vaccine, manufacturer, etc…" is now replaced with "ideally, the vaccine record will document the type of vaccine, manufacturer, etc….."

Section 2: Special Situations. Section 2A describes considerations for Tdap in pregnant women. ACIP recommends a Td booster for protection against Td during pregnancy, but providers may consider Tdap instead of Td in certain situations, such as an increased risk of pertussis, tetanus booster protection, wound management, and primary series vaccination. Providers who choose to administer Tdap instead of Td during pregnancy should inform patients about the lack of safety and immunogenicity data on Tdap in pregnant women; the potential for early infant protection; and unknown effects of maternal antibodies on the infant response to DTaP.

The second or third trimester is preferred when Td, TT or Tdap vaccines are administered to pregnant women to minimize the association between the vaccine and pregnancy AEs. Providers are encouraged to report Tdap in pregnant women to the appropriate manufacturer's registry regardless of the trimester of administration due to the current lack of data on the use of Tdap in pregnant women.

Section 2B outlines situations with an increased risk for pertussis. Providers may substitute Tdap for Td during pregnancy to provide protection against pertussis in the following situations: (1) adolescents scheduled for routine or catch-up Tdap vaccination; (2) HCWs and child care providers in contact with infants <12 months of age; (3) pregnant women employed by institutions with a pertussis outbreak; and (4) pregnant women who reside in communities with increased pertussis activity. Providers are referred to Section 2A for additional guidance.

Section 2C highlights options for protection against maternal and neonatal tetanus. ACIP recommends Td booster vaccination if ≥10 years have elapsed since the last Td dose. Providers may defer the Td booster until delivery and administer Tdap as soon as feasible in the immediate postpartum period if Td immunity is likely to be sufficient until delivery. Td immunity will most likely be adequate until delivery in the following groups: (1) pregnant women <30 years of age who had a childhood series of DTP or DTaP and at least one Td booster; (2) pregnant women ≥30 years of age who had a childhood series of DTP and at least two Td boosters; and (3) pregnant women with protective levels of serum tetanus antitoxin.

ACIP recommends Td during pregnancy for women who will not have sufficient tetanus and diphtheria immunity until delivery in the following situations: (1) for protection against tetanus, (2) if traveling to a diphtheria endemic area, and (3) in compliance with the woman's personal choice to have the booster during pregnancy. Providers may choose to substitute Tdap for Td during pregnancy to add protection against pertussis. Section 2D notes that a Td booster may be recommended for wound management if ≥5 years have elapsed since the previous Td dose. Providers may choose to substitute Tdap for Td during pregnancy.

Section 2E addresses pregnant women with unknown or incomplete tetanus vaccination. ACIP recommends a three-dose primary series of Td vaccine with dose 2 given ≥4 weeks after dose 1 and dose 3 given ≥6 months after dose 2. Td is preferred for the first two doses that should be administered during pregnancy. Providers may choose to substitute Tdap for one dose of Td during pregnancy. Providers are referred to Section 2A for additional guidance.

Section 2F provides information for postpartum women who received tetanus toxoid- or diphtheria toxoid-containing vaccines <2 years previously. No studies have evaluated the risk of adverse local and systemic reactions at intervals <2 years since the last dose of tetanus toxoid- or diphtheria toxoid-containing vaccine. Higher rates and more severe local systemic reactions are likely with higher serum titers of antitoxin. These outcomes are caused by a short interval between and an increasing number of

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doses. Providers may consider Tdap for these postpartum women after obtaining a history of AEs following previous doses. Providers are referred to the "Safety Considerations" section for additional guidance.

Section 2G summarizes alternatives to Tdap in postpartum women to reduce the risk of pertussis. Providers should encourage vaccination of household and child care provider contacts of infants <12 months of age. Providers are referred to the "cocoon strategy" in the Adult Tdap provisional recommendations for additional guidance. Providers are urged to inform patients about the symptoms of pertussis and the effectiveness of early antimicrobial prophylaxis. Providers are referred to CDC's published guidelines in the *MMWR.*

Section 3: Contraindications and Precautions. Section 3A describes the contraindications for use of Td and Tdap: a history of serious allergic reaction to any component of the vaccine or for Tdap but not Td, a history of encephalopathy not attributable to an identifiable cause within seven days post-vaccination with pertussis components. Section 3B highlights precautions and reasons to defer Td or Tdap, namely GBS, with onset ≤6 weeks following tetanus toxoid-containing vaccine, moderate or severe acute illness until resolved, or a history of Arthus reaction following a previous dose. Reasons are also outlined to defer Tdap, but not Td: for adults 19-64 years of age, an unstable neurological condition (e.g., cerebrovascular event or acute encephalopathy) and for adolescents 11-18 years of age, a progressive neurological disorder or uncontrolled epilepsy until stable. Additional sections of the Tdap statement include guidance on reporting AEs after vaccination and the Vaccine Injury Compensation Act.

ACIP Vote on the Draft Recommendations for Tdap in Pregnant Women

Dr. Gilsdorf expressed concern about ACIP issuing a routine recommendation for the use of Tdap during pregnancy in the absence of solid data. She noted that the cocooning strategy for postpartum Tdap was successful with rubella and should be applied in this situation until better information is collected for ACIP to make a more informed decision. Dr. Campbell strongly recommended changing the "postpartum Tdap" language in Section 1A to administer the dose "prior to discharge (or as soon as feasible)." This revision would address the issue of women who deliver and will not present to their healthcare providers again until six weeks postpartum. Dr. Campbell was uncertain about the approach that would be taken to define a "community with increased pertussis activity" in Section 2B.

Dr. Murphy provided additional details in response to questions posed by Dr. Campbell and Ms. Stinchfield. First, a "community with increased pertussis activity" is defined by local and state public health agencies. Second, recent FDA data showed that as of May 26, 2006, 13 cases of women who inadvertently received Tdap while pregnant were reported to two manufacturers' registries. Of 12 reports to one manufacturer, four were from a post-marketing study and the remaining eight were spontaneous reports. No additional data are available.

Dr. Baker was uncertain about the feasibility of obtaining more data in response to ACIP's request for additional evidence. No safety and efficacy trials in pregnant women are underway and manufacturers have no incentive for conducting these types of studies. She urged CDC to gather data on the morbidity of pertussis in pregnant women.

Because the workgroup is not supporting a recommendation for routine vaccination with Tdap in pregnant women at this time, Dr. Baker strongly encouraged CDC to disseminate data each year on the number of pertussis deaths among infants <4 months of age. She reported that the AAP liaison to the Pertussis Working Group was one of the few workgroup members who favored a routine recommendation of Tdap during pregnancy at this time. Due to the number of infant deaths and hospitalizations from pertussis,

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she implored ACIP to reconsider its position. Dr. Powell announced that AAP issued a statement advising providers to administer Tdap to teens without concerns about pregnancy.

Similar to Dr. Baker, Dr. Powell was also uncertain about the workgroup's recommendation because pertussis morbidity and mortality are inversely related to age. He conveyed that the population in most need of protection from pertussis is infants prior to active immunization. This goal can be achieved through passive vaccination by boosting the mother. Dr. Iskander asked the workgroup to delete "second and third trimester" from Section 2A on "Td, TT or Tdap vaccine in pregnant women." He explained that this language was extracted from ACIP's previous influenza recommendations before the substantial burden of influenza morbidity was documented.

Dr. Treanor did not see a need to collect additional safety data on the use of Tdap during pregnancy. Instead, he was more interested in evidence that demonstrated a tradeoff between the advantages of more maternal antibody and protection of young infants versus the disadvantages of suppression from maternal immunization. Dr. Plotkin raised the possibility of CDC and WHO gathering more data by conducting a study in an area of the developing world with a high rate of pertussis. The cohort could be pregnant women immunized with a paucivalent vaccine and the design could be utilization of antibodies to measure infection and disease. He pointed out that the study would be ethical in this setting so long as infants were followed and given a fourth dose after the Expanded Program on Immunization schedule to avoid harm to immunity.

Dr. Decker described two efforts that are underway to gather more data on vaccines in pregnancy. First, NIH is organizing a Phase I study on third-trimester administration of Tdap in ~50 pregnant women. Second, New Hampshire public health agencies and sanofi pasteur are conducting comprehensive surveillance in response to a large pertussis outbreak that recently occurred in New Hampshire. The cohort includes HCWs and pregnant women who were immunized with ADACEL®. The study is expected to produce a strong body of evidence on antibody responses of pregnant women, responses of infants and seventh-month cord blood.

Dr. Baker provided additional details about the design of the NIH randomized Phase I trial among 45 pregnant women 18-40 years of age. Eligibility criteria include a trisomy and alpha-fetoprotein risk screen. An amniocentesis will be required for all subjects with a risk >1 out of 270. Each infant will be bled a minimum of three times. The cohort is expected to be enrolled over a two-year period and only 30 of 45 subjects will receive Tdap. In addition to the NIH trial and other ongoing efforts, Dr. Baker urged CDC to gather evidence to determine the level of interference that will result in pertussis disease to infants.

Dr. Pickering urged the workgroup to incorporate language into the Tdap statement that advises providers about appropriate actions in the event an unlicensed rather than the licensed vaccine is administered to adults. He also raised the possibility of CDC making efforts at this time to prepare for a future pertussis outbreak. This approach would facilitate more rapid data collection on vaccines in pregnant women than Phase I studies.

Dr. Murphy confirmed that CDC has taken steps in this regard by convening an expert panel to identify specific study design criteria for vaccine trials in pregnant women and a follow-up study of their infants. One possibility would be to apply criteria that FDA used to license the vaccines because FDA's determination of efficacy was based on comparative bridging immunogenicity from infant trials. However, additional discussion is needed in this area.

Dr. Abramson called for a motion on the draft recommendations for the use of Tdap in pregnant women. Dr. Morse moved as follows: "ACIP adopts the Pertussis Workgroup's proposed recommendations, but will change the "postpartum Tdap" language in Section 1A to administer the dose "prior to discharge (or

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as soon as feasible)." The motion was seconded by Dr. Gilsdorf and **passed by a majority vote.** The disposition of the vote is as follows:

- **14 in favor:** Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Poland, Stinchfield, Treanor, Womeodu.
- **1 opposed:** Abramson.
- **0 abstentions**.

Adult Immunization Schedule (AIS) for October 2006-September 2007

Dr. Gregory Poland, the Adult Immunization Workgroup Chair, summarized the major changes to the October 2006-September 2007 AIS. A hatched bar was inserted to indicate that Tdap is a one-time recommendation. HPV was included with a line to illustrate the vaccine is recommended up to 26 years of age. The bar on varicella was revised in anticipation of the recommendation for the use of zoster vaccine in persons >60 years of age. A chart was added to show recommended vaccines by medical and other indications for consistency with the childhood immunization recommendations. The chart includes hatched bars for the Tdap and HPV vaccines.

Revisions were made to six existing footnotes. Footnote 1 for tetanus, diphtheria and pertussis was revised to reflect recommendations for the administration of Tdap to adults <65 years of age; the use of Tdap and Td in pregnant women; the use of Tdap in persons with close contact to infants; and licensure of only one of two Tdap products for use in adults. Footnote 3 for MMR was revised to reflect new recommendations to administer a second dose of mumps vaccine to high-risk adults born during or after 1957, such as HCWs, international travelers and students in post-secondary schools. The footnote was also revised to reflect recommendations for HCWs born before 1957. The need to strongly consider a routine one-dose policy and a second dose during an outbreak is emphasized.

Footnote 4 for varicella was revised to reflect recommendations for the new definition of "immunity to varicella." A routine second dose is recommended for all adults without evidence of immunity. The previous date of 1966 for U.S.-born persons to be considered immune to varicella was changed to 1980. The previously specified date of 1966 for history of varicella disease for non-U.S.-born persons to assume immunity was deleted. Footnote 5 for influenza was revised to reflect expanded recommendations to vaccinate close contacts of children 24-59 months of age. Footnote 9 for hepatitis B was revised to reflect recommendations to vaccinate any adult seeking protection from HepB vaccine infection.

Footnote 10 for meningococcal was revised to reflect existing recommendations to consider re-vaccination after 3-5 years if the patient previously received the polysaccharide vaccine and remained at high risk. A new footnote was added for HPV to reflect recommendations for routine vaccination of all adult women through 26 years of age and delayed vaccination of pregnant women until the completion of the pregnancy.

A date was added to the box on page 1 for consistency with the childhood/AIS. Text was also incorporated into the box to indicate zoster and other new vaccines and highlight typhoid, rabies, travel vaccines and other vaccines not listed on the routine AIS. The broken red line was deleted. The purple bars were retained are now the sole legend to highlight vaccination of persons with specific risk factors.

Dr. Abramson called for a motion on the revised AIS. Dr. Poland moved as follows: "ACIP accepts the October 2006-September 2007 AIS as presented." The motion was seconded by Dr. Finger and **unanimously approved by all 15 voting members**: Abramson, Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Morse, Poland, Stinchfield, Treanor, Womeodu.

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Update on Pneumococcal Vaccines

Dr. John Moran, of CDC, provided an update on the use of pneumococcal vaccines to reduce morbidity and mortality in an influenza pandemic. Influenza infection increases susceptibility to invasive pneumococcal disease (IPD). CDC formed an internal workgroup to assess the potential need for antibiotic stockpiles to treat bacterial complications of an influenza pandemic. The workgroup estimated that the proportion of pandemic influenza cases complicated by secondary bacterial pneumonia is 5%-20% and the proportion of secondary pneumonia caused by *S. pneumoniae* is 50%.

Various studies have demonstrated the effectiveness of pneumococcal vaccines against disease caused by vaccine serotypes. The pneumococcal conjugate vaccine (PCV7) reduces carriage and has been found to be >95% effective against IPD caused by vaccine serotypes and 6%-37% effective against pneumonia. The pneumococcal polysaccharide vaccine (PPV23) does not reduce carriage and has not been found to be effective against non-bacteremic pneumonia in high-risk groups. However, PPV23 has demonstrated efficacy of 55%-75% against IPD caused by vaccine serotypes. Data collected from the 2004 Active Bacterial Core Surveillance Program showed the proportion of cases caused by vaccine serotypes. PPV23 has 23 serotypes and covers 83% of infections in adults and 83% of infections in children >2 years of age. PCV7 has seven serotypes and covers 24% of infections in adults and 14% of infections in children <9 years of age.

Outcomes of a randomized controlled trial of a 9-valent pneumococcal conjugate vaccine (PCV9) for the prevention of pneumonia were published in 2004 (Madhi, *et al.*). The study was conducted in South Africa with a vaccine that includes nine serotypes that cause 87% of IPD in South African children. An analysis of children hospitalized with pneumonia from whom influenza A virus was recovered found only 170 such cases per 100,000 among vaccinated children versus 306 per 100,000 among controls; a 45% efficacy for preventing influenza A-associated pneumonia. The efficacy rate was found to be 34% among HIV-uninfected children and 57% among HIV-infected children.

ACIP recommends that all U.S. infants receive a series of three PCV7 shots, but published data from the 2004 NIS showed that in only 13 states had >80% of children received three shots by the age of two and in eight states fewer than 60% of 2-year-old children had received three shots. The median coverage was 71.7% in all 50 states and the District of Columbia.

ACIP recommends that all persons ≥65 years of age receive PPV23, but data from the 2003 Behavioral Risk Factor Surveillance Survey (BRFSS) showed that one-third of older Americans are unprotected. Only five states had ≥70% coverage, three states had <60% coverage, and the median coverage was 64.5%. ACIP also recommends PCV23 for persons 18-64 years of age with diabetes, but 2003 BRFSS data showed that less than one-half of diabetics have protection of PPV23. The median coverage was 37.1% with only four states having >50% coverage and nine states having <30% coverage. These data indicate that existing ACIP recommendations for the prevention of pneumococcal disease by immunization are not fully implemented.

Several potential options can be considered for the use of pneumococcal vaccines. Implementation of the current recommendations could be encouraged to increase coverage to 90% in each state. The current recommendations could be expanded for the use of PPV23, PCV7 or both vaccines in populations for whom pneumococcal vaccine is not now routinely recommended. High-risk and elderly persons could be regularly re-vaccinated with PPV23 (no more than two doses are currently recommended for any group). PCV7 could be used in older children or adults. The age for universal vaccination with PPV23 could be lowered below 65 years.

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If a pandemic was imminent, all persons could be considered to be “high risk” because they would be at increased risk of developing pneumococcal disease as a result of being at increased risk of developing influenza. The current recommendations could be unchanged until a pandemic was imminent and then changed to recommend age-appropriate pneumococcal vaccine for all persons. However, this plan would require stockpiling of one or both vaccines.

CDC acknowledges that these options present several challenges. In the United States, only one manufacturer is licensed to produce PCV7 and only one manufacturer is licensed to produce PPV23. Logistical barriers to administering the vaccines during a pandemic are likely. The duration of protection is uncertain, particularly with PCV7. The value of continuous administration of boosters is unknown; individuals may become less responsive to successive re-vaccinations. Stockpiling would pose an additional logistical problem because PCV7 and PPV23 require constant refrigeration and have limited shelf lives.

Strategies to prioritize populations have not been identified to date, such as by age group or persons most likely to develop influenza or pneumococcal disease. For example, IPD is most common among very young and very old persons with the lowest attack rate in 2005 at 5-17 years of age. However, the highest attack rates for influenza during the 1918 and 1957 pandemics were among persons 5-19 years of age. Dr. Moran asked ACIP members for their thoughts on how the currently licensed pneumococcal vaccines might be used for influenza preparedness.

Dr. Hull raised the possibility of CDC combining attack rate data for both influenza and pneumococcal disease to calculate an overall risk profile. He also responded to CDC’s question of whether each state would consider using its individual pandemic influenza resources to increase pneumococcal vaccine coverage. He explained that states would need to address this issue in the context of a comprehensive preparedness program rather than a stand-alone activity. As a result, states must consider the additional resources and extra burden required to undertake this effort.

Ms. Stinchfield asked CDC to consider HCWs in pandemic preparedness if a decision is made to expand the current target groups. Dr. Womeodu encouraged CDC to include nursing homes and other facilities that house elderly persons in pandemic influenza planning. She requested that an explicit process be developed to retain and care for elderly persons in existing facilities rather than transferring these individuals to an emergency department during an influenza pandemic. Dr. Treanor acknowledged the need for CDC to clearly distinguish between improving coverage in existing target groups recommended for pneumococcal vaccine and increasing vaccine use in non-traditional target populations during a pandemic.

Dr. Morse was in favor of lowering the age of universal vaccination with PPV23 to < 65 years rather than stockpiling vaccine. Dr. Wallace conveyed that three PCV7 doses do not necessarily correlate with the current estimates for protection because these data are based on previous supply issues, vaccine shortages and catch-up vaccination. In response to Dr. Poland’s question, Dr. Moran clarified that the Haemophilus vaccine would most likely be unimportant during a pandemic due to the dramatic decrease in *Haemophilus influenzae B* (Hib) disease covered by this vaccine.

Dr. Whitley-Williams, the National Medical Association liaison, urged CDC to consider the significant gaps in both pneumococcal and influenza vaccine coverage among minority adult populations; make efforts to narrow these gaps during pandemic planning; and identify resources to increase pneumococcal vaccine coverage. Dr. Moran confirmed that CDC would continue its internal discussions on the possibility of using PPV23 to reduce gaps in incidence between whites and minority populations.

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Dr. Litjen Tan, the American Medical Association (AMA) liaison, urged ACIP to continue its dialogue on using pneumococcal vaccines to reduce morbidity and mortality in an influenza pandemic. AMA recently distributed a pamphlet to 350,000 members describing actions physicians can take in their individual practices with respect to pandemic planning. The pamphlet reiterated and encouraged implementation of ACIP's existing recommendations on PPV23. Dr. Tan asked ACIP to explore the possibility of issuing new guidance on pneumococcal vaccines. Ms. Kelly Moore, of the Tennessee Department of Health, suggested using the strong community-level interest in influenza pandemic planning to increase vaccine coverage and link pneumococcal vaccines to pandemic planning and preparedness.

Several manufacturers responded to Dr. Abramson's questions about the actual shelf lives of pneumococcal vaccines and current efforts to develop additional conjugate vaccines with more strains. Dr. Jeffrey Silber, of Merck, clarified that the shelf life of a vaccine is based on the stability of serotypes. For example, PPV23 is actually 23 different vaccines in one vial and could essentially have 23 different shelf lives. Dr. Andrew MacKnight announced that GSK is currently making progress on Phase III studies of a 10-valent pneumococcal vaccine.

Dr. Peter Paradiso, the liaison for Pharmaceutical Research and Manufacturers of America, announced that other countries are adopting PCV7 due to the high coverage rate of the vaccine and the tremendous reduction in pneumococcal disease. He also informed ACIP that Wyeth Vaccines is developing a 13-valent vaccine with increased coverage of serotypes 6A and 19A. The new vaccine has the potential to play a critical role in antibiotic resistance and the use of a conjugate vaccine in adults. Wyeth is currently collaborating with FDA to design the overall program for the vaccine and will initiate the Phase III trial of the 13-valent vaccine in the near future. Dr. Paradiso confirmed that Prevnar has a 2-year shelf life in the bottle.

Dr. Abramson closed the discussion by announcing that key ACIP members and CDC staff would engage in dialogue to determine the need to form a new Pneumococcal Workgroup.

HERPES ZOSTER (HZ/SHINGLES) VACCINE

The series of presentations and ACIP's discussion on the HZ/shingles vaccine are set forth below.

Evaluation of the Vaccine Cost-Effectiveness

Dr. James Pellissier, of Merck Research Laboratories, presented Merck's cost-effectiveness evaluation of ZOSTAVAX® in preventing zoster and post-herpetic neuralgia (PHN) in older adults in the United States. Merck used several data sources to demonstrate the safety and efficacy of ZOSTAVAX® and its cost-effective price of $150 in immunocompetent persons and other individuals ≥60 years of age. These data were also used to support recommendations of ZOSTAVAX® and show that the vaccine is comparable to other adult preventative measures. The data sources included the pivotal Shingles Prevention Study (SPS), commonly accepted cost-effectiveness thresholds, and sensitivity analyses with a variety of decision-making thresholds for cost-effectiveness. Merck designed the cost-effectiveness evaluation with conservative analyses, robust conclusions, plausible ranges of input parameter values, and a broad scope of scenarios and age cohorts.

HZ and PHN are debilitating diseases that have an unmet medical need for better management. HZ occurs through the reactivation of latent VZV. The disease is typically characterized by prodromal pain and an acute rash accompanied by moderate to severe pain. The lifetime risk of developing HZ is

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approximately 30%, but up to ~50% of persons ≥85 years of age will develop ≥1 HZ episodes. HZ complications occur in 15%-40% of cases with PHN being the most common complication. Depending on age, 10%-33% of all HZ cases lead to PHN. The overwhelming burden associated with HZ and PHN is borne by the elderly. For purposes of the cost-effectiveness evaluation, Merck used the SPS definition of PHN as "persistent pain >90 days after the onset of HZ."

The SPS was a large, randomized and double-blind placebo controlled clinical trial that showed the ZOSTAVAX® live attenuated VZV vaccine to be generally well-tolerated and efficacious in subjects ≥60 years of age. Key SPS results on ZOSTAVAX® are highlighted as follows. HZ incidence was reduced with vaccine efficacy of 51%. The proportion of PHN cases was decreased with vaccine efficacy of 47% among subjects ≥70 years of age who were given HZ. The incidence of PHN in the overall cohort was reduced with vaccine efficacy of 67%. The safety profile was found to be excellent.

Merck conducted research to gain insight into the potential value of ZOSTAVAX® to society and payers. The payer perspective addressed direct medical costs, while the societal perspective included direct medical costs, lost work and productivity, and other indirect costs. The study was designed with a model-based decision analysis to estimate expected HZ, PHN and complications avoided; health care resource utilization (HCRU) costs avoided; QALYs gained; and the cost-effectiveness or marginal cost per QALY gained. A cohort-based and age-specific model published in 2001 served as the foundation for the Merck model (Edmunds, *et al.*). Merck designed the model to accommodate inputs from the SPS, literature, ancillary studies, and the existing HZ and PHN knowledge base. The model provided lifetime projections of HZ, PHN, healthcare resource use and QALYs.

The six categories of data that were input into the Merck core model are described as follows. One, vaccine characteristics included vaccine efficacy for HZ and PHN, price and durability of the vaccine effect. Two, epidemiologic data included age-specific HZ-related death rates and HZ/PHN incidence, life expectancy, duration of HZ/PHN cases, and the rate of zoster-related complications. Three, HCRU and cost data included outpatient and emergency room visits, hospitalizations, prescription fills, and other healthcare factors, such as home care, tests and procedures. Four, quality of life data included QALY weights for HZ-associated pain states and duration of pain by severity. Five, indirect cost data included work and productivity losses attributable to HZ, PHN or related complications, age-specific employment rates, and wage rates. Six, other parameters included the cohort size, vaccine recipient population, and the 3% discount rate for costs and outcomes.

Merck took several actions to model the long-term efficacy of ZOSTAVAX®. Vaccine efficacy results were extracted from the SPS and analyzed by age of vaccination. A maximum likelihood was estimated to identify the best fitting age-dependent models. Fitted results of the model indicated a reduction in efficacy by age, a 0% waning rate, and an average duration of efficacy of ≥12 years. The large MedStat insurer database served as the source for epidemiologic and HCRU data. The data showed much higher incidence rates for immunocompromised persons compared to immunocompetent persons, but ZOSTAVAX® will only be indicated for immunocompetent persons. Merck accounted for this potential flaw by conducting analyses with data from all individuals and immunocompetent persons to bind results.

Key results from Merck's cost-effectiveness evaluation of ZOSTAVAX® are summarized as follows. Model costs ranged from $437-$4,818 for acute HZ, PHN, and ocular, neurological, skin and other complications. QALY weights were assigned for non-pain QALYs and mild, moderate and severe HZ pain based on weights from the literature, Merck's base case QALY weight and SPS data. All HZ data and immunocompetent data were used to project the lifetime impact of ZOSTAVAX® on a cohort of 1 million vaccine recipients ≥60 years of age. The estimates were based on avoiding HZ and PHN cases, related complications, HZ-related deaths, hospitalizations, emergency room and outpatient visits, and prescriptions. The number of these outcomes avoided ranged from 35-438,998; the number of QALYs

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gained ranged from 4,169-6,706; and the overall costs of HZ, PHN and complication cases avoided ranged from ~$74-~$93 million.

Based on a total price of $168 for the vaccine and an administrative fee, the projected cost-effectiveness of ZOSTAVAX® for the U.S. population ≥60 years of age ranged from $15,390-$22,474 from the payer perspective and $14,450-$21,524 from the societal perspective. A cost per QALY gained of $50,000 is frequently cited as the threshold, but cost-effectiveness indicators typically vary among decision-makers. However, studies published in 2005 and 2006 showed that costs per QALY gained for other adult preventive measures ranged from $10,000-$60,000 (Neumann and Turner, respectively). The interventions analyzed in these studies included hypertension medication, influenza vaccination, cholesterol management, and osteoporosis, mammographic and colon cancer screening.

Merck also compared the ZOSTAVAX® cost-effectiveness results to a recent assessment conducted by the National Commission on Preventive Practices (NCPP) on the value of 25 preventive services recommended by ACIP and the U.S. Preventive Services Task Force. The NCPP study used a scale of 1-5 to score each preventive service based on its clinically preventable burden and cost-effectiveness. Of 25 services evaluated, only 11 received scores of ≥7. ZOSTAVAX® would have received a score of 7 if the vaccine's cost-effectiveness and number of QALYs saved were entered into the NCPP model. The ZOSTAVAX® result is comparable to the cervical cancer and cholesterol screening scores. Merck also analyzed the cost-effectiveness of ZOSTAVAX® for persons in age groups other than ≥60 years. The data showed extremely reasonable cost-effectiveness ratios for persons up to the 85-90 year age range.

Merck performed sensitivity analyses of the vaccine's waning rates and probabilistic sensitivity analyses to determine the durability of ZOSTAVAX® and robustness of the overall results. Each input parameter was simultaneously varied across the respective ranges according to assigned probability distributions. The sensitivity analyses showed that ZOSTAVAX® was cost-effective even when durability of only five years was assumed. The probabilistic sensitivity analyses demonstrated that ZOSTAVAX® would most likely be cost-effective at much lower decision-making thresholds. However, the model was found to be sensitive to the vaccine price, age of the vaccine recipient, PHN costs, duration of vaccine efficacy, QALY losses associated with pain states, and complication costs.

In addition to the sensitivity of the model, Merck also recognized that several caveats created biases either in favor of or against ZOSTAVAX®. For example, complication costs covered all HZ patients with complications. No distinction was made between all individuals and immunocompetent persons. Costs for several important variables were excluded from the model, such as medication costs, QALYs lost to complications, costs related to care givers and care giver burden, and work and productivity costs for persons >65 years of age. Moreover, PHN costs were only included up to one year, but these cases may have a much longer duration. Costs per HZ case did not vary by case severity. Efforts are underway at Merck to address these caveats in the model.

Dr. Pellissier provided additional details on Merck's cost-effectiveness study of ZOSTAVAX® in response to ACIP's questions.

- Results from the probabilistic sensitivity analysis differed from other analyses because each input parameter varied by its input distribution. The expected value could be lower or higher than the probability of 50% depending on the distribution of the outcome.
- Long-term vaccine efficacy was modeled by analyzing the take, initial efficacy and waning of the vaccine. Various functional forms for the fitting process were examined and SPS data for all ages were used. Efficacy data for years 1-5 were applied and maximum likelihood estimation models were fit. The efficacy level across years 1-5 for the age of vaccine was flat, but Merck acknowledges the weakened ability to trust forecasts ≥30 years in the future.

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- Merck fitted a waning parameter in the model due to the expectation of waning. The data set used in the study showed that the waning rate would be the same regardless of age. The results should be interpreted based on the sensitivity analysis because these data cover the entire spectrum. Extremely reasonable results were still seen even with a pessimistic assumption of only an average durability of five years.
- The probability of complications was ~10% in general based on the likelihood of having a complication in one of four categories: ocular, neurologic, skin or other complications. These complications were weighted by the observed proportion in the Olmsted County, Minnesota study. None of the biases observed in favor of or against ZOSTAVAX® overwhelmed the other biases.

Drs. Abramson and Lieu responded to a question posed by Dr. Andrea Gelzer, the liaison to America's Health Insurance Plan. The ACIP members are currently exploring strategies to standardize cost-effectiveness data presented to ACIP. However, a balance must be made between standardizing information and acknowledging differences between desired outcomes of vaccines, such as decreased pain, morbidity or mortality. Dr. Lieu welcomed the opportunity to further address this issue with the liaisons pending the results of ACIP's discussion.

Dr. Neuzil pointed out that the ZOSTAVAX® cohort will be followed for efficacy over a longer period of time and will be ≥7 years ahead of any population immunized with a licensed vaccine. She emphasized that knowledge gained about the duration of protection can be incorporated into the models to resolve uncertainties at the time the vaccine is licensed.

Projected Cost-Effectiveness of Vaccinating the Elderly to Prevent Shingles

Dr. Ismael Ortega-Sanchez, of CDC, presented preliminary data from CDC's cost-effectiveness study of vaccinating elderly persons in the United States to prevent shingles. Death is an extremely rare outcome of shingles, but severe pain and suffering are a significant burden of the disease. A new vaccine in immunocompetent elderly persons has been shown to markedly reduce the burden of illness from shingles and PHN. CDC designed its study to identify the value of preventing a case of shingles from a payer and societal perspective and determine whether vaccination of the elderly to prevent shingles would provide a public health value.

CDC's cohort-based decision analysis model for the study was age-specific and based on the current U.S. population. The model incorporated assumed probability distributions, focused on an immunocompetent population, used a Monte Carlo simulation algorithm to estimate results, and projected health economic outcomes from 60-99 years of age. The six major categories of data included in the model were epidemiologic data, quality of life and vaccine efficacy data, HCRU data and cost parameters. With these data, the model estimated HZ prevention parameters, cases of shingles and PHN prevented, burden prevented, and cost-effectiveness ratios.

Because shingles causes impairment and disability that in turn leads to a lower quality of life, most of the expected benefits from prevented reactivation of HZ virus (shingles) are in terms of reductions in morbidity and prevention of quality of life losses. The primary outcomes measured in the study were QALYs and costs per QALY gained. QALYs gained measure years of life saved, years of function and health preserved. The cost utility analyses included changes in quality of life as a key outcome. The secondary outcomes measured in the study were the number of vaccinees to avert one case of shingles and PHN and the cost per outcome averted for the cost of each shingles and PHN case.

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The CDC model used various sources to collect data for the model, including the published literature, MedStat, the U.S. Census Bureau, the Zoster Utility Evaluation (ZUE) study, and the Bureau of Labor Statistics (BLS). These sources were used to gather epidemiologic data, cost estimates, vaccine efficacy data, hourly and lifetime earnings, age-specific incidence of shingles, and data on the U.S. population and impact of disease on quality of life due to pain and suffering.

The ZUE study was an extremely important data source for CDC's cost-effectiveness analysis of shingles vaccination. The joint research project between CDC and Harvard measured the economic value of preventing zoster by assessing medical and non-medical care use; evaluating the patient's monetary and indirect costs; and estimating intangible values of prevention in standard shingles scenarios with a time tradeoff technique. In the ZUE study, "intangible values of prevention" were defined as the amount of time in perfect health at the end of life an individual would be willing to trade to avoid, for example, a month with a certain level of pain and complication due to shingles.

The ZUE study population included two groups. Patients with recent shingles or PHN were recruited from two sites and interviewed by telephone. Community members were selected to be representative of the U.S. general population in terms of race, ethnicity and socioeconomic status. This group completed web-based self-administered surveys. The public cohort had significantly more conservative scores for level and duration of pain than the patient cohort (e.g., public preferences express lesser decrements in quality of life than those of patients).

Analyses in the CDC cost-utility model were conducted using the patient and public perspectives regarding the impact in the quality of life under different scenarios of pain intensity and duration. CDC also used ZUE and MedStat data on medical and non-medical resource use; cost by shingles case; and cost per case with and without persistent pain for 30-89 days and ≥90 days. CDC used these data sources to analyze several outcomes, such as use of inpatient or outpatient services; length of hospitalization; work and leisure time lost, time spent by other care givers; other out-of-pocket expenses; and number of prescriptions, medical visits or encounters, emergency department or doctor visits and telephone calls for advice.

CDC designed the model based on several assumptions; most are standard cost-effectiveness assumptions. Among the specific shingles and PHN assumptions made for this study, CDC had that the reactivation recurrence would be 1%-1.5% after five years. The proportion of immunocompetent persons would be age-specific with a mean of 90% among persons ≥60 years of age. The baseline health status would be age-specific with a mean of 0.86 among persons ≥60 years of age using quality adjustment weights. Duration of vaccine efficacy would be age-specific. Vaccine local reactions and fever would be 31% and 1.4%, respectively, among vaccinees. Vaccine administration would cost $20 with a range of $15-$50. The discount rate for all costs and health outcomes would be 3% with a range of 0%-5%.

The preliminary results of CDC's cost-effectiveness analysis are summarized as follows. If after five years, 68% of vaccine efficacy remains, vaccination of 1 million persons would prevent 58,000 shingles cases, 7,000 complications, 32,000 PHN cases with pain >30 days, and five deaths. The number of vaccinees needed would be 17 to prevent one shingles cases, 143 to prevent one complication, 31 to prevent one PHN case, and 194,000 to prevent one death. Vaccination of 1 million persons ≥60 years of age would prevent 285,000 ambulatory visits, 28,000 emergency department visits, 6,000 days of hospitalizations, 176,000 prescriptions, 700,000 lost work hours, and 4 million lost hours for other activities. Shingles costs saved before vaccination would be ~$49 million. Using the patient perspective on QALY scores, the number of QALYs gained with vaccination would be 11,919 non-discounted and 8,782 discounted. Overall, shingles vaccination would prevent 43% of medical and non-medical resources.

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CDC performed several sensitivity analyses to determine the number of PHN cases prevented per 1 million persons ≥60 years of age; the cost per QALY saved by score perspective and vaccine effectiveness; and the cost per QALY saved by vaccine price for three vaccine efficacy duration scenarios. The sensitivity analyses showed that QALYs and cost per QALY gained were highly sensitive to the vaccine cost, QALY scores perspective, vaccine effectiveness for PHN and duration of vaccine-induced protection.

CDC acknowledges both the strengths and weaknesses of the study. On the one hand, healthcare utilization, out-of-pocket expenses and productivity losses were captured from actual patients. Data on quality of life changes from shingles were extracted from a large sample size with solid response rates and diverse healthcare and geographic settings. QALY scores were estimated with a parallel comparison between patients and community controls. The survey questions asked patients to provide responses on hypothetical scenarios and their actual illness.

On the other hand, indirect increments of healthcare utilization by patients with persistent pain were not assessed. Medical cost ascertainment to cases by level of pain and duration was limited. The scores were inconsistent because patients placed both high and low values on PHN. No clear distinction was made between extreme opinions and response errors. Questions on time compensation were modified, particularly those related to time traded from the end of life. Overall, CDC's preliminary data from the analyses demonstrated that a shingles vaccination program could be cost-effective for a cohort of immunocompetent persons ≥60 years of age. The conservative analyses did not consider indirect costs for PHN and immunocompromised cases.

Dr. Ortega-Sanchez provided additional details on CDC's preliminary cost-effectiveness study of shingles vaccination of elderly persons in response to ACIP's questions.

- CDC gathered data on the dollar amount persons would be willing to pay for the shingles vaccine or to avoid pain, but this information is still being analyzed. CDC will use these data to develop a cost-benefit analysis and expects to present this component of the study during the next ACIP meeting.
- The patient cohort and community controls were well matched by age in the ZUE study, but not educational level.
- CDC did not use incidence data for shingles or PHN from the SPS control group. Instead, CDC used the following data sources to estimate age-specific incidence of shingles: U.S. data by Donahue from 1990-1992; U.S. data from the MedStat database from 1993-2003; U.S. data from Olmsted County in 2005; and U.K. data by Hope-Simpson from 1947-1962. These data sources were based on conservative estimates.
- CDC incorporated BLS data into the model to estimate hourly wages for specific age groups. The data showed that persons in the indicated age group for shingles vaccination would earn ~$18/hour. However, CDC's economic analysis did not include an hourly rate for leisure time.

Dr. Pellissier noted that Merck also did not use incidence data for shingles or PHN from the SPS control group. He clarified that telephone reminders, refrigerator magnets and other methods were used to educate the SPS cohort on ascertainment of shingles. Utilization of SPS incidence data would have strongly biased the Merck study in favor of the vaccine. As a result, Merck estimated shingles incidence for its economic model based on the cost of care.

Dr. Abramson announced that Medicare Part D will cover 75% of the cost of the shingles vaccine excluding the administrative charge. More information on this issue will be presenting during the October 2006 ACIP meeting. Dr. Neuzil was uncertain of CDC's rationale in solely focusing on the efficacy of the

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vaccine against shingles. Solid data that demonstrate the efficacy of the vaccine against both PHN and shingles would strengthen CDC's cost-effectiveness models.

Dr. Patrick Liedtka, of the Merck Vaccine Division, highlighted key points from Merck's discussions with CMS, Medicare Part D plans and private managed care plans over the past year. Out-of-pocket costs for ZOSTAVAX® are not anticipated to be more significant than those for other vaccines. Of the total target population of persons ≥60 years, >90% is expected to have extremely robust healthcare coverage of ZOSTAVAX®. Several large managed care plans in the country have already decided to cover the vaccine with no co-payment to enrollees in the indicated group.

Dr. Jeffrey Koplan, of Emory University, advised CDC to attribute a dollar figure to leisure time because older persons in the indicated age group for shingles vaccination may place a higher value on leisure time lost than work time lost. He also asked ACIP to consider the actual uses of cost-effectiveness analyses. Although these data are used to assist in developing healthcare and medical prevention policies, the information can also be used to establish and justify the price of vaccines. Dr. Koplan encouraged CDC to perform a sensitivity analysis to determine cost-effectiveness using a worst-case scenario for each variable of the vaccine. Dr. Ortega-Sanchez confirmed that CDC incorporated a Monte Carlo simulation algorithm into the model to obtain ranges of specific values probability distributions.

Overview of the ZOSTAVAX® Storage, Handling and RMP

Drs. Joan Benson and Adrian Dana, of Merck, described Merck's plans to educate healthcare providers on properly storing, handling and administering ZOSTAVAX®. Merck will apply its solid experience and lessons learned with frozen vaccines to ZOSTAVAX®, but will also implement unique strategies in these efforts. ZOSTAVAX® will be administered by internists, but this provider population typically has less experience with immunization than pediatricians. Merck will continue its ongoing discussions with the Shingles Workgroup and CDC to further refine the plans.

The following storage and administration requirements will be printed on the package. ZOSTAVAX® should be stored frozen at an average temperature of –15°C or colder until reconstituted for injection. The vaccine should be immediately administered after reconstitution to minimize loss of potency. Merck will use its three existing general educational activities on the storage and handling of adult vaccines for ZOSTAVAX®. First, the "Ready Set Vaccinate" provider education module will provide information to physician offices on storage, handling and all other aspects of immunization services. Second, live web cast educational programs will be aired on delivering safe and effective immunization services. Third, well-trained sales representatives will deliver information to physician offices on maintaining a vaccine storage temperature control log.

Specifically for ZOSTAVAX®, Merck will provide education to physician offices with appropriate freezer storage capabilities upon FDA approval of the vaccine. Physician offices without adequate freezer storage capabilities will be informed of alternate vaccination sites with capacity to store, handle and administer ZOSTAVAX®. Support services will be provided to physicians and office staff who request additional information. Merck administered a survey to 27,936 internist and family physician offices to determine existing freezer storage capabilities. Of all respondents, 59% had appropriate freezers and 29% had inappropriate freezers. For purposes of storing ZOSTAVAX®, a "freezer" is defined as having a separate door.

For physician offices with adequate storage and handling capabilities, sales representatives will request restocking of ZOSTAVAX®. Resources will be delivered to educate these offices in properly storing and handling the vaccine. For physician offices without adequate storage and handling capabilities, sales

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representatives will continue to reinforce the importance of adult vaccination. These offices will be informed of alternate vaccination locations to refer patients who are interested in receiving ZOSTAVAX®.

Merck will conduct medical education forums to educate providers on the ZOSTAVAX® product label and proper vaccine storage and handling. All physician offices that stock and administer ZOSTAVAX® will be given educational resources, including storage and handling guides, office reference materials, quick reference freezer door magnets, and inserts to the "Ready Set Vaccinate" education module. The distribution packaging for ZOSTAVAX® will prominently display warnings of frozen vaccine in the package that should be placed in the freezer immediately upon receipt. Storage instructions in each package will be required to be handled before the vaccine storage compartment is opened.

Providers will be informed about their ability to immediately obtain assistance and resolve concerns related to any Merck vaccine through the Merck National Service Center. Customer service representatives will be available during business hours and will also have an FDA-approved algorithm that can accurately assess the viability of frozen vaccines where the cold chain has been broken. Providers will also be made aware of their ability to return a Merck product that has expired or was damaged upon receipt.

The ZOSTAVAX® RMP will augment safety data from clinical trials of 21,000 adults and will include the following components. Merck's passive surveillance system will be used to provide routine safety monitoring. The Varicella-Zoster Virus Identification Program will be expanded to include reports and clinical specimens from physicians of zoster-like or varicella-like rashes temporally associated with the vaccine; potential transmission of the vaccine virus to contacts; potential central nervous system events in temporal association with the vaccine; and inadvertent exposure to or vaccination of immunocompromised persons. The existing pregnancy registry will be expanded to include ZOSTAVAX®. Studies will be conducted to address ZOSTAVAX®'s duration of protection and concomitant use with other routine adult vaccines, including pneumococcal polysaccharide and tetanus-containing vaccines. Post-marketing safety studies will be launched to obtain additional safety data.

The SPS will be expanded to collect persistence of efficacy data from ~7,000 vaccine recipients through an additional 4-6 years for a total of ten years post-vaccination. Merck completed the study on concomitant use with ZOSTAVAX® and the influenza vaccine and is currently analyzing the data. Several post-marketing studies are planned for ZOSTAVAX®. A placebo-controlled general safety study will compare serious AEs between 6,000 ZOSTAVAX® subjects and 6,000 placebo subjects. A large-scale observational study will analyze 20,000 vaccinated subjects in an MCO setting to gain additional knowledge on the safety of the vaccine in routine clinical practice. A high-dose observational study will analyze 5,000 subjects to obtain more information on the safety and potency of ZOSTAVAX® at higher doses. A randomized, placebo-controlled and double-blind study will assess the safety of ZOSTAVAX® among 300 subjects receiving low to moderate maintenance doses of corticosteroids.

Drs. Benson and Dana were pleased to announce the filing of Merck's refrigerator formulation for ZOSTAVAX®, but the timeline to approve this vaccine is unknown at this point. Overall, Merck will use its comprehensive RMP to follow the safety of ZOSTAVAX®. Merck will continue its strong commitment to increase and improve delivery and access to adult vaccines.

Drs. Benson and Dana provided additional details about the ZOSTAVAX® storage, handling and RMP in response to ACIP's questions.

- Merck has made strong efforts to distinguish clearly between its varicella-containing vaccines. The ZOSTAVAX® and VARIVAX caps have different colors. The commercial and generic names begin with "zoster" for ZOSTAVAX® and "varicella" for VARIVAX.

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However, efforts are underway at Merck to make the products even more distinct in the future.

- Merck develops periodic safety update reports every six months for all its vaccines to analyze problems related to confusion with the product, deliveries of inaccurate vaccines and other issues.
- The alternate vaccination sites will serve as a referral source for physician offices without adequate storage and handling capabilities or practices with no interest in administering ZOSTAVAX®. The sites include pharmacy chains and vaccine service providers who have indicated an interest in participating in the program. The sites will be encouraged to complete and return a notification of vaccination letter to the referring physician to ensure a record is maintained.

Considerations for Shingles Vaccine Recommendations in the United States

Dr. Rafael Harpaz, of CDC, reported that the Shingles Workgroup reviewed data on the burden and epidemiology of shingles and PHN, results of the SPS, and cost-effectiveness data to draft recommendations on shingles vaccination in the United States. Shingles is a reactivation of VZV that occurs decades after initial chickenpox and leads to a crop of blisters in the dermatomal distribution. Excruciating pain is nearly a universal component of shingles. PHN is the key sequela of shingles and is an incapacitating and prolonged condition that can last up to years. The effectiveness of PHN prevention and treatment is partial and inconsistent.

The risk of shingles increases ten-fold with age with annual rates of ~0.1% in children and ~1% in elderly persons. The risk of shingles progressing to PHN with pain lasting >90 days from rash increases three-fold with age. The progression from shingles to PHN is 6% in young adults and 20% in elderly persons. Immunosuppression is less common, but is still a high risk factor for shingles. However, the live attenuated ZOSTAVAX® vaccine is not licensed for immunosuppressed persons. The incidence of shingles and PHN in the United States is ~4/1,000 per year or ~1 million cases annually. The lifetime risk of developing HZ is 25%-30% with 100,000-200,000 new PHN cases occurring annually.

The pivotal SPS included >38,000 enrollees and demonstrated overall vaccine efficacy of 51% for HZ and 67% for PHN. However, vaccine efficacy for HZ and PHN ranged from 18%-74% depending on different age groups of 60-69 years, 70-79 years and ≥80 years. The SPS showed that vaccine efficacy for HZ and PHN declined in year 1, but remained stable through 48 months of follow-up. A protective effect was seen in persons who developed shingles despite vaccination history. The slight excess in serious AEs observed in a sub-study was not seen in the full SPS population and did not indicate causality due to a temporal or organ system pattern. Overall, the SPS found the vaccine to be safe.

The catalog price of ZOSTAX is $150 for a one-dose regimen. Merck's cost-effective analysis showed that the vaccine would be cost-effective from both a societal and payer's perspective at an average cost of $19,487 per QALY. For prevention purposes, ~22 persons would need to be vaccinated to prevent one shingles case and 65-100 persons would need to be vaccinated to prevent one PHN case. CDC's cost-effective analysis showed that the vaccine would be cost-effective from a societal perspective at a cost of $14,800-$34,900 per QALY. For prevention purposes, 17 persons would need to be vaccinated to prevent one shingles case and 31 persons would need to be vaccinated to prevent one PHN case. The cost per shingles and PHN cases prevented was $3,300 and $6,400, respectively.

The Shingles Workgroup has not reached consensus on the three draft recommendations at this time because the CDC and Merck cost-effectiveness analyses and data from the package insert were only recently presented. However, the workgroup is now soliciting ACIP's input on these issues. One, the

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workgroup's consensus opinion on whether ACIP should recommend universal or permissive shingles vaccination for persons ≥60 years of age is pending additional cost analysis data from CDC and Merck. However, the majority of members support a universal recommendation.

The workgroup is considering several issues to decide on a universal versus permissive recommendation. The burden of disease is substantial. The vaccine is safe and moderately effective. Survey data show interest by patients and providers. Preliminary results demonstrate that the vaccine is cost-effective from a societal perspective, but the workgroup acknowledged the evolving nature of economic tools to value pain and the sensitivity of these tools to assumptions. The main burden of pain is borne by the individual rather than the payer or society. Shingles is not contagious. Lost productivity and severe disease or death are likely to be less important to retirees and immunocompetent persons. However, PHN may be worse than death in extreme cases. Vaccine financing by Medicare, VA and private insurers will depend on the nature of ACIP's recommendation. Permissive language may reduce overall access and lead to social disparities.

Two, the workgroup is divided at this time on whether ACIP should extend guidance on shingles vaccination to persons 50-59 years of age beyond the package label. The majority of members supported no guidance for cohorts outside the package label. A minority of members were in favor of considering vaccination for this age group and highlighting the physician prerogative. No members expressed an interest in recommending shingles vaccination for persons 50-59 years of age at this time.

The workgroup is considering several issues to decide on these three options. The vaccine is not licensed for persons 50-59 years of age. ACIP has no history in making off-label recommendations for large cohorts. This guidance would establish a precedent and would also have broad implications for future ACIP recommendations. Physicians currently have the prerogative to vaccinate off-label, but specific language from ACIP may change practices. Persons 50-59 years of age have less pain with shingles than those in older age groups, but the burden of disease is still substantial and accounts for lost work productivity in this large population. No efficacy data have been produced to date on shingles vaccination in this population.

The SPS Phase III study demonstrated the plausibility of vaccine efficacy in subjects ≥60 years of age, but the data also showed that efficacy was highest in the youngest age strata. However, immunogenicity studies on persons 50-59 years of age included a minimal number of subjects and imperfect correlates of protection. Cost-effectiveness of vaccination in this population from a societal perspective is still unknown. Surveys indicate fair interest by providers of vaccination for persons 50-59 years of age.

Three, the workgroup is divided at this time on whether ACIP should restrict the shingles vaccination recommendation to persons <80 years of age. The majority of members supported a recommendation for all persons ≥60 years of age. A minority of members were in favor of restricting the recommendation to persons 60-79 years of age only and awaiting additional cost analysis data for this population.

The workgroup is considering several issues to decide on these two options. Persons >80 years of age are included in the package label. No specific safety concerns have been identified in this population. Vaccine efficacy against shingles is low in this age group with 0 confidence intervals. The SPS study was large, but power to detect effects was lower in persons >80 years of age. Vaccine efficacy would be likely in the context of results in younger cohorts. The risk of developing PHN and pain from shingles is reduced in vaccinees >80 years of age. Durability of protection from the vaccine out to four years was lowest in persons >80 years of age. The incidence of shingles and the risk of pain and PHN were found to be highest in the oldest population. However, persons >80 years of age are the most vulnerable and least aggressive age group to seek care. This population has the weakest ability to tolerate medications for controlling PHN and pain due to co-morbidities and poly-pharmacy.

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In addition to the three draft recommendations, the workgroup is also requesting ACIP's guidance on other issues for shingles vaccination. First, should ACIP give consideration to additional groups? These populations would include (1) mildly immunosuppressed persons with diabetes or patients on low-dose steroids, TNF-blockers and other immunomodulatory drugs; (2) persons with a prior episode of shingles because this population has not been formally studied to date; and (3) currently immunocompetent persons with an anticipated immunosuppressed status and a high risk of shingles, such as pre-transplant patients, early asymptomatic HIV patients, and patients who will undergo chemotherapy or immunosuppressive therapy for cancer, rheumatoid arthritis, lupus or other autoimmune diseases in the future.

Second, should ACIP address implementation issues? These recommendations would include (1) administration of the vaccine with the next scheduled visit, catch-up vaccination or another approach; (2) concomitant administration with pneumococcal, influenza and other adult vaccines; and (3) vaccine storage issues. Third, should ACIP provide guidance on post-marketing surveillance? These recommendations would include monitoring vaccine safety and duration of protection and identifying the need for boosters.

Dr. Poland expressed concern about ACIP delaying its vote on the shingles vaccine until the next meeting. He listed several reasons for ACIP to take action at this time. One of the largest published vaccine efficacy studies in history has demonstrated high morbidity rates of shingles among 1 million persons in the United States. Solid data have shown that the vaccine is cost-effective, safe and effective. HCWs and the public have expressed strong interest in the vaccine. FDA has licensed the vaccine. The manufacturer proposes to conduct one of the most extensive sets of post-marketing studies that has ever been implemented for a vaccine in history. Financing issues cannot be resolved until ACIP issues formal recommendations for use of the vaccine. Dr. Poland raised the possibility of placing a notice in the *Federal Register* of ACIP's vote on the shingles vaccine at this time and calling the vote by telephone.

Dr. Anne Schuchat, of CDC, emphasized that ACIP's vote on the shingles vaccine would be illegal and inappropriate from a federal perspective at this time because the public was not given advance notice. However, she pointed out that the time leading up to the October 2006 ACIP meeting could be used to present additional cost analyses, gather other data, identify outstanding gaps and answer the workgroup's questions. Drs. Abramson and Pickering added that ACIP votes must be published in the *Federal Register* at least 15 days in advance of a meeting. A notice was not published about ACIP's vote on the shingles vaccine. This requirement can be overruled in the event of a disease outbreak or other "emergency," but the shingles vaccine does not meet this criteria.

Dr. Neuzil made a formal statement for the record in her role as ACIP's liaison to ACP. ACP is the nation's largest medical specialty society with ~120,000 members representing general internists and sub-specialty physicians. The Adult Immunization Advisory Committee (AIAC) oversees ACP's vaccine issues and strongly favors a universal recommendation for all immunocompetent adults $\geq$60 years of age to receive HZ vaccine. AIAC's position is that this recommendation would be consistent with evidence from a high-quality and randomized controlled trial that supports the safety and efficacy of the vaccine. The recommendation would also address the substantial burden of illness and suffering associated with HZ. AIAC's overall opinion is that a universal recommendation is the only strategy to ensure optimal uptake and access to the vaccine for all eligible patients.

Dr. Sandra Fryhofer is a member of the ACP AIAC. As a practicing general internist in Atlanta, Georgia, she has first-hand knowledge of the pain, suffering and devastating effect on quality of life caused by shingles. Of the total population, 2-3 of every 10 persons will suffer from shingles at some point in their lives. The complications from shingles can range from an uncomfortable rash to eye and skin problems, scarring, nerve paralysis, pneumonia, encephalitis or death. Excruciating pain from PHN can last for months or years and may be more severe than chronic cancer pain, post-surgery pain or labor pain

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according to pain comparison scores. Data show that the shingles vaccine can reduce the number of cases by 50% and decrease overall pain by 40%. Dr. Fryhofer urged ACIP to issue a universal recommendation for the shingles vaccine to all eligible persons ≥60 years of age to ensure no individual in need will be denied access to the benefits of the vaccine.

Childhood/Adolescent Immunization Schedule (CAIS) for 2007

Dr. Calugar described ongoing efforts by the Childhood/Adolescent Immunization Workgroup to develop the 2007 CAIS and refine the existing format. In 1983, the childhood immunization schedule included vaccines to protect from diphtheria, tetanus, pertussis, measles, mumps, rubella and polio. At this time, children received five shots by 2 years of age and no more than one shot at a single visit due to the combination of the DTP and MMR vaccine and oral administration of the polio vaccine. By 1996, the childhood immunization schedule included the addition of the varicella and Hib vaccines; the inclusion of new recommendations for HepB vaccine, including its use in adolescents; the introduction of colored bars for catch-up vaccination and ranges of acceptable ages for vaccines; and other significant modifications.

Since 1983, the CAIS has been increasingly more complex. The current CAIS covers 14 vaccines and ages 0-18 years. Yellow bars represent the range of recommended ages; green bars represent catch-up immunization; a purple column emphasizes the importance of the visit at 11-12 years of age; and a red box describes special populations. Italics are used to emphasize that the HepB vaccine dose at 4 months of age is permissible if combination vaccines were used after the birth dose. Italics are also used to underscore that the Hib vaccine at 6 months of age is not required if PedVaxHIB or COMVAX vaccines were administered.

The workgroup updates the CAIS each year with new ACIP recommendations, but the members recognized that additional efforts must be made for 2007. Most notably, the rotavirus and quadrivalent HPV vaccines were licensed and recommended in 2006. ACIP approved new policies for existing vaccines in 2006. Influenza vaccination recommendations were extended to children 24-59 months of age and dose 2 of the varicella vaccine was approved. CDC staff, the CDC hotline and workgroup members routinely receive feedback on the CAIS from the field. The most common concerns are related to the CAIS being overcrowded and overwhelmed with pictures and information; the need for a better approach than italics for the HepB vaccine dose at 4 months of age; and the poor appearance of the purple bar for the assessment at 11-12 years of age. Some HCWs reported that the footnotes are too detailed, while others supported more informative and comprehensive footnotes.

Concerns from the field and the increasing complexity of the CAIS prompted the workgroup to develop a better and more user-friendly format while incorporating ACIP's new recommendations into the 2007 CAIS. To undertake this effort, the workgroup partnered with the University of Michigan Child Health Evaluation and Research Unit to conduct focus groups with 102 pediatricians, family practitioners, public and private-sector immunization providers, and nurses. The focus groups were held in diverse settings, including private pediatric and family practice offices, adolescent and school-based clinics, local public health departments, federally qualified health centers, and an open session for immunization providers during the National Immunization Conference.

The focus groups were designed to address three major topics: (1) feedback on the current CAIS; (2) impressions about several alternative formats the workgroup developed based on previous input; and (3) changes to include in future CAISs. Key results of the focus group discussions are summarized as follows. The respondents generally agreed on six issues. Separate childhood and adolescent schedules would be helpful and easier to read. The color legend should be placed on the side rather than the bottom of the CAIS. The purple bar for the assessment at 11-12 years of age should be deleted. The red

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dotted box for special populations is confusing and a colored bar should be used instead. Footnotes in a bulleted rather than paragraph format would be easier to read. Placement of the minimum age at vaccination in the footnotes was preferred.

Opinions about the following issues varied among respondents. Some respondents believed the italicized text for the HepB vaccine was overwhelmed by other information and could be confused as a four-dose series. Other respondents noted that the italicized text clarified the administration of only three the HepB vaccine shots. The respondents believed the italicized text for the Hib vaccine at six months was useful in reflecting differences in administration of different products, but agreement was not reached on a clear approach to distinguish among various brands.

The respondents did not believe the existing format for meningococcal conjugate vaccine (MCV4) reflected usual practice. Several respondents pointed out the need to emphasize MCV4 vaccination of adolescents at high school entry. The respondents questioned the order of vaccines in the CAIS. The respondents did not reach agreement on the overall format for the adolescent component of the CAIS. The respondents noted that catch-up vaccination should be emphasized, but the recommendations should not be overwhelmed with colors and other features. Some respondents supported shorter footnotes because the Red Book, web sites and other resources could be reviewed for additional information. Other respondents were in favor of more detailed and comprehensive footnotes because providers do not have sufficient time during routine practice to locate additional references.

The workgroup is now proposing that the following changes be made to the CAIS based on the focus group results. The color legend should be placed on the side. Special populations should be represented with purple bars. The red box should be deleted. Vaccines should be placed in chronological order of administration. Users of the CAIS should be referred to footnote 1 to obtain more information about permissible administration of the HepB dose at four months of age when combination vaccines are given after the birth dose. ACIP's rotavirus vaccine recommendation should be abbreviated in the CAIS as "Rota."

The italicized font for Hib vaccine at six months of age should be retained because this approach was well accepted by most focus group respondents. Influenza immunization should be extended through 59 months of age for consistency with ACIP's recommendation. In anticipation of changes to the varicella vaccine recommendation, the CAIS should be revised to illustrate the administration of dose 1 at 12-15 months of age and dose 2 at 4-6 years of age. The footnotes should be reorganized into a bulleted format. The minimum age for administration of each vaccine should be highlighted on the first line of each footnote. Two special bullets should be incorporated for the HepB dose at 4 months of age and brand names of the Hib vaccines.

Schedules for age groups of children 0-6 years and 7-18 years should separated based on responses by immunization providers to several alternative drafts of the CAIS. For the schedule of children 7-18 years of age, the color legend should be placed on the side. The purple column for the assessment at 11-12 years of age should be deleted. This visit should be emphasized with the title and all vaccines in the column in bold. Tdap, the HPV series and MCV4 should be placed at the top of the column due to the importance of these vaccines during the young adolescent visit. The footnotes should be reorganized into a bulleted format. Based on the focus group results, the workgroup developed two drafts of the new immunization schedule for children 7-18 years of age with the same content and different formats. "Alternative B" was designed with dashed colored lines rather than bars.

The workgroup will take several actions in preparation of the October 2006 ACIP meeting. The focus group research will continue. Collaborative efforts will be undertaken with subject matter experts on the content of the footnotes and catch-up schedule. Field tests will continue to be conducted to obtain input on the schedule for children 0-6 years of age; the preferred format for the schedule for adolescents 7-18

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years of age; updates to catch-up schedules; and black-and-white formats. A decision will be made on the best approach to convey information about MCV4 immunization because the focus group respondents pointed out that MCV4 catch-up vaccination during the high school entry visit might create confusion among providers. The workgroup intends to present and solicit ACIP's approval on the final schedule during the October 2006 meeting and publish the approved schedule in the *MMWR* in January 2007.

Dr. Middleman strongly recommended developing a separate adolescent immunization schedule due to the dramatic shift in the care of children at 11-12 years of age. Most notably, morbidity and mortality from risky behaviors serve as the primary risk to this age group rather than vaccine-preventable diseases. She pointed out that a separate adolescent immunization schedule and a solid statement about the importance of adolescent immunization as a component of broader care would emphasize the shift in care and strengthen general preventive care and healthcare visits in this population.

Dr. Middleman noted that a separate adolescent schedule would also underscore the importance of immunization, highlight the critical need for preventive care across the life span, and provide a strong link between adolescent and adult immunizations. This change could play a significant role in advancing the adolescent preventive care field and enhancing other types of care in this traditionally underserved population.

On the one hand, Dr. Poland and Ms. Stinchfield were in favor of Dr. Middleman's suggestion for a separate immunization schedule for adolescents beginning at 11 years of age. If ACIP approves the recommendation, Dr. Poland urged CDC to develop the childhood and adolescent immunization schedules with similar formats to the adult immunization schedule. Dr. Georges Peter, of Brown Medical School, served on NVAC when the recommendation was adopted to change the "pediatric immunization standards" to "childhood and adolescent immunization standards." He pointed out that Dr. Middleman's suggestion for separate immunization schedules for pre-adolescent and adolescent age groups would be consistent with the terminology NVAC previously approved.

On the other hand, Dr. Calugar noted that the focus group results differed from Dr. Middleman's suggestion. Although most respondents also supported separate childhood and adolescent immunization schedules due to programmatic issues, children 0-6 years and adolescents 7-18 years were the preferred age cutoffs between the two groups. Dr. Gary Freed, the NVAC liaison, emphasized the critical need to apply feedback from practitioners in the field who actually use the CAIS.

Dr. Wallace confirmed that CDC and the Childhood Adolescent Immunization Workgroup would use the focus groups to more vigorously test the adolescent schedule. Collaborative efforts would also be undertaken with AAP, SAM and other relevant groups to develop and pilot alternative immunization schedule formats prior to the October 2006 ACIP meeting. Dr. Wallace mentioned that CDC and the workgroup would also need to address requests from the field to issue immunization schedules for all age groups at the same time. Dr. Abramson asked the workgroup to report on the field test results of the alternative immunization schedule formats during its presentation to ACIP in October 2006.

Update on the Multi-State Mumps Outbreak in the United States

Dr. Jane Seward, of CDC, reported on the U.S. mumps outbreak that occurred in 2006 with a comparison to the U.K. mumps outbreak of 2004-2005. The mumps vaccine was licensed in the United States in 1967 and a routine childhood recommendation was made in 1977. Mumps cases substantially declined, however, a resurgence in mumps cases occurred in the late 1980s. A two-dose measles, mumps and rubella (MMR) schedule was implemented in 1989 that contributed to a dramatic decline in mumps cases

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with <300 cases reported each year since 2001. In 1998, the *Healthy People 2010* goal was established to eliminate indigenous mumps transmission in the United States. Despite the small number of cases reported each year, some small, isolated outbreaks have occurred.

For example, in February 2006, CDC published a report in the *MMWR* of a mumps outbreak that occurred at a New York State summer camp in 2005 with 31 cases of unvaccinated counselors and two-dose vaccinated campers. The index case was identified as an unvaccinated camp counselor from the United Kingdom. In March 2006, CDC published a dispatch in the *MMWR* of a mumps epidemic of ~600 cases that occurred in Iowa in 2006.

CDC took several actions in response to the outbreaks. Activities were coordinated at the national level with ACHA, CTSE and the Association of Immunization Managers. Information was shared with public agencies and private organizations. Guidance documents were distributed to summer camp associations and healthcare settings. The media were alerted and documents were placed on the CDC web site. A national health advisory was issued. Several CDC divisions provided technical support and expertise to support mumps surveillance and clinical activities, epidemiological investigations and laboratory diagnostics.

CDC used its National Notifiable Disease Surveillance System (NNDSS) as a key data source during the mumps outbreaks. CDC also received biweekly reports of mumps cases from states with case classifications, hospitalizations and deaths to ensure that data would be timely and consistent with information posted on state web sites. CDC collaborated with affected states and published an updated dispatch on the multi-state mumps outbreak in the *MMWR* in May 2006. Of 4,602 cases reported as of June 20, 2006, 1,940 were from Iowa and 1,920 were from seven other outbreak-related states (OB-7): Illinois, Kansas, Missouri, Nebraska, Pennsylvania, South Dakota and Wisconsin. Five states had travel-related cases or cases related to temporary residence in one of the mumps outbreaks. The outbreaks in Iowa and the OB-7 states peaked between the weeks of April 8-May 6, 2006 and then declined.

Of 3,680 cases reported from Iowa and the OB-7 states, 65% were among females. The median age of cases was 22 years with a range from <1-96 years. NNDSS provisional data showed that the incidence of mumps per 100,000 persons in all eight outbreak-related states ranged from 65.3-0.7 with the highest rates in Iowa, Kansas, South Dakota and Nebraska. However, incidence rates are expected to increase in Wisconsin and Illinois because NNDSS reports from these states are not up-to-date at this time. By age group, the incidence of mumps cases was highest in persons 18-24 years in all eight outbreak-related states.

Mumps cases primarily occurred among college students and HCWs, but a few outbreaks were reported in schools and child care centers as well. Transmission remained fairly focused with little or no spread to infants or populations that refused vaccine. As of June 17, 2006, Iowa reported that 7% of its cases were unvaccinated, 14% had received one MMR dose, 50% had received two MMR doses, and 30% had an unknown vaccination status. However, CDC acknowledges that reporting information on vaccination status of cases through NNDSS is incomplete and is now encouraging states to submit up-to-date information.

Laboratory data of the 2006 mumps outbreaks showed isolation of the G genotype from 21 specimens submitted by nine states. Clinical data reported through NNDSS showed that 81% of 3,860 mumps cases had a history of parotitis and some cases reported serious complications, including meningitis, encephalitis, orchitis, deafness or hospitalization. However, 11 of 66 hospitalizations reported by the state biweekly reports were not related to mumps. No deaths were reported among any of the mumps cases. Preliminary data from CDC's epidemiological and laboratory investigations showed attack rates of 2% and 3.8%, respectively, in two highly affected college campuses in Iowa. Coverage rates of two MMR doses were found to be 97% and 77%, respectively, among college students at these two campuses.

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CDC's college roommate contact study in Iowa showed a vaccine failure rate of ~8% among two-dose recipients.

CDC is partnering with several groups in other epidemiological and laboratory investigations. The sensitivity and specificity of immunoglobulin M (IgM) test kits that are not FDA-approved are being compared to the CDC capture assay in collaboration with Iowa and Wisconsin state health laboratories. A waning immunity study was completed at an unaffected college campus in Nebraska with 450 MMR two-dose students in collaboration with FDA and Merck. Cross-neutralization studies are underway in collaboration with FDA, Merck and Japanese agencies. CDC will continue to partner with the Kansas and Iowa public health departments to conduct additional studies on vaccine coverage, efficacy and failure; viral shedding; mumps risk factors in college settings; attitudes and adherence to isolation; costs of the mumps public health response; and infection control and nosocomial transmission among HCWs.

The large U.K. mumps outbreak occurred in 2004-2005 with 72,000 reported cases and the highest incidence among persons 15-24 years of age. The U.K. and U.S. epidemiology differed because 67% of cases were unvaccinated in the United Kingdom, 30% had received one MMR dose, and 3% had received two MMR doses. The U.K. mumps incidence was 20-50 times higher than in the United States prior to the outbreak and 70 times higher during the outbreak based on an assumption of 5,000 cases in the U.S. outbreak.

Differences in the U.S. and U.K. mumps vaccination programs played a key role in the higher incidence in the United Kingdom. For example, the U.S. mumps vaccination program was established 21 years before the U.K. program. The United States implemented a two-dose MMR schedule seven years before the United Kingdom. Coverage of one MMR dose in the United States is 11% higher than the United Kingdom. Coverage of two MMR doses in the United States is >20% higher than the United Kingdom due to U.S. school entry requirements.

CDC used ACIP's 1998 MMR statement and the joint 1997 ACIP/Healthcare Infection Control Practices Advisory Committee (HICPAC) recommendations as policy to guide outbreak response to the mumps outbreak. However, discrepancies were identified between policy and evidence of immunity. On the one hand, ACIP's MMR statement recommended two doses for school-age and college-age students for measles control and elimination. The ACIP/HICPAC guidance for HCWs recommended a one-dose mumps policy, placed minimal emphasis on the importance of mumps immunity, and merely stated that immunity to mumps would be "highly desirable." On the other hand, the evidence of immunity for mumps through vaccination supported one dose for all age groups.

ACIP convened a conference call on May 17, 2006 to address these discrepancies. CDC and the Iowa Department of Public Health presented scientific evidence to demonstrate that a second MMR dose would provide additional protection and effectiveness of >10%. Key points from ACIP's updated recommendations on the control and elimination of mumps are highlighted as follows. Based on changes in evidence of immunity through vaccination, children 1-4 years of age and low-risk adults should receive one MMR dose. School-age children, students in post-high school educational facilities, international travelers and HCWs should receive two MMR doses. HCWs without other evidence of immunity should routinely receive two MMR doses. HCWs born before 1957 should consider one MMR dose in a non-outbreak setting and should strongly consider two MMR doses during an outbreak. Children 1-4 years of age and low-risk adults affected by an outbreak should be given a second MMR dose. ACIP's updated mumps recommendations were published in the *MMWR* on June 1, 2006.

CDC has identified several potential reasons for the mumps outbreaks. Importation or the index case was not detected. Recognition of the outbreak was delayed because physicians are no longer familiar with mumps, the disease has been modified by vaccine, and some early cases were ruled out due to negative IgM. Colleges have the potential for high transmission and lower two-dose vaccine coverage

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than other school settings. Adherence to isolation guidelines may be poor in college settings. Vaccine effectiveness of 90% and two MMR doses may result in the accumulation of susceptible persons with sufficient capacity to periodically sustain transmission and sizeable outbreaks. Waning immunity could contribute to mumps outbreaks. However, CDC acknowledges that high vaccine coverage at the community level, vaccine effectiveness and a relatively low incidence rate most likely prevented 30,000-40,000 mumps cases.

Dr. Seward and other CDC staff provided additional details on the mumps outbreaks in response to ACIP's questions.

- The position of several state epidemiologists is that differences in college immunization rates most likely played a stronger role than other variables in the mumps outbreaks.
- CDC is continuing its collaborations with FDA and Merck on neutralizing antibody testing to determine susceptibility, seronegativity and a decline in neutralizing antibody levels among persons who were vaccinated ≥15 years previously.
- The index case in the Boston measles outbreak was identified as a male from India ~35 years of age with the D8 genotype. Aggressive actions were take to administer >10,000 MMR doses to persons 25-40 years of age because NHANES data show that this population has the highest susceptibility of measles of 20%. The vaccination status was unknown in many of the measles cases.

Dr. Martin Myers, of the National Network for Immunization Information, pointed out that the dissemination of inaccurate information on the MMR vaccine in the United Kingdom contributed to the U.K. outbreak in addition to differences between the U.S. mumps vaccination program. The distribution of inaccurate information in the United Kingdom may have played a role in the U.S. mumps outbreaks as well.

Update on the Rotavirus Vaccine

Dr. Umesh Parashar, of CDC, described activities that have occurred since ACIP adopted recommendations and passed the VFC resolution for the rotavirus vaccine in February 2006. ACIP's recommendations were submitted to the *MMWR* on April 5, 2006 and are expected to be published on August 11, 2006. Merck data show that from February 6-June 28, 2006, 670,000 doses were distributed in both private and public sectors throughout the country. The commercial and VFC prices for the rotavirus vaccine were established at $63.25 and $52 per dose, respectively. ACIP's provisional recommendations can now be accessed on the NIP web site.

Of 22 rotavirus vaccine-related reports submitted to VAERS as of June 23, 2006, two were intussusception cases. Case 1 was reported from a study in Mexico of a male child 6 months of age with onset of symptoms two days after dose 3. The child had a concomitant common cold and intussusception resolved after a second attempt at air enema. Case 2 was a female child 2.5 months of age with onset of symptoms six days after dose 1. The child required surgery and resection of necrotic bowel. The child's older sibling had diarrhea 1-2 days prior to the onset of symptoms in the case. CDC is now analyzing clinical specimens and tissues from the surgical resection to detect rotavirus, the specific vaccine strain, adenovirus or other agents.

In addition to daily monitoring of VAERS reports by CDC and FDA, other safety monitoring activities of the rotavirus vaccine will be conducted as well. CDC will use its VSD birth cohort of ~80,000 infants to detect and formally evaluate risk signals that are identified through passive reporting or other mechanisms. Merck will conduct active surveillance of a different managed care birth cohort of ~44,000 infants. CDC,

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FDA and Merck will continue to convene biweekly conference calls to discuss updated data from various systems, share information and develop plans for future studies.

A study that is in press and will be published in *Pediatrics* in August 2006 provides estimates of the number of naturally occurring intussusception cases that would be temporally associated with rotavirus vaccination by chance alone (Tai, *et al.*) In anticipation of concerns raised by such reported cases, CDC calculated the number of natural intussusception cases that would occur within two weeks after rotavirus vaccination. Vaccine coverage rates for DTaP and the age-specific incidence of intussusception were incorporated into the model. The model was designed with a "strict" schedule of vaccine administration at 2, 4 and 6 months of age and a "free" schedule of vaccine administration any time in the first year of life.

The results of CDC's analysis are summarized as follows. After doses 1-3 of the rotavirus vaccine, a total of 138 intussusception cases would occur within two weeks with the strict schedule and a total of 182 cases would occur within two weeks with the free schedule. Thus, within two weeks of administration of a rotavirus vaccine dose by chance alone, ~130-180 natural intussusception cases would occur. Most cases would occur after doses 2 and 3. Fewer temporally-associated intussusception cases would occur with the strict schedule compared to the free schedule. The overall incidence of intussusception per 100,000 doses would be 4.59 cases with the strict schedule and 4.76 cases with the free schedule.

In addition to monitoring the safety of the rotavirus vaccine, CDC will also monitor its effectiveness. The existing New Vaccine Surveillance Network with sentinel sites at Cincinnati, Rochester and Vanderbilt will be used to monitor and evaluate post-licensure vaccine effectiveness against laboratory-confirmed hospitalizations and emergency department visits for rotavirus diarrhea. Active and population-based surveillance will be performed in three U.S. counties. Specimens will be collected and tested for rotavirus from children <3 years of age who are hospitalized or who visit emergency rooms or outpatient clinics for diarrhea. Vaccine effectiveness will be evaluated by monitoring disease trends over time and conducting a case-control study in the field.

CDC will use its existing laboratory network of 12 laboratories throughout the country to monitor the impact of the rotavirus vaccine against virus strains. To date, the laboratory network has characterized ~3,000 strains. CDC will apply the surveillance system prospectively to identify unusual strain patterns that emerge in the future.

***Ex Officio* Reports**

NVAC. Dr. Gary Freed covered the following areas in his first *ex officio* report to ACIP as the new NVAC Chair. NVAC was recently charged with addressing vaccine financing. The IOM's two previous studies on this issue did not lead to conclusions that were universally accepted or adopted. The inability to reach agreement on this topic to date is based on two different perspectives in the vaccine financing community. On the one hand, some persons believe the entire system is damaged and a completely new process should be developed. On the other hand, some persons believe specific components of the current vaccine financing system are sub-optimal and contain significant gaps. Moreover, new recommendations and government programs create problems or emphasize particular elements in the current system that should be changed.

Dr. Freed announced that NVAC will most likely address specific components of vaccine financing associated with the most significant problems at this time. NVAC will achieve this goal by convening a new Vaccine Financing Workgroup over the next three months with representation by NVAC, ACIP and selected professional organizations, and governmental agencies. Other interested groups will be provided opportunities to give testimony or make presentations to the workgroup. NVAC's preliminary

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discussions to date have resulted in general agreement to charge the workgroup with identifying optimum solutions to improve the financing of vaccines for children, adolescents and adults throughout the nation.

Health Resources and Services Administration (HRSA). Dr. Geoffrey Evans covered the following areas in his report for HRSA. As of April 2006, >5,000 claims were submitted in response to the Omnibus Autism Proceeding. The hearing on the autism and autism spectrum disorder litigation is expected to be held in late 2007 or early 2008. The first phase of discovery and data collection is nearly complete. The court has given petitioners a deadline of 2006 to early 2007 to submit expert witness reports for the next phase of the litigation. Based on results of a recent industry survey to manufacturers of all vaccines covered under the National Vaccine Injury Compensation Program, the number of vaccine lawsuits is extremely low with the exception of the ongoing autism litigation.

Dr. Evans announced that legislation is pending in both the House and Senate to add an excise tax for the conjugate and polysaccharide meningococcal vaccines. A bill was also recently introduced in the House to add an excise tax for the HPV vaccine. The U.S. Court of Appeals for the Federal Circuit made three decisions in 2005 and 2006 that would relax the standard for the claims court to make a ruling on off-table vaccine claims. Based on two decisions, the Special Master could rely on medical records and medical opinion, but would not be required to use scientific literature. Several claims court judges have reversed vaccine claims based on these two decisions. Dr. Evans committed to providing ACIP with regular updates on all three decisions as new developments occur.

NIH. Dr. George Curlin covered the following areas in his report for NIH. HHS and NIH are supporting several manufacturers to produce H5N1 influenza vaccines for clinical testing at NIH. The clinical trials are designed to assess vaccine safety and determine whether certain adjuvants or routes of administration can improve immunogenicity of influenza vaccines. NIH's vaccine studies for influenza viruses with pandemic potential are being conducted by various manufacturers and cover multiple viruses, age groups and vaccine types. Research is also being planned to analyze strategies to optimize the dose required to protect persons against pandemic influenza.

Novartis, sanofi pasteur and Baxter are now conducting studies of inactivated H5N1 influenza vaccines, while MedImmune will conduct a study of the H5N1 LAIV in the future. Novartis and sanofi pasteur are currently analyzing and verifying safety and immunogenicity data on use of inactivated vaccines in adults, children and elderly persons. The studies are also analyzing inactivated vaccines on the basis of an adjuvant and an intradermal versus intramuscular route of administration. The manufacturers expect to produce reports from these studies later in 2006. In January 2006, sanofi pasteur published a report in the *New England Journal of Medicine* on prime and booster doses of a two-dose inactivated vaccine schedule for adults. Dr. Curlin encouraged ACIP and members of the public to access www.clinicaltrials.gov to obtain additional information on all of NIH's clinical trials.

Public Comment Period

Ms. Laura Bono, of the National Autism Association, made the following comments for ACIP's consideration. Her son was developing normally at 16.5 months of age, but his speech and social skills discontinued soon after receiving four different vaccines on the same day. The 50 µg of thimerosal he received from the four shots were 45 times the EPA limit for mercury for an infant of his weight. Her son is now 17 years of age and has been diagnosed with ~20 different conditions caused by mercury toxicity since receiving the four shots at 16.5 months of age.

Ms. Bono pointed out that experts from CDC and other groups have made public statements about the risks of thimerosal-containing vaccines. However, data on the subset of children who develop autism

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from thimerosal-containing vaccines have been deleted from research to avoid embarrassing NIP. A study that showed no association between thimerosal and autism was published in *Pediatrics* in November 2000.

Ms. Bono further noted that misguided and uninformed policymakers are approving heavy metal-containing vaccines without knowledge of the most recent research on heavy metal toxicity. She emphasized the critical need for ACIP and other vaccine policymakers to take four important actions. One, appropriate heavy metal toxicity tests should be conducted before vaccines are approved. Two, research should be performed on the relationship between thimerosal and autism. Three, the issue of "safe" vaccines should always be paramount during the decision-making and approval process. Four, ACIP should state a preference for thimerosal-free and aluminum-free vaccines for pregnant women and children.

Cmdr. Stephen Kay, of the U.S. Navy, made the following comments for ACIP's consideration. His son was developing normally after his birth in April 1999, but he began displaying traditional autistic characteristics soon after receiving 281.37 µg of mercury from routine immunizations during his first year of life. His son is now 7 years of age and was diagnosed with mercury poisoning in 2003. The developmental pediatrician who made the diagnosis gave his son no longer than three months to live if the mercury poisoning had not been detected at that time. His son's speech, social skills and other developmental milestones are no longer comparable to other children his age. The financial responsibility in providing medical care for his son continues to place an enormous burden on the entire family. On behalf of his son and other similarly affected children, Cmdr. Kay urged ACIP to recommend thimerosal-free and aluminum-free vaccines.

Mr. Scott Bales is the Vice President of the Autism Society of America-Georgia Chapter. He made the following comments for ACIP's consideration. Mr. Bales is 48 years of age and attributes his autism to vaccines that were administered to him as an infant, but are now banned. He described several challenges encountered by the vast majority of the adult autism population, such as chronic sensory problems, allergies and other health issues; frequent emergency department visits; sexual exploitation; dependence on others for care; reliance on public financial assistance programs; and an inability to obtain and retain employment. He conveyed that adults with autism are unique compared to adults with other conditions. Most notably, organizations for cerebral palsy, muscular dystrophy and other "physical" disabilities have no interest in including or assisting autistic adults due to the complexity of this disease. Mr. Bales urged ACIP to recommend the removal of heavy metals from vaccines.

Closing Session

Dr. Abramson thanked the ACIP members, liaison and *ex officio* representatives, and members of the public for attending and participating in the meeting.

With no further discussion or business brought before ACIP, Dr. Pickering adjourned the meeting at 3:31 p.m. on June 30, 2006.

I hereby certify that to the best of my knowledge, the foregoing Minutes of the June 29-30, 2006 ACIP Meeting are accurate and complete.

This document has been archived for historical purposes.

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Date

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

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