CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL IMMUNIZATION PROGRAM

RECORD OF THE MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

February 21-22, 2006

Meeting held at the Centers for Disease Control and Prevention
Atlanta, Georgia

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Acronyms Used In This Report

AAFP	American Academy of Family Practitioners
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetrics and Gynecology
AE (SAE)	Adverse Event (Seriours AE)
AIS	Adenocarcinoma In-Situ
AMA	American Medical Association
ASC	American Society for Colposcopy
ASCCP	American Society for Colposcopy and Cervical Pathology
ASCUS	Atypical Squamous Cells Of Undetermined Significance
CB®	Cost Benefit (Ratio)
BRFSS	Behavioral Risk Factor Surveillance Survey
CAP	Condom-Availability Programs
CDC	Centers for Disease Control and Prevention
CER	Cost Effectiveness Ratio
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
D&C	Dilation and Curettage
DCPC	Division of Cancer Prevention and Control
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DSTD	Division of STD Prevention
DTaP	Diphtheria, Tetanus, Acellular Pertussis (vaccine)
ED	Emergency Department
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
FRC	Famiy Research Council
GMC	Granulocyte Macrophage Colony
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HPV	Human Papilloma Virus
HSIL	High-Grade Squamous Intraepithelial Lesions
HZ	Herpes Zoster
ID	Intradermal
IDSA	Infectious Disease Society of America
Ig	Immune Globulin (IgA, class A, IgG, class G)
IGIV	Intravenous Immune Globulin
IM	Intramuscular
IND	Investigational New Drug
IPV	Injected Polio Vaccine
LAIV	Live Attentuated Influenza Vaccine
MMR(V)	Measles, Mumps, Rubella (Varicella) vaccine
MPSV	Meningococcal Polysaccharide Vaccine
NACCHO	National Association of County and City Health Officials

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NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NCID	National Center for Infectious Diseases
NFID	National Foundation of Infectious Diseases
NHANES	National Health and Nutritional Examination Survey
NHIS	National Health Interview Survey
NIH	National Institutes of Health
NIP	National Immunization Program
NSFG	National Survey of Family Growth
NVPO	National Vaccine Program Office
NVSN	National Vaccine Surveillance Network
OPV	Oral Polio Vaccine
PAP	Papanicolau (cancer test)
PHN	Post-Herpetic Neuralgia
PPD/TST	Purified Protein Derivative/Tuberculin Skin Test
PRV	Pentavalent Human Bovine Reassortant Rotavirus Vaccine
QALY	Quality Adjusted Life Year
REST	Rotavirus Efficacy and Safety Trial
RFI	Request for Information
RRP	Recurrent Respiratory Papillomatosis
RV	Rotavirus
SAM	Society for Adolescent Medicine
SEER	Surveillance, Epidemiology and End Results
SES	Socioeconomic Status
SNS	Strategic National Stockpile
SPS	Shingles Prevention Study
STD	Sexually Transmitted Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VFC	Vaccines for Children (Program)
VLP	Virus-Like Particles
VSD	Vaccine Safety Datalink
VZV	Varicella Zoster Virus
VZIG	Varicella Zoster Immune Globulin
WHO	World Health Organization

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

MINUTES OF THE MEETING
FEBRUARY 21-22, 2006

OCTOBER 26, 2005

A meeting of the Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention's (CDC) National Immunization Program (NIP) at the CDC Global Communications Center in Atlanta, Georgia, on February 21-22, 2006. This report is organized according to the meeting agenda, which was posted on CDC's ACIP website and distributed at the meeting. ACIP Chairman Dr. Jonathan Abramson convened the meeting at 8:02 a.m., welcoming all in attendance (see Attachment #1).

OPENING COMMENTS

ACIP Executive Secretary Dr. Larry Pickering made several announcements:

- He welcomed the new NIP Director, Dr. Anne Schuchat; Dr. Robert Davis, director of the CDC Immunization Safety Office (ISO); and Dr. Jean Smith, Assistant to the NIP Director for Immunization Policy.
- New liaisons present were Dr. Jeffrey Duchin, for the NACCHO.
- Dr. Renee Jenkins attended for Dr. Patricia Whitley-Williams (NMA), as did Dr. Mark Whitaker for Dr. Andrea Gelzer (AAHP). Dr. Charles Helms (NVAC) was absent.
- The ACIP home page is www.cdc.gov/nip/acip and the email address is acip@cdc.gov.
- The remaining 2006 ACIP meeting dates are June 29-30 and October 25-26.
- ACIP Protocol: A quorum of ACIP members must be maintained to conduct committee business. In the absence of a quorum (eight members) of members qualified to vote, the ACIP charter allows the Executive Secretary to temporarily designate ex officio members as voting members. If voting, the ex-officio members are asked to disclose any potential conflicts of interest. ACIP members with potential conflicts of interest are asked to disclose all vaccine-related work and financial interests, and to refrain from any discussion or vote that is related to such matters. When needed, however, limited waivers of such conflicts of interest can be granted to enable the members to provide their expertise to the Committee. Waivers may be issued, for example, to members who also conduct clinical vaccine trials, or who serve on a Data Safety Monitoring Board (DSMB). Those members may provide information to the committee and discuss other vaccines produced by the same company, but they may not participate in discussion on the vaccine involving their conflict, nor in any related votes.
- Meeting time is reserved for public comment at scheduled intervals, but may also

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occur during open discussion if time permits and the Chair recognizes a speaker.

- Slide presentations from this meeting were posted on the ACIP website after the meeting.

The members and liaisons then introduced themselves (see Attachment #1). Those reporting potential conflicts of interest were Mr. Beck (awaiting a decision from the Office of General Counsel about stock), Dr. Gilsdorf (uncompensated, independent safety monitor for an NIH-sponsored vaccine trial, but not compensated); Dr. Harry Hull (discussing potential projects with MedImmune); Dr. Greg Poland (chairs a Merck DMSB, serves on the DVC scientific advisory board and has conducted clinical trials for Chiron, Merck, and Vaxgen); and Dr. John Treanor (conducting influenza vaccine clinical trials for Merck, GlaxoSmithKline (ID Biomedical); Protein Sciences Corporation, and conducting laboratory studies for AlphaVax).

HUMAN PAPILLOMAVIRUS VACCINE

Background

Dr. Janet Gilsdorf, HPV Working Group Chair

Overview: Summary of HPV vaccine Working Group activities

- The HPV vaccine Working Group was formed in February 2004; members include representatives from ACIP, FDA, NIH, NIP, DSTD, DCPC, NCID and Consultants/liaisons from AAP, AAFP, ACOG, SAM, IDSA, ACHA. There have been presentations from industry, academia and at least monthly conference calls to review trial data.
- Two HPV vaccines are in development. Both vaccines have a three-dose schedule; GSK's bivalent targets females and Merck's quadrivalent targets both genders. Both companies outlined product development plans and initial data for ACIP in February 2005 and Merck's efficacy data were presented that October.
- On this day, presentations addressed the background on HPV biology, epidemiology, and cervical cancer in the U.S.; preliminary efficacy, immunogenicity, and safety data for the GSK bivalent HPV vaccine; efficacy, immunogenicity, and safety data for the Merck quadrivalent HPV vaccine; modeling data on cost effectiveness/impact of HPV vaccine; HPV-related sexual behavior; and considerations regarding recommendations for use of the Merck HPV vaccine.

The Biology of HPV

Presenter: Dr. Doug Lowy, NCI

Overview: HPV biology. Disclosure: Dr. Lowy is an inventor of the VLP vaccine technology that is patented by NIH and licensed to Merck and GlaxoSmithKline.

Cervical cancer is the second most common cancer of women worldwide. It represents about 10% of all cancers of women with ~70% of these cancers being caused by HPV-16 and HPV-18. HPV16 also causes other mucosal epithelial cancers. The HPV vaccines target HPV-16 and HPV-18. The Merck vaccine also targets HPV-6 and HPV-11, which cause most external genital

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warts. Nongenital, common or flat warts are also caused by HPV, but by types other than those in the vaccines.

The capsid of the HPV virion is composed of 360 copies of the L1 the major structural protein (arranged as 72 pentamers), and a smaller number of copies of L2, the minor structural protein. . L1 contains the immunodominant neutralization epitopes, which are conformation-dependent and predominantly type-specific. When L1 is expressed in cells, it is sufficient to form virus-like particles (VLPs) whose structure resembles authentic virion capsids. The L1 VLPs contain the neutralization epitopes, so that they induce high titers of neutralizing antibodies. When L1 and L2 are co-expressed in cells, they associate with each other and form L1/L2 VLPs. In studies with animal papillomaviruses, systemic immunization with L1 VLPs was highly protective against high-dose experimental viral challenge, and L1/L2 VLPs did not confer additional protection. Therefore, vaccine development has focused on L1 VLPs. The animal studies also showed that neutralizing antibodies are probably the main protective activity induced by the VLPs, since passive transfer of immune IgG is protective. The vaccine was active prophylactically, but not therapeutically against established lesions. Heterologous neutralizing antibodies were not protective, implying that the protective factor is type-specific. The neutralizing antibodies can work by interfering with the binding of the virus to the cell, with its cellular uptake upon binding, or with its uncoating inside the cell.

HPVs infect stratified squamous (i.e., multilayered) epithelia. To establish a persistent infection, the virus must infect cells in the basal epithelial layer, which contains the epithelial stem cells and is the main source of dividing cells in this tissue. Access of the virus to the basal cells is believed to require microtrauma to the epithelium. Microtrauma in the genital area can lead to the acquisition of HPV infection through sexual intercourse with an infected partner. Chronic infection is established because the viral genome resides in the basal stem cells or in long-lived basal cells.

Several factors may contribute to the ability of the neutralizing antibodies induced by the vaccine to protect against infection of the female genital tract. One is that IgG is the main immunoglobulin in the female genital tract, and neutralizing IgG antibodies, which are the main class induced by systemic immunization, are transudated into the female genital tract. Another is that the epithelial microtrauma that in the absence of neutralizing antibodies predisposes to infection may provide access to the systemic antibodies, thereby increasing the local concentration of neutralizing antibodies.

The L1 VLP vaccines are unlikely to be directly therapeutic, particularly for the intermediate and high-grade dysplasias, as these lesions express little or no L1 protein. The vaccines might theoretically have some therapeutic activity for low-grade lesions, as they do express L1 protein. However, most of the L1 protein is in the upper layers of the epithelium, and resolution of the lesion would require that the L1 protein in the lesion produce a sufficiently robust reaction to destroy the basal cells that harbor the viral genome. It is more likely that the VLP vaccine may reduce HPV spread from an infected site to a previously uninfected site by neutralizing the virus that comes from a lesion. In summary, the L1 virion immunodominant epitopes are conformation-dependent. Preclinical studies indicate that vaccination with L1 VLPs induce neutralizing antibodies that are predominantly type-specific. Systemic immunization could

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deliver these antibodies to sites of microtrauma from sexual intercourse. In addition to preventing new infection, an L1 VLP vaccine might reduce HPV spread, but it is not likely to treat established lesions, particularly moderate- or high-grade dysplasias..

HPV Epidemiology in the U.S.
Presenter: Dr. Eileen Dunne, DSTDP

> Overview: HPV infection and disease burden of HPV-associated conditions in the U.S., principally among women; sexual transmission; laboratory diagnostic methods, treatment; issues of immunity and serology.

The prevalence of HPV infection is high in both males and females. Of the >100 HPV types, approximately 60 types are cutaneous and cause the common skin wart. The 40 mucosal types are divided into high-risk types and low-risk types. High-risk HPV types are epidemiologically associated with cervical and other anogenital cancers. Of those, two of the most important are HPV-16 and HPV-18. The most common of the low-risk HPV types are HPV-6 and HPV-11. Multiple HPV types are often detected, but HPV-16 is the most common type, with a 10% cumulative incidence at two years after first sexual intercourse. HPV persistence is associated with increased risk of cervical cancer precursors and cervical cancer. Information on HPV infection among men is limited, but natural history studies are ongoing. There is limited utility for HPV serology as a marker of cumulative incidence because serological tests will underestimate past or current HPV infection.

The HPV types associated with cervical cancer around the world were analyzed by Clifford et al (*Br J Cancer*, 2003) in a meta-analysis of studies evaluating cervical cancer biopsy samples for HPV types. Types 16 and 18 were consistently associated with >70% of cervical cancers worldwide. The conditions associated with HPV-16, -18, -6, and -11 were listed, indicating the potential benefit of a quadrivalent HPV vaccine. Other than cervical cancer, HPV-16 and -18 also cause a high proportion (80%) of high- and low-grade cervical abnormalities; anal and anogenital cancers, and ~10% of head and neck cancers. The low-risk Types 6 and 11 cause 90% of genital warts and recurrent respiratory papillomatosis, as well as low -grade cervical abnormalities.

Among HPV-6 and -11 associated conditions are genital warts and recurrent respiratory papillomatosis (RRP). The peak prevalence of genital warts appears to be at ages 20-29 years in both men and women; one study demonstrated the incidence rate at 157/100,000 persons. These warts recur in 30% of cases and cause multiple treatment visits. RRP is a condition in which warts grow in the respiratory tract, a rare but debilitating and recurrent disease that can require multiple surgeries. It is most common in juveniles and is most likely maternally transmitted. Estimated prevalence of juvenile-onset RRP is 1-4/ 00,000 children aged <18 years, and incidence is 0.1-2.1/100,000 children. A voluntary RRP registry indicates a median of 13 lifetime surgeries, with a range of 2-179 surgeries.

HPV acquisition occurs soon after sexual initiation, with most infections clearing quickly, but some persisting. The lifetime cumulative incidence is high, models have demonstrated >80% of

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persons have had infection with HPV by age 50. Persistent infection is associated with high grade cervical intraepithelial neoplasias (CIN) which can lead to cervical cancer. Screening with the routine Pap tests can usually detect these early for treatment.

Transmission of HPV occurs primarily by sexual contact, usually sexual intercourse. However, other types of sexual contact can transmit HPV, but transmission occurs much less frequently. Transmission is determined by per partner transmission probability, infectiousness, and average number of partnerships formed per unit time. There is no epidemiologic data on HPV transmission probability per sex-act, or per partnership, however models estimate that 0.4 as a median probability of per-sex act transmission, and 0.6 as a probability of transmission per-partnership, in another. This would mean that transmission would likely occur by three sex acts. Sex, age, infection site, immune status, and HPV type may also contribute to risk of transmission.

With regard to HPV laboratory methods, there is no culture for HPV, detection of DNA is used to measure infection. HPV DNA detection occurs by PCR or, in a cervical cancer screening and management clinical setting, by a hybridization assay (the Digene Hybrid Capture II). This HCII test detects 13 high-risk HPV types. Other tests available include HPV serology, which is an ELISA type-specific antibody serology (IgG or IgA) test to L1 VLPs. This test can test for serum or mucosal antibodies, and there is poor standardization of methods.

There are certain challenges to describing the epidemiology of HPV infection in the U.S. There is no culture for HPV infection, detection of DNA is used to measure infection. Presence of HPV DNA does not necessarily indicate infectious virus. National incidence and surveillance data are very limited, as there is not routine testing for HPV infection, nor is there reporting of HPV infection or HPV-associated conditions. And, HPV infection or HPV-associated conditions are not always associated with antibody detection.

- U.S. national HPV prevalence has been estimated at 20 million people or 15% of Americans aged 15-49 years. Estimated incidence is 6.2 million infections annually (>50% of sexually active men and women over their lifetime).
- The 2002 National Survey of Family Growth and 2003 Youth Risk Behavioral Survey indicate that ~7% of young persons have had sex before age 13 years, 25% by age 15 years, and 48% by 17 years. An estimated 14% of females and 18% of males aged 15-19 years have had ≥2 sex partners in the last 12 months.
- A review of HPV prevalence studies (Revzina NV. *Int J STD*/AIDS, 2005) showed high HPV DNA prevalence among U.S. women in all clinic settings (e.g., STD, family planning clinics). Not surprisingly, the highest prevalence was in STD clinics (49-90% of females had HPV infection).
- A CDC cross-sectional analysis of HPV infection among women having a Pap test in six U.S. cities (N=5500, aged 14-65 years) from 2003 to 2004, found the highest prevalence (40%) of high-risk HPV infection among 14-19 year-olds. Prevalence of HPV infection decreased with older age. HPV prevalence by race/ethnicity was similar; somewhat lower among Asian women, but not significantly when age-adjusted.
- The prevalence of HPV of any type was 26.9% among college women aged 18-25

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years (N=3262), as determined by less sensitive urine methods (Manhart L, *STD*, in press). Prevalence of HPV ranged from 0.2-5.8% among types 6, 11, 16 and 18, with Type 16 being the most common. The same data analyzed by number of sex partners found 14% HPV prevalence in these women, even with one sex partner. This rose with increasing numbers of lifetime sex partners.

- Winer et al (*Am J Epidemiol,*2003:157) followed young college women after sexual initiation, and found HPV was acquired soon after first sexual intercourse. Two years after first sexual intercourse, cumulative incidence of any HPV infection was 40%, and >50% four years later. At 2 years, type-specific cumulative incidence was 0.9-10.4% percent,; the highest acquisition was for HPV-16.

Persistent HPV is often defined as infection detected at more than one visit, usually at four to six months apart. That is an important predictor for high-grade cervical cancer precursors and invasive cervical cancer (10% by Schlecth et at, *JAMA*, 2001; and 14.1% by Moscicki et al, *J Pediatr*, 1998). Other risk factors have included HPV Type 16; immune status; smoking; multiple HPV-type infections; older age; and certain STDs, including chlamydia and herpes. Immune response to infection is important to clear infection, but the immune response to HPV remains unclear.

Data on type-specific HPV immunity are few, but some studies demonstrate few women later re-acquire the same type of infection if that type has been cleared. This suggests short-term, type-specific immunity. There are no longitudinal cohort studies to assess immunity over a lifetime. Natural history studies have found no cross-protection between HPV types.

HPV infection in men has been less studied, but the few existing studies demonstrate equal HPV prevalence to that of females, depending on the site and sample collected. Several ongoing longitudinal studies are assessing HPV clearance and persistence, and the development of HPV-associated conditions among men. Weaver (2004) estimated prevalence at 35% among 318 university students aged 18-25, and Baldwin (2003) estimated 28.2% in 443 STD clinic patients aged 18-70. Men's HPV risk factors include sexual behavior, immune status, and in some, lack of circumcision. Some studies identified STD history or inconsistent condom use associated with HPV infection as well. HPV Types 16 and 18 are associated with anal, penile, and head and neck cancers among men, and HPV-6 and -11 are associated with anogenital warts and RRP among men.

As described earlier, HPV serology is an ELISA-based detection of antibodies to VLPs. The tests are type-specific, but since many infected persons do not develop antibodies, ELISA likely underestimates the true burden of infection and disease. HPV-16 seropositivity in the U.S., estimated from NHANES data, was low at 2.4% for those aged 6-11 years old, and 13% for those 12-59 years.

Cervical Cancer in the U.S.

Presenter: Dr. Herschel Lawson, Division of Cancer Prevention and Control

Overview: Review of cervical cancer and other HPV-related cancers in the U.S.; surveillance, disease burden, screening, diagnosis: costs: cervical cancer, cervical cancer

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precursors, other HPV-related cancers

Worldwide, breast cancer is the most common cancer among women. Cervical cancer incidence is much lower in industrialized countries than those less developed, where it is the second most common cancer in women. The higher burden of disease is very likely due to the absence of screening programs in a large part of the developing world.

Surveillance data on U.S. cervical cancer incidence are collected and housed in the National Program for Cancer Registries (NPCR), administered by CDC/DCPC, and the NIH/NCI Surveillance Epidemiology and End Results program (SEER). The NCHS, in CDC, houses cervical cancer mortality data.

Cancer incidence in 2002 was 12,000 cases, of which 80% were squamous cancers and 20% adenocarcinomas (glandular cancers). There were ~4000 cervical cancer deaths. The American Cancer Society estimate for 2005 is 10,000 cases and in 2002, there were 9.2 cervical cancer cases per 100,000 women, similar in proportion to cancers of the bladder, pancreas, kidney, leukemias and renal disease. That rate was the product of a dramatic decline from the late 1950s, when the Pap tests became common. However, there are still racial disparities in the incidence and mortality of cervical cancer, with black women still having higher rates than white women. The incidence and mortality rates also rise with age, peaking in the late 30s to early 40s, and then again in the mid- to late 60s. Death rates increase with age in all groups.

Interestingly, cervical cancer incidence and death is geographically skewed, highest along the Appalachian mountains, in concentrated pockets of the Ohio and the Mississippi River valleys, along the Texas-Mexico border, and scattered throughout the country.

The greatest risk factor (60%) for cervical cancer in the U.S. is not being screened or being screened at intervals that are greater than 5 years. Of the 40% of cancers detected in women screened, false negative tests, loss to follow-up after positive cytology, and mismanagement made up 25-40% of cases and rapidly progressive or hard to detect, uncommon cancers such as adenocarcinomas made up 14%-22% of cases. The conventional Pap test has been largely replaced in the last ten years by liquid-based cytology. Surveys suggest that 85% of cytology testing is currently performed using the liquid-based method. Slides of the two methods were shown. The conventional cytology test is known to be less sensitive than liquid-based cytology, but more specific than the liquid-based cytology. As a result, more false-positive results have occurred requiring additional testing for more women ultimately not found to have cervical cancer or pre-cancer.

The NCI reporting system for abnormal Pap results was outlined: atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells, cannot rule out high-grade disease (ASC-H), low-grade (LSIL) and high-grade squamous intraepithelial lesions (HSIL), and squamous cell cancer. For glandular cells, atypical glandular cells (AGC) are reported, as are adenocarcinoma in-situ (AIS); and adenocarcinoma.

Three organizations have issued cervical cancer screening recommendations, ACOG, the USPSTF, and the ACS. They agree that screening should begin at about age 21, or within three

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years of beginning sexual activity. The recommended intervals for screening vary from one to three years.

BRFSS and NHIS data from 2000 were charted to show the prevalence of cervical cancer screening cytology done in the U.S. Overall, 82% of women are screened, but more women are screened who have insurance than those without it, and fewer foreign-born than native-born women are screened. (Swan J et al, *Cancer* 2003;97:1528-40). There are also racial/ethnic disparities, with Asian women least likely (at 71%) to be screened.

HPV testing. The FDA has approved only one HPV test, the previously-mentioned Hybrid Capture II. This is a hybridization assay that amplifies signals with long synthetic RNA probes that are sensitive to the 13 high-risk HPV types. It is easy to perform in the clinical laboratory and can be automated. The FDA approved this for triage (e.g., to determine if an ASC-US Pap test is associated with a high-risk HPV type) and for primary screening to complement the Pap test in women aged ≥30 years. In the latter group, if both tests are negative, a three-year screening interval should be used. ACOG, ASC, and the ASCCP recommend using the HPV DNA test.

The number of Pap tests done annually in the U.S. is not known, but the NCI estimates that a base of ~50-60 million Paps per would produce ~2 million ASC-US results; 1 million LSILs (an acute HPV infection); ~ 300,000 HSILs, and ~15,000 cancer reports (A. Hildesheim, NCI). Not all of the cancer Pap reports turn out tol be invasive cancer. Normal follow up of abnormal cytology may include a repeat test, or HPV DNA, vaginal and cervical inspection, colposcopy with directed biopsy, endocervical curettage, and manual pelvic examination.

Cost. CDC modeled HPV's direct costs at ~$4 billion dollars a year, almost all of which (90%) stems from abnormal cervical cytology and treatment of cervical neoplasia. Cervical cancer costs accounted for 4% of the total, and management of anogenital warts accounted for the remaining 6%. Oncogenic HPV is also associated with anal, vulvar, and vaginal cancer, as well as cancer of the penis. About 15-20% of oropharyngeal cancer is attributable to HPV types.

GSK HPV Vaccine Clinical Trial Data
Presenter: Dr. Gary Dubin, GSK

Overview: New data from the GSK HPV vaccine-development program.

GSK's vaccine is designed to prevent cervical cancer in women, particularly from the most common types, HPV16- and -18, which cause 70% of cervical cancers. The vaccine uses an adjuvant to enhance immune responses to the VLPs. Long-lasting protection is a goal, as the vaccine indication will go down to age ten years to prevent invasive cervical cancer and the precursors associated with oncogenic HPV infection.

The GSK vaccine's VLPs are made from the recombinant L1 proteins of HPV-16 and-18. These self-assemble to VLPs that resemble intact virions and prompt immune responses such as the generation of neutralizing antibody. The vaccine has 20 μg of each VLP of HPV-16 and-18, plus two adjuvant components: aluminum hydroxide and alum plus monophosphoryl lipid A (ASO4).

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The latter boosts the immune response to VLPs.

Phase I and II studies assessed vaccine safety, immunogenicity, dose ranging of the VLP components, and different adjuvant formulations. In phase IIa studies, the adjuvant vaccine was compared to that with only aluminum hydroxide salts and GMT antibody titers were charted for HPV-16 and-18. The women received three shots at 0, 1, and 6 months and were followed (to now) for up to 48 months. Peak responses of the adjuvant vaccine exceeded the other, and approximately two-fold higher GMT functional or neutralizing antibody has persisted. That was one reason this formulation was carried forward for testing.

Two phase IIb studies were outlined. HPV-001 was an efficacy, immunogenicity and safety study in the U.S., Canada and Brazil. This followed 1113 subjects over two years for virologic and cytologic end points, and biopsy-confirmed CIN lesions. HPV-007 extended -001 for another two years.

New data. To date, the AS04 adjuvant has been assessed in vaccines under development other than HPV in 40 completed and 3 ongoing studies involving >16,000 subjects and 43,000 vaccine doses. The AS04 vaccines have been generally safe and well tolerated. The two largest programs are, 1) of a genital herpes simplex virus (gD ASO4) vaccine now in large Phase III trials, including a collaborative NIH efficacy trial; and 2) the development program for Fendrix®, which is targeted to hemodialysis patients who respond poorly to the standard hepatitis B vaccine. It was approved by the E.U. in early 2005.

HPV-001 efficacy study. This double-blind, randomized controlled trial involved 1113 women assigned to either the HPV vaccine or alum control, followed for 18-27 months from enrollment. The endpoints were HPV-16 and-18 infections and associated cytologic abnormalities and cervical lesions. The vaccine was shown to be safe and well tolerated, inducing antibody responses at titers higher than natural infection in almost all subjects. Efficacy was high, with 100% protection against persistent (6 months) HPV-16 or -18 infection, and the same for biopsy-confirmed CIN lesions with demonstrated HPV-16 or-18 in the DNA; protection from abnormal HPV-16/18 Pap smears was 93%. There was also preliminary evidence found of protection against other oncogenic HPV types (31 and 45), which are phylogenetically related to HPV-16 or -18.

HPV-007 was a long-term, blinded follow-up to -001, which evaluated the same end points as the initial trial over another 36 months. Preliminary interim analysis has been done of the first 12 months of follow-up, providing a total of 48 months with the parent studies. The extension involved 776 subjects randomized to the intent-to-treat cohort. Efficacy was assessed against incident infection for HPV-16 or-18; persistent infection (6- and 12-months), abnormal cytologies associated with HPV-16 and-18, and biopsy-confirmed CIN lesions. The demographic characteristics of the enrolled subjects were outlined.

Immunogenicity. Study -001 revealed a peak antibody response to HPV-16 and -18 at month seven. By about month 18, antibody titer declines to a plateau at about one log lower than the peak, but still tenfold higher than that from natural infection with either HPV-16 or -18. Over 98% of subjects maintained seropositivity for HPV-16 or -18, even to month 53.

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Efficacy. VE was 100% over two years of follow-up against persistent infection and CIN lesions. VE was also 100% during the extension phase to year four against 12 month persistent infection and CIN lesions, showing good duration of protection. In addition, the vaccine was most efficacious against the end points with the highest predictive values for cervical cancer (i.e., 12 month persistent infection or a CIN lesion). No subjects in the vaccine group developed either CIN 1 or CIN 2 or worse lesions associated with HPV-16 or -18, although some of the controls did. Efficacy also was ~96% for ASC-US or worse cytologies associated with HPV-16 or-18.

Vaccine efficacy was also maintained for the four years of follow-up against virologic end points (incident infection and 6- and 12-month persistent infection, with efficacy levels of 94.7%, 96% and 100%, respectively). Study -007 looked for evidence of waning protection, which might be signaled by increasing numbers of endpoints in vaccine recipients. Instead, during the HPV-007 study, VE against incident infection with HPV-16 or -18 remained high, at 95.8% and 100%, respectively ─ in fact, higher than those seen in the first two years of follow-up.

Conclusions. Almost 100% seropositivity was maintained out to 53 months after study enrollment. Protection did not wane through a mean of 48 months for virologic, cytologic or histopathologic end points (including incident and persistent infections). There were no vaccine-related serious adverse events in any portion of the studies.

Phase III studies are underway. One is GSK's multicenter, double-blind, randomized controlled trial (HPV-008) in 14 countries using hepatitis A vaccine as the control, and involving >18,000 women aged 15-25 years. NCI is doing a second Phase III study (HPV-009) similar to GSK's, but in a population-based efficacy study in Costa Rica with six study centers and 7500 women aged 18-25 years. Both studies are assessing VE against CIN 2-plus lesions associated with HPV-16 and -18 as the primary end point, and both have independent DSMBs.

Additional "age-bridging" trials are being done to extend down to age 10 and past age 25. This is hoped to provide protection before sexual debut, as well as protect women aged >25 who remain at risk of new HPV infections.

- HPV-012, which targets preteen and adolescent girls, is an immunological bridging study to compare the immune responses of girls aged 10-14 to those aged 15-25 years, as well as safety and reactogenicity. *Results*: The safety profile was similar between the 10-14 year-olds and the 15-25 year olds, but the 10-14 year-olds' GMTs were more than two-fold higher than those of the 15-25 year-olds. There were no serious adverse events related to vaccination and the reactogenicity profile was the same for all the groups.
- Recently completed, HPV-013 studied safety and immunogenicity in 10-14-year-old girls. Those data should be presented in the near future.
- HPV-014 is an immunological bridging study of women aged 25 years, comparing their immune responses to those of the 15-25 year-old efficacy cohort.

A timeline of the Phase III studies was shown from 2005 to 2009, involving >30,000 subjects. The efficacy studies HPV-008 and HPV-009 will go at least through 2009, as will the long-term follow up of the adolescent safety study to examine the kinetics of antibody responses, especially in the 10- to 14-year age range over time. Another long-term follow-up to 2007 will be done to

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compare immune responses of women aged >25 to those aged 15-25 years.

Data will be released over the next few months for HPV-013 (adolescent safety data), HPV-014 (immunobridging 15-25 years and 26-55 years), more data from HPV-007 (overall efficacy against cytological/histological endpoints regardless of HPV DNA lesion status), and health economic modeling data.

GSK plans to apply for U.S. licensure by year's end, and also will file for European licensure this year. Post-licensure work will study efficacy in >5000 women aged >25 years, assessing persistent infection and CIN over at least three years; the vaccine's co-administration with routine adolescent vaccines; and safety and immunogenicity in HIV-positive women. Phase IV studies being planned include long-term follow-up (10-15 years) of cancer and pre-cancer among >5,000 Phase III subjects in Finland. Other Phase IV studies should begin in 2007.

GARDASIL® Presentation
Presenter: Dr. Eliav Barr, Merck & Co., Inc.

> Overview: GARDASIL® description; GARDASIL® clinical trials design, focusing on the choice of efficacy endpoints and target populations; clinical trials results.

The primary analysis of Merck's Phase III trials in adolescents and young women have been completed. The vaccine targets HPV types 16, -18, -6 and -11. HPV-6 and -11 are responsible for >90% of genital warts and recurrent respiratory papillomatosis (RRP) lesions in both boys/men and girls/women. These types also cause 10% to 15% of CIN 1 lesions. Because HPV-6 and -11 related CIN 1 lesions are morphologically indistinguishable from the HPV-16 and-18 CIN 1 lesions, they therefore are treated as precancerous, imposing an additional economic and psychologic burden.

Studies of GARDASIL® have been conducted in women and in men. While the clinical sequelae of HPV infection are better understood in women vs. men, HPV infection imposes a heavy burden on men (cancer, RRP, genital warts). Men also represent the primary mode of HPV transmission to women.

GARDASIL® is a quadrivalent, virus like particle (VLP) vaccine. It is not a live virus. It has four VLP types manufactured in yeast with Merck's proprietary aluminum adjuvant. It is given in three doses at day 1, month 2 and month 6. The vaccine must be stored at 2oC to 3oC. FDA has granted priority review for Merck's December 2005 application for licensure and the action date is June 2006. Prophylactic administration of the vaccine has been shown to prevent HPV-16 and -18 related cervical, vulvar, and vaginal cancer, as well as HPV-16 and-18-related CIN 2, CIN 3, and AIS, and VIN 2/3 and VaIN 2/3, the precursor lesions to vulvar and vaginal cancer. Prophylactic efficacy was demonstrated for all four HPV types for infection, low-grade dysplastic lesions, genital warts, and low-grade flat warts, for 9-15-year-old boys and girls and 16-26-year-old adolescent and young adult women. Future applications will provide data to extend the age indication to young adult men and women aged >26 years.

Study design. The trials' primary end points were prophylactic efficacy for HPV-related cervical,

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vulvar, and vaginal cancers and their precursors, genital warts, and persistent infection. Additional end points were the vaccine's impact on HPV disease burden in women and on the course of existing HPV vaccine-type infection.

End points. Clinical trials for a vaccine to prevent cervical cancer are not possible because HPV infection takes ~20 years to become cancer, and due to the requirement to provide cervical cancer screening women during the trial thereby treating subjects before they develop the cancer). So, intermediate end points were selected: initial HPV infection (which normally clears), HPV-related CIN 1 (important from a health-economics perspective), and most important, CIN 2/3 and adenocarcinoma in situ, the intermediate and obligate precursors to cervical cancer and the targets of screening programs. Preventing CIN2/3 and AIS prevents cervical cancer. Demonstration of prophylactic with respect to CIN2/3 and AIS cause by vaccine HPV types was approved by the FDA advisory committee as the basis for U.S. licensure.

HPV-related vulvar and vaginal cancers have the same natural history. Vulvar cancer incidence is rising among young American women. HPV, primarily HPV-16 and-18, being involved in ~70% of vulvar and vaginal cancer biopsies. Their immediate precursors are the VIN 2/3 and VaIN 2/3 lesions, which have a high rate of progression to cancer.

Immunogenicity. It will be particularly important to protect 9-15 year-old children using prophylactic HPV vaccines, as such subjects are sexually-naive and HPV infection occurs shortly after sexual debut. The efficacy of GARDASIL(R) in 16- to 26-year-olds was bridged to pre-adolescents using an immunogenicity bridging program. Long-term efficacy data are being generated to find immune correlates and to define the duration of immune response to GARDASIL®, in order to address HPV's lifelong risk for women. Also pursued were data on co-administration with other common adolescent vaccines. Vaccine safety was evaluated in all the populations indicated, and a pregnancy outcomes follow-up program in clinical trials of GARDASIL vaccines was established. Understanding the vaccine-pregnancy interaction is important, since the vaccine will be administered for women of childbearing age.

HPV infection risk is closely tied to sexual debut. The proportion of 10- to 14-year-old subjects with evidence of HPV disease is low. However, after sexual debut, the proportion of the female population with evidence of HPV disease rises dramatically. The peak incidence of new HPV disease in women occurs between ages 16 and 25 in both men and women. The clinical efficacy trials focused on 16-26 year-olds, the period of highest risk to acquire HPV, as well as the period of most cytologic abnormalities and rates of CIN. This group would benefit dramatically from a prophylactic HPV vaccine. Immunogenicity bridging studies were done to demonstrate an immune response in the younger age group. Studies are being done to evaluate the VE for women aged ≥24 years. Those efficacy data should be available in 2007.

Clinical trials were outlined, involving 27,000 women and children on four continents. The goal was to include broad SES and ethnic background, sexual behavior, and concomitant disease information to allow generalization to the overall population. Different Pap test abnormality management also was considered, as seen in the U.S. and around the world. Centralized cytology, biopsy processing, and HPV typing will ensure accuracy in the end-point ascertainment (diagnoses of HPV-related clinical disease). VE will be analyzed for preventive

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and prophylactic efficacy, and post-exposure prophylaxis therapeutic efficacy will be investigated). The validation programs were presented for approval to regulatory authorities.

- *Protocol 005 (P005)* involved 2391 women aged 16- 23 years old, 400 of whom will be followed through seven years.

- *P007* involves 1155 women aged 16-23 years old. An immune memory evaluation will begin in year 5. (booster dose given at Year 5) is nearly complete.

- *Future I trial of VE for CIN1/warts* involves 5442 women aged 16-23 years.. The CIN (any grade) endpoint was chosen to evaluate the vaccine against the full spectrum of clinical HPV disease. CIN 1 usually resolves on its own, but incurs high healthcare costs. VE for HPV-6, -11, -16, and -18 related CIN was 100%, highly statistically significant. Because HPV-6 and -11 significantly contribute to CIN 1 incidence, that VE is important to maximally reduce morbidity, the costs of cervical cancer screening and HPV disease in women. VE was 100% for external genital lesions mostly due to HPV-6 and -11. The study is ongoing to allow for evaluation of the efficacy of the vaccine over a longer period of time. The study is expected to end by the end of 2006.

- *Future II trial of VE for CIN 2/3 and AIS* involved 12,167 women aged 15-26 years. This also could be extended, and it will be followed by a duration of efficacy registry study in the Nordic region. A study of Norwegian HPV surveillance and VE on disease burden/population effectiveness will also be done. *Future II Results:* VE for both HPV-16 and-18 components was demonstrated a statistically significant difference: no cases in the vaccine group, and 21 cases in the placebo group. The study is ongoing to allow for evaluation of the efficacy of the vaccine over a longer period of time. The study is expected to end by the end of 2006. In addition, subjects in the Nordic region will be followed for long-term duration of efficacy. A study of Norwegian HPV surveillance and VE on disease burden/population effectiveness will also be done.

- *Studies of prespecified prophylactic efficacy* analyses in the integrated database of efficacy studies were also conducted. These studies involved a total of 20,541 subjects who were randomized and received at least one dose of vaccine/placebo. This integrated analysis showed:
    - 100% prophylactic efficacy with respect to HPV 16- and HPV 18-related CIN 2/3 and AIS, a highly statistically significant result.
    - 100% prophylactic efficacy with respect to HPV 16- and HPV 18-related CIN 3 and AIS (include high grade cervical dysplasia, squamous carcinoma in situ, and adenocarcinoma in situ).
    - 100% prophylactic efficacy with respect to HPV 16- an dHPV 18-related VIN 2/3 and VaIN 2/3, the precursors to vulvar and vaginal cancer.

- *A Phase III Immunogenicity trial* will involve 4800 boys and girls aged 9-15 years has been completed. It will be followed by a 36-month extension to study VE in adolescents to evaluate the duration of vaccine immunogenicity in this population.

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- *An efficacy study of women aged to 45 years* will be done, concurrently with a study of VE in 16- to 26-year-old men

The baseline characteristics of the trials' participants were outlined: mean age of 20, most sexually active, diverse history of past pregnancy, common use of hormonal contraception; relatively high rate of chlamydia. Overall, ~12% (14% in the U.S.) had a diagnosis of ASC-US or worse, suggestive of cervical intraepithelial neoplasia. Some (27%) of the women were HPV-positive to at least one vaccine, but most were so to only one HPV type.

There were two analysis populations: 1) per protocol, the primary specified analysis, consisting of women naive to the relevant HPV type at enrollment, who remained so throughout the three-vaccination regimen; and who received the full 3 dose regimen. Case counting started 1 month after completion of the 3-dose vaccination regimen; and 2) modified intention to treat, consisting of women naive to the relevant HPV type at enrollment. Case counting started 1 month post-dose. The MITT population was the broadest possible baseline naive population. They included people who became infected before they received the full vaccination regimen, subjects who received only one or two doses of vaccine, or in an non-ideal manner, or who had violated the protocols in many different ways. VE was still 94% and 95% respectively, for CIN and for external lesions.

VE in women infected with vaccine HPV types. Study data demonstrated that women positive for one HPV type benefited from continuing VE for the other three HPV types, at ~90% for CIN and the same for external genital lesions. A new analysis also demonstrated VE to modify the natural history of HPV disease. Serology and cervical-vaginal cytology was done at Day 1 to test for active HPV infection. VE was explored for two groups: 1) women who were seropositive and PCR negative, that is, those who were infected before enrollment and whose immune response cleared that infection. The study explored whether the vaccine could induce an immune response to help prevent progression to CIN 2/3. Also explored was 2) whether the vaccine could help women who were infected with a vaccine HPV type but had not mounted an immune response to that infection and 3) whether the vaccine could help women positive to both tests, who had chronic infection and a high level of CIN 2/3. VE was in doubt here, because these women had already mounted an immune response and failed to clear infection.

Results. The vaccine was efficacious in women with evidence of previous HPV infection but who cleared that infection. The low event rates were consistent with the protective effect of natural immunity to HPV. But the event rates were not zero, and 100% VE suggested an ability to prevent recurrence of the disease caused by the relevant HPV type. For women with early infection or who failed to mount an immune response to the infection, GARDASIL® reduced progression to CIN 2/3 by 28% but the lower bound of the 95% confidence interval for efficacy included 0%, so this is only a trend that needs to be evaluated further . And as expected, the vaccine could not do much to help women with chronic HPV infection to create further anti-HPV.

An analysis of VE for CIN 2/3, regardless of the causal HPV type was done for two groups: 1) those who were naive to all vaccine HPV types (no testing was done for non-vaccine HPV types), to approximate adolescents just before sexual debut, and to evaluate VE to prevent the

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development of cervical cancer overall, and 2) an “all-comer” population of women who are sexually active and present for care. Cases were counted immediately after vaccination for incident disease caused both by vaccine and nonvaccine HPV types.

Preliminary data indicate a steadily rising benefit for the vaccinated naïve group compared to the placebo group, that becomes increasingly apparent with each screening round and resulting in a dramatic reduction in the overall rates of CIN 2/3 caused by any vaccine HPV type. For the second, “all-comer” population, which included women infected or with CIN 2/3 at baseline, the same pattern emerged. While prevalent disease is clear, the VE even for CIN 2/3 becomes visible very shortly after the follow-up begins, and is increasingly apparent over time. The same pattern repeated for genital warts.

The cost implications of these outcomes to health economics are evident. Even the short-term follow-up of the Phase III studies have already shown a significant decline in the number of women with abnormal Paps that require a visit for colposcopy. A reduction by 20% of the 3 million annual ASC-US cases in the U.S. equates to 600,000 less tests; a 33% reduction of the 300,000 HSILs per year equates to 100,000 less cases. The clinical trials referred women to biopsy for almost any lesion, and a reduction was still evident. That is expected to increase over time, as are genital biopsies and genital definitive therapy.

The Phase III program will end early. When the overwhelming VE was demonstrated with a favorable safety profile, the DSMB mandated that women in the placebo groups receive accelerated vaccination.

The finding of 100% efficacy precluded the ability to find an immune correlate of efficacy. With no breakthrough cases due to waning immunity, the minimum protective anti-HPV level could not be determined. However, the results after 48 months of follow-up showed persistent anti-HPV levels. These declined to a plateau level paralleling the anti-HPV levels in women who are seropositive and PCR negative at baseline from a natural immune response that cleared HPV infection. Additionally, the 100% VE determined against persistent infection and HPV-16 related CIN 2/3, with no breakthrough infections, reflects well upon long-term protective efficacy. The Scandinavian population-based, long-term follow-up will assess that. The women enrolled were vaccinated in 2002; U.S. vaccination is expected to begin in June of 2006. The Scandinavian cohort will be a good sentinel cohort, and will be analyzed over time for breakthrough infections. That will inform any possible need for booster doses.

Finally, Merck explored whether anti-HPV levels are needed to protect against infection and disease or if, like hepatitis B, a vaccine might just induce a strong anamnestic response that aborts disease even in the absence of detectable serum anti-HPV. Merck followed the 24% of women in the trials who vaccinated, mounted high anti-HPV 18 levels, but then nominally sero-reverted by Month 24. High levels of protection remained for HPV-18 related disease when followed over six-month intervals, even in the 24% of the population who had no detectable anti-HPV-18. That suggests long-term vaccine protective efficacy and a potential anamnestic response, and the latter is the sign of long-term vaccine efficacy.

Also interesting is that pre-adolescents seemed to mount an immune response even more intense

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than that of the adults. Recent data of sentinel adolescent cohorts also show adolescents' immune response remaining much higher than that seen in adults, even a year after the vaccination regimen. That is important because month 18, one year after dose 3, is the where the plateau begins.

An analysis was done to evaluate whether administration of one dose of vaccine in women who are seropositive at baseline will induce an anamnestic response. These women had much higher anti-HPV levels two months after dose 1 than women who were baseline naïve, and given the two-month lapse, that could even be an underestimation of the initial high anti-HPV level in such women. A mechanistic study is now underway to see if a long-term administration of a dose at five years after enrollment provides the same kind of anamnestic response. Preliminary data are encouraging that these vaccines can induce memory immune responses that are highly active and result in a robust reconstitution of anti-HPV levels, indicating likely long-term protection.

Safety data were shared from a cohort of 27,000 enrolled women, divided into groups receiving monovalent vaccines or other quadrivalent vaccine formulations, and those receiving GARDASIL.® Serious adverse event rates were very low, at 0.5% for the other vaccines versus GARDASIL's ® 0.4%. Women in both groups recorded events on their vaccine report cards. Serious vaccine related adverse events were rare and the discontinuation rate was extremely low. Systemic events were comparable. Injection site adverse reactions were slightly higher in the GARDASIL® group, but half of those were from the injection itself, and were comparable to the reactogenicity seen with other adolescent vaccines. Rates of fever were slightly higher in the GARDASIL group, but most were very low grade; very high-grade temperature rates were the same to placebo.

Children aged 18-26 years, 9-17 year-old girls and 9-15 year-old boys received GARDASIL, and were compared to adult women. Injection site AEs were lower in the children, as were systemic AEs, while serious AEs were comparable. The safety profile appeared to be unaffected by the baseline HPV status of the recipient.

Pregnancy outcomes evaluated included medical history during the pregnancy, mother and child's outcomes in the neonatal period, causes of spontaneous abortion, and elective termination were all examined. Infants were followed to the end of the study to look for late events not detected in the neonatal period. Natural history studies of pregnancy in which pregnancy screening with beta-HCG is used indicate rates of spontaneous abortion at 15%-20%, but the clinical trial's use of beta-HCG screening found rates of 28%-33%. Congenital abnormalities occur in ~3%-4% of live births in the general U.S. population.

Approximately10% of subjects became pregnant during the trial, even though subjects were instructed to use contraception during the vaccination phase of the study. Of the known outcomes (those "unknown" had just not given birth when the database was closed) live births were predominant, with rates comparable between the two vaccination groups. In terms of pregnancies that began close to vaccination versus pregnancies ≥30 days of vaccination, the normal-baby outcomes were comparable, as were spontaneous losses. Rates of both elective and spontaneous abortions within 30 days of a vaccination were slightly lower in the group that received GARDASIL® compared to the placebo group.

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The rates of congenital abnormalities were comparable to those in the general population and similar between the GARDASIL® group (15) and the placebo group (16). But the distribution was slightly different; five cases occurred within 30 days of the vaccination of the GARDASIL® group, and none in the placebo group; and the opposite occurred for those becoming pregnant ≥30 days after vaccination, with ten in the GARDASIL® group and 16 in the placebo group. The five cases involved common congenital anomalies associated with late fetal injury far after vaccination. Merck's developmental and reproductive toxicology preclinical modeling also showed no association of congenital anomalies to GARDASIL® vaccination, even during pregnancy and even at the most vulnerable period. The DSMB, study steering committee, and an expert teratologist were in consensus that GARDASIL® does not impact pregnancy outcomes in any way.

Post-licensure evaluation includes a large pharmacovigilance program involving 35,000 women. It will monitor general safety and pregnancy outcomes, establish pregnancy registry, and evaluate long-term efficacy. Through the central Nordic registry, long- and short-term efficacy and safety will be evaluated on a population basis in real time.

Discussion of the presentations to this point included:

- The SAE rate for those PCR negative was 0.6, but twice that for those PCR positive. The SAE rates, particularly in the seropositive population, were multiple events that were not vaccine related (e.g., motor vehicle accident, sports injuries), presenting no signal.
- *Since teenage girls develop genital warts earlier than males, are they not the transmission route to young men?* The answer lies in data on the age of the young women's first partner for their sexual debut. The partner is typically substantially older and more experienced than the girl. A survey in Iceland indicated on average a three-year older partner. Transmission is probably back and forth, but for herd immunity, vaccination of men will be important for HPV.
- *The bridging to age groups was done based on serum antibody from vaccine administered intramuscularly, but natural infection produces little serum immunity. Given that, is that a good correlate of efficacy?* Dr. Barr defined the bridging as a standard approach for many vaccines to examine populations in which efficacy cannot be measured, compared to populations in which efficacy is demonstrated. The only other way to definitively show this will be through very long-term, efficacy data. But the fact that the vaccine-induced anti-HPV responses were higher in children than adults, where the VE was definitive, satisfies the prerequisites to bridge that VE to the younger population. Dr. Dubin agreed, and added that the role of serum antibody in protection is proven by preclinical animal studies showing passive antibody transfer to other animals who then resisted challenge. Additionally, most of antibody in cervical secretions is transudated from serum antibody. Measurement of cervical antibody levels is not feasible, both from a collection standpoint and due to no standardized methodology for measuring cervical secretion antibodies. Those considerations support the use of serum antibodies as a reasonable measure of the immune system element that mediates protection, particularly since the vaccine study data indicate that the cervical antibody levels will correlate reasonably well with the serum levels.
- Dr. Dubin commented that data on HPV incidence or prevalence indicate that oncogenic

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HPV infections have some relationship to age at infection. The highest rates are among younger women and they drop with age. Whether this pertains to less exposure in women aged >25, or to partial protection that's acquired from previous exposures, is unclear. Either way, although the absolute rates are lower in older women than those younger, new incident infections occur; and the overall absolute risk continues even with older age. Dr. Barr agreed. Merck's Phase III database showed the highest infection incidence in 18-year-olds, that that slowly declines with age. But no data can indicate whether age of receipt changes VE; all that is known from current data is that the VE is comparable regardless of the age of the recipient.

- Dr. Barr reported that antibody levels were somewhat higher among people who were PCR positive but serologically negative, but not as dramatically high as among the baseline seropositives.
- Dr. Plotkin asked Dr. Lowy for his opinion of whether an L1/L2 vaccine might provide additional breadth of immunity. He answered that in vitro studies show that the L2-only vaccine can induce cross-neutralizing activity, but at substantially lower titers than with the L1-VLP vaccine. The immunodominance of the L1 vaccine causes animals, exposed to L1/L2 VLPs, to be essentially naïve to the L2. L2 has not been used in human clinical studies.
- Dr. Martin Meyers asked Dr. Dunne if there was any chance that the 2.4 prevalence rate in children aged 6-11years might come from maternal infection, or early sexual encounter. She could not say, since these data were from NHANES, which does not collect data on sexual risk or other exposure.
- Since the antibody concentrations after the three-dose schedule are so much higher than those from natural infection, Dr. Georges Peter if consideration was given to a two-dose primary schedule, or one dose that is boosted five years later. Dr. Dubin responded that the significant rise in antibody titers at the third dose, greater than that after the second dose, also suggests that two doses do not convey the maximum immune response. That level may still be protective, something that could be shown if a correlate of protection is ever developed. For now, the overriding consideration has been the greater duration of protection afforded by such a significant boost, something important in a vaccine to be given down to age ten years or even younger.
- Dr. Abramson asked what Merck would seek in its FDA licensure application as regards issues of pregnancy, since many recipients could potentially be pregnant. Dr. Barr said that Merck states that pregnancy should be avoided during the course of vaccination, and then provides all the information on the vaccine. There are no data on the use of this vaccine in pregnant women. For that reason, they would recommend that FDA label the vaccine as Pregnancy Category B, to avoid the use during pregnancy, and allow flexibility in the dosing regimen to accommodate pregnant women.

Cost Effectiveness of HPV Vaccination

Presenter: Dr. Harrell Chesson, Division of STD Prevention

Overview: Ongoing and published cost-effectiveness studies of HPV vaccination in the United States.

Models are important in evaluating the cost-effectiveness of HPV vaccination, because many

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factors affect the costs and benefits of HPV vaccination, such as: vaccine efficacy, coverage and duration, HPV infection natural history, rates of HPV transmission, and cervical cancer screening factors such as coverage and frequency. Many of these factors are unknown or not known with precision at this time. Models are the only way to take these factors into account and project the possible impact of HPV vaccine.

The literature on HPV vaccine cost-effectiveness (CE) has used Markov models (also called cohort models or health-state transition models) of the natural history of HPV infection. HPV transmission, and occasionally the natural history of HPV infection, are addressed with dynamic models.

The advantages and disadvantages of each were outlined. Since the Markov models do not include HPV transmission effects (or herd immunity), they are not as useful when the effect of transmission is important (e.g., cost/benefit of adding males to a female-only vaccination program). Leaving out the transmission effects could understate the vaccination's benefits. However, the Markov models may be able to establish a reasonable upper bound of the cost per quality-adjusted life-year (QALY) gained by vaccination.

Dynamic models do include HPV transmission effects, or herd immunity, so they can better evaluate vaccination scenarios in which transmission effects are important. But, while the inclusion of transmission may make them more realistic, it also introduces additional uncertainty from parameters such as sexual-mixing behaviors and transmission probabilities.

A Markov model of the natural history of HPV infection was shown. It plotted a person's movements from one state of health to another at defined and equal intervals, or Markov cycles. The probability of transition can be made dependent on characteristics such as age. The dynamic compartmental model of HPV transmission places the population into a few compartments (e.g., vaccinated, susceptible, infected) that can then be further stratified based on characteristics such as age, sex, and sexual activity level. The rate at which persons move from compartment to compartment can be a function of many factors (e.g., moving from susceptible to infected depends in part on HPV prevalence). Differential equations are used to model the spread of infection over time.

Markov models. Three studies using the Markov model to evaluate the CE of HPV vaccination in the U.S. were outlined:

- Sanders and Taira (*Emerging Infectious Diseases*,2003;290:37-48) examined the benefits of adding an HPV vaccine to current U.S. cervical cancer screening. They assumed that 71% of women were screened every two years. Their model examined a vaccine targeted against high-risk HPV types in general. In the base case analysis, age of first vaccination was 12 years; vaccine coverage was 70% and VE was 75%. Female-only vaccination was estimated to reduce cervical cancer incidence in the vaccinated cohort by 20% at a cost per QALY of $22,800; with a lifetime duration of protection, the cost per QALY was $12,700.
- Goldie et al (*Journal of the National Cancer Institute*, 2004;96:604-615) examined the benefits of adding a vaccine for HPV-16 and -18 to the current U.S. cervical cancer screening. The assumptions about current screening practices were based on reports that

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67% of women were screened within one year, 28% had been ≥1 year since their last screening, and 5% had never been screened. In the base case analysis, age of first vaccination was 12 years; vaccine coverage was 100%, and VE was 90% Vaccine duration was lifelong and the vaccination costs was $377 per series *Results:* Cost per QALY gained for female-only vaccination was $24,300. As VE rises from 70%-100%, the 46% reduction in the lifetime risk of cervical cancer increases to 66% and the cost per QALY drops from ~$33,000 to ~$20,000.

- Kulasingam and Myers' model also examined a vaccine targeted against high-risk HPV types in general. In the base case analysis, age of first vaccination was 12 years; vaccine coverage was 100% and VE was 90%, with a 10 year duration of protection. This study focused on the cost per life-year gained rather than the cost per QALY gained. They found the most CE strategy costing <$50,000 per life year gained to be vaccination plus biennial screening, delayed until age 24 years. That resulted in ~$45,000 per life-year gained, compared to a strategy of no vaccination and screening every three years beginning at age 18.

In the sensitivity analyses across the Markov model studies, the cost per QALY gained for female-only vaccination ranged from <$10,000 to >$100,000. The CE estimates were most sensitive to cervical cancer screening issues such as frequency and age of initiation, but the duration of VE also impacted the CE. The CE effectiveness estimates were least sensitive to reasonable changes in the natural history parameters and the screening test characteristics.

Dynamic models. The dynamic model used by Taira et al. (*Emerging Infectious Diseases* 2004:10(11):1915-23) examined vaccine targeted to HPV-16 and -18 with 90% efficacy. The Merck modelers, Elbasha and Dasbach (in progress) examined a quadrivalent vaccine with 90% efficacy against low-risk types and 70% efficacy against high-risk types.

Both models assumed vaccination at or before age 12 years with 70% vaccine coverage. The vaccine duration ranged from ten years to lifetime; vaccination cost per series was $300-$500.

Merck's model set a per-partnership HPV-transmission probability of 0.8 for male to female transmission and 0.7 for female to male. The frequency of annual cervical cancer screening ranged from 0.6%-60.4%, varying by age. The study population was divided into 15 age groups and three sexual activity groups, the latter based on rate of new sex partners per year. There was assortative mixing, meaning that sex partners are more likely to be of similar age and sexual activity level than would be expected if partners were selected randomly. The QALY cost for two strategies was charted: no vaccination and cervical cancer screening only, and addition of female vaccination to the screening program. The cost per QALY gained of adding female vaccination to an existing cervical cancer screening program was $728. The Merck model posited an 8% reduction in steady-state cervical cancer incidence for those aged ≥12 years, with a ten-year duration of immunity, and incidence reduction rose to ~35% with a lifetime duration of immunity.

The Taira model was a hybrid dynamic-Markov model. While the dynamic model generated HPV incidence estimates, the Markov model was used to convert the incidence estimates to QALYs and costs. The assumed per-partnership transmission probability was 0.35 for the

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youngest age groups, which decreased gradually to 0.15 for the oldest group. The population was divided into nine age groups and four sexual activity groups, with assortative mixing by age and sexual activity level. The cost in QALYs again was charted for no vaccination and screening only, and female vaccination added to screening. Again, the latter increased the total cost (by $244 per woman) but it also increased QALYs by .0167 per woman (or 6.1quality-adjusted life-days), yielding a CE ratio of about $14,500 per QALY. This model showed a 62% reduction in the lifetime risk of cervical cancer and a 95% reduction of lifetime cervical cancer cases related to HPV-16 or -18 in the vaccinated cohort.

The cost per QALY as estimated using the Markov models ($22,000-$24,000) exceeded that of the dynamic models ($700-$14,600) in part because the Markov models excluded the benefits of herd immunity. Additionally, the Merck model's lower cost per QALY is attributable in part to the inclusion of the benefits of preventing HPV-6 and -11. However, these are base-case estimates, and the estimated CE ratios can vary substantially when base-case assumptions are varied. The limitations of the models must be considered, including the uncertainty of HPV transmission dynamics, the duration of naturally acquired immunity, and the non-inclusion of all possible vaccination effects (e.g., possible decreased positive predictive value of the Pap with rising vaccination coverage). The models do not consider that AEs may incur cost or reduce QALYs; that vaccination may affect sexual behaviors or health-seeking behaviors; or the prevention of other HPV-related cancers besides cervical cancer. Including the benefits of reducing other HPV-related cancers would improve the estimated CE of vaccination, as would the inclusion of averted indirect costs such as productivity loss due to cervical cancer. It is possible that small changes in a large number of parameter values could affect the results; as such more comprehensive sensitivity analyses may be warranted. Finally, future studies will further examine the CE of male vaccination and other factors affecting vaccination CE, such as age at vaccination and catch-up vaccination.

Mathematical Modeling of HPV Vaccine

Presenter: Dr. Geoff Garnett, Imperial College, London

Overview: Impact of HPV vaccines, considering transmission dynamics and disease progress, modeled in two ways; one focusing on the interaction between HPV types and cervical cancers and the other focusing on age of vaccination and catch-up programs.

Modeling was presented of a quadrivalent HPV vaccine delivered in the setting of routine cervical cancer screening. The model included the natural history of HPV infection and disease, estimated parameters and calibration, vaccine impact on cervical cancer, precancerous abnormalties and genital warts, the impact of vaccinating women alone versus both genders, duration of vaccine-derived protection, and age of vaccination and catch-up programs. Inclusion of coinfections could make the model complex beyond utility.

A modeling framework was shared to describe HPV-16's and -18's natural history process, delineated to precancers, neoplasias, and three types of lesions. The model's focus was on CIN2 LSIL and HSIL, considering both screening and natural regression of infection (transient infection), and effective treatment of chronic infection, through to stage four cervical cancer and death. For HPV-6 and -11, which lead to lesions and warts rather than cancer, the model

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assumed a population of infected susceptibles who are vaccine protected, or not. The latter would be either asymptomatic or symptomatic with warts, which could either regress back to an asymptomatic stage, recur, or reach immunity. Another variable considered was loss of vaccine protection leading to renewed susceptibility. Type-specific natural immunity of five years, and then lifelong, was assumed.

The model was calibrated based on data on sexual behavior and age of sexual debut reported by the National Survey of Family Growth, which was compared to observed prevalence of HPV infection (Marhart et al, 2005) as well as to SEER mortality data. Future analysis will include age-specific patterns of infection and disease.

High transmission probabilities per sexual partnership were required to generate the observed prevalence of HPV infection, and cohort studies' observed mean durations of acute infection were used. The baseline no-screening model inserted the HPV type-specific proportions of cervical cancer incidence which, when combined, produced ~ 12/100,000 deaths annually. Screening was then introduced to the model and increased over 30 years to a high coverage of 85% of women screened biannually. Shortening the period of chronic infection decreased the prevalence of infection; and since chronic infections are also infectious, HPV transmission was also reduced. Then, with vaccine introduction, vaccine-type HPV decreased. The rates of decrease differed due to each type's different basic reproductive characteristics. Those with a lower reproductive rate are more sensitive to reductions in the duration of infection.
Declines in mortality, LSIL and HSIL were charted, based on the same assumptions of 70% vaccine coverage among women and 85% coverage of biannual screening. Two scenarios were charted: a worst-case scenario where vaccinees stop screening (assuming they are protected) and a best-case scenario of rising reductions in cervical cancer cases and deaths due to screening, assuming lifelong vaccine protection.

For LSIL and HSIL combined, screening detection reduced cases per 100,000 screened women from ~350 to ~100-150. More analysis of the difference between high- and low-grade incidence is needed, which stemmed from the duration of naturally-acquired immunity or the difference between modeled and actual screening. More work also is needed to determine why the model's assumptions produced a dramatic increase in the age-specific patterns of disease and prevalent lesions with older age. Adding 70% vaccination of men to the model produced additional decreases (~16%) in mortality among women, as the vaccination of men reduced the transmission of HPV from men to women.

The impact of vaccine without boosters was charted, comparing no vaccination to lifelong and ten-year protection. The latter was divided between screened vaccinees and vaccinees that drop screening. With screening, the 10-year duration of protection group had a lesser reduction in mortality than those with presumed lifelong protection, but still a reduction. With 10-year duration of protection, vaccinees who drop out of screening had an increase in mortality compared to the scenario of no vaccination.

A model was described which addressed the age of vaccination and use of catch-up programs. This deterministic model assumed 100% lifelong duration of naturally- and vaccine-derived protection, and compartmentalized women and men in a susceptible-vaccinated-immune

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structure. Younger adults to age 44 years were stratified by age in weeks. The HPV transmission probability was estimated by comparing the model's prevalence at different times to observed data for HPV-16 prevalence in the age groups. Sexual debut by a percentage of the population was presumed by a given age.

For 70% vaccine coverage at ages 12, 15, and 18 years, the charted data indicated that vaccinating older age groups would have a more immediate impact on outcomes such as LSIL, HSIL, and cervical cancer. The more immediate impact arises because those in the older age groups are more likely to be sexually active, allowing vaccination to affect infection spread patterns immediately. But over time, vaccinating the younger population has a bigger impact; charted data showed 72% of HSIL cases prevented by 2050 with vaccination at age 12, versus 67.5% at age 15 and 51.4% at age 18. With added vaccination of males, those proportional of cases prevented by 2050 rose to 84.9%, 79.9%, and 60%, respectively. The same pattern resulted for invasive cervical cancer cases, with vaccination at 12 providing the biggest impact over the long term. The same scale was seen with additional vaccination of males.

Catch-up programs were also analyzed, defined as accomplishing coverage across the desired age groups immediately on program roll-out. In this case, the model assumed vaccination of all 12-, 13-, 14-, and 15-year-olds, to reach a wider proportion of the sexually active population at once and to reduce infection spread, followed by vaccination of 12-year-olds thereafter. Again, the charted data showed the greater effect of vaccinating at the younger age, before the sexually active period, and a similar pattern was seen between HSIL and cervical cancer cases prevented.

Data were then graphed assuming a 12-year-old vaccination program, followed by catch-up vaccination programs at 3-, 6-, 9-, and 12-year intervals after vaccination. Diminishing returns were apparent with the increasing ages involved in the catch-up program, which was related to the proportion already infected when vaccinated. Catch-up vaccination done up to 6 years after initial vaccination at age 12 (i.e., age ~18, or even 21) would produce an effect, to prevent another ~12%-20% of cases, but there was little effect thereafter. The same pattern was true for cervical cancer cases.

Finally, modeling the ages at vaccination assuming a ten-year duration of protection (and no booster) showed a tradeoff between the benefit of early vaccination, pre-sexual debut, versus the lost vaccine protection at the older and still sexually active ages. Nonetheless, vaccinating 12-year-olds remained the best long-term strategy, although the benefit was not as large. Adding a booster again increased reductions in disease incidence.

Behavioral Issues Related to HPV Vaccination

Presenter: Dr. Nicole Liddon, Division of STD Prevention

Overview: Possible sexual behavioral issues resulting from HPV vaccines.

Concerns have been expressed that an unintended consequence of HPV vaccine could be increased sexual risk behavior among vaccinated adolescents believing they are protected from an STD. That concern could influence vaccine implementation, if only due to parental fear of an increase in their child's sexual risk, and pediatricians' reactive reluctance to even raise the issue.

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Behavioral disinhibition is defined as an increase in unsafe behaviors in response to perceptions of safety caused by introduction of a preventive or therapeutic intervention. This is not a new concept. There have been concerns about sexual disinhibition related to the use of anesthesia in childbirth and increased sex within marriage, and to increased sexual risk if penicillin were used to treat syphilis. Today, issues of needle exchange programs and condom use continue such discussions.

YRBS data indicate that 7.4% percent of children from grade 9 through 12 have had sex before age 13; ~33% of 9th graders are sexually active, rising to ~66% by 12th grade. Of all 9th grade (not just those sexually active) 10.4%, have had four or more sex partners, as have 20.3% of all 12th graders. Data from the National Survey of Family Growth are consistent with those findings. By age 15, ~25% of both males and females have had vaginal sex, rising to ~70% percent by age 18 for females and 19 for males. Clearly, these data point to a need for vaccination in early adolescence, before sexual initiation and multiple sexual partners.

The underlying hypothesis to the concern about disinhibition is that fear of HPV will motivate abstention from sex or at least prompt safer sex behaviors. Some of the factors influencing initiation of sexual activity were outlined. These indicated that the decision to have sex by adolescents is based on multiple and layered influences by family, peers and even school and community factors. It is rarely related to a single factor, such as HPV risk. In fact, NSFG data reveal that 15-19 year-old virgins' fear of an STD (including HIV) was only cited by 10% percent of males and 7% of females as a reason not to have sex.

Data from Merck's HPV vaccine clinical trials, emergency contraception, and condom-availability programs (CAP) were summarized to address the issue of sexual behavioral disinhibition among adolescents.

- The Merck data of new male sex partners per person-year among North American women showed no increase in new sex partners per person-year after enrollment in the HPV vaccine trial, compared to self-reported activity beforehand.
- Data from three randomized trials looking at young, sexually active women who attend healthcare clinics for reasons not related to emergency contraception, showed no differences between intervention (provided contraception) and control groups.
- Data from the impact of CAPs includes both sexually active and sexually inactive U.S. adolescents. Overall, the studies show no significant change in the percentage of young people who have ever had sex, after having condoms available, or between schools that have CAPs and those without.

Conclusion. Adolescent sexual behavior onset indicates early adolescence as the best time for HPV vaccine delivery. Various studies suggest that disinhibition will be unlikely to result. Sexual disinhibition is measurable and can be monitored, something being considered by the CDC and others (e.g., through NSFG and YRBS data collection).

Options for ACIP Recommendation on HPV Vaccine

Presenter: Dr. Lauri Markowitz, Division of STD Prevention

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Overview: Additional considerations by the HPV Working Group for vaccine recommendations, for discussion at the June ACIP meeting.

The Working Group has focused on developing recommendations for use of the quadrivalent vaccine based on several assumptions: 1) the possible mid-2006 U.S. licensure of the quadrivalent vaccine for HPV-6, -11, -16, -18, and 2) its later licensure for use in males (pending data on efficacy for prevention of infection or disease in males). Also assumed is 3) that GSK's bivalent HPV-16/18 vaccine will be licensed for use in females at a later date.

A variety of background information needs to be considered for recommendations. This includes data on vaccine and clinical trials, burden of HPV related disease and epidemiology, sexual behavior, vaccine acceptability, programmatic issues and impact and cost effectiveness.

Data from the clinical trials show that very high VE in 16-26 year-old females against the clinical trials' vaccine-HPV type end points; protection has been shown through 2½-31/2 years after dose 3; and the vaccine is safe, with only minor injection site pain reactions. Postvaccination seroconversion rates in 9-26 year-olds substantially exceed those achieved after natural infection, and are highest in those vaccinated at younger ages. Antibody titers decline over time after the third dose, but plateau by 18 months, remaining higher than those after natural infection for several years.

Among the unknowns are a serologic correlate of protection (due to the trials' high efficacy), the duration of protection or need for a booster, and missing data on efficacy among males. There are also knowledge gaps about HPV infection and natural history that might impact vaccination.

Duration of protection is unknown for any new vaccine when first licensed. The quadrivalent HPV vaccine has some similarities to hepatitis B vaccine that may be instructive. Both are subunit vaccines with an alum adjuvant. Hepatitis B vaccine provides long-term protection, and although antibody titers wane in some individuals who receive hepatitis B vaccine, exposure/infection with hepatitis B usually does not result in chronic carriage or clinical disease. Direct comparisons are limited by the fact that hepatitis B is a systemic infection while HPV is mucosal or cutaneous. Questions have been raised concerning whether an anamnestic response will protect individuals from persistent HPV infection and sequelae. Clearly follow-up studies are needed to monitor duration of protection from HPV vaccine .

Other background information for recommendations also considered by the Working Group includes was outlined. *Vaccine acceptability* is relatively high among providers and parents, but more for vaccination of older adolescents. Education about and recommendations from professional organizations could further acceptability.

Cost Effectiveness – Models for impact and cost effectiveness of HPV vaccine are complicated due to the multiple HPV types, complicated natural history, and the long time between infection and health outcomes. The vaccine will not negate the need for cervical cancer screening, since HPV other than the vaccine types cause ~30% of cervical cancers. The models evaluated the impact of HPV vaccine in the setting of cervical cancer screening.

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Both the Markov and dynamic models show that high HPV vaccine coverage could prevent most vaccine-type-associated cancers and precursor lesions, reducing the 10,000 annual cervical cancers in the U.S. by ~70%. While the impact on cervical cancer will not be seen for many years, the impact on precursor lesions will be seen sooner.

In the Markov models cost effectiveness has been approximately $24,000/QALY for bivalent HPV vaccine in females – with wide range in sensitivity analyses. In dynamic models, which include impact of herd immunity, the vaccine appears more cost effective. Work is ongoing using dynamic models to further evaluate the impact and cost effectiveness of quadrivalent vaccine.

The Working Group's possible recommendations for the ACIP to consider in June include:

1. Recommendation for routine vaccination of females aged 11-12 years with three doses of quadrivalent HPV vaccine. The vaccination series can be started as young as nine years, at the discretion of the physician. (This depends on the FDA's indication of the lower age of vaccination.)
    a. The rationale in support includes HPV infection's high prevalence, the inability to target high-risk groups, and the modeling showing more impact with routine vaccination.
    b. This strategy would result in vaccination of more females before sexual debut, resulting in greater prevention impact. Implementation of a three-dose schedule at this age is also aided by the fact that other vaccines are recommended at this age and a young adolescent healthcare visit is recommended by professional organizations.
    c. There is no evidence of waning immunity and ongoing studies will monitor duration.
2. Upon vaccine introduction, there will be unvaccinated older females who could benefit from the vaccine, and FDA approval through age 26 years is expected. The options to vaccinate 13-26 year-olds include:
    a. Vaccination of all females aged 13-26 years who are not been previously vaccinated.
    b. Permissive recommendation for all age groups with a specific recommendation for a more limited age range.
    c. Further modeling will be done and discussed for this age group.
3. Vaccination of males. It is expected that licensure will be at a later date, when there are efficacy data in males. Possible initial ACIP statement wording could be similar to, "HPV vaccine is not licensed for use in males. Studies in males are under way and results are awaited."

The Working Group will continue discussion of the quadrivalent vaccine recommendation options, and modify them as needed after the FDA licensure. The draft recommendations and options will be circulated before the June ACIP meeting. Future discussions will develop recommendations for the bivalent HPV vaccine.

Discussion by the committee of the HPV presentations included:

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- The main arguments against recommendations to immunize to age 26 involved feasibility more than any other issue (e.g., to catch up) and still-incomplete cost effectiveness data.
- Dr. Lieu asked about the sensitivity of the CE analysis to the cost of vaccine, and how likely the analysis' costs will match the vaccine cost. Dr. Chessen answered that the analysis is sensitive to vaccine cost, since that is a large part of the cost per QALY. In some cases, doubling the vaccine cost more than doubles the cost per QALY. Dr. Feinberg reported that Merck has not yet determined the vaccine's cost. But relevant data are continuing to emerge and are expected to make the true value of the vaccine apparent. The latter needs to be stated to provide the context when the vaccine price is announced.
- Dr. Hull observed that low SES, undereducated women will not be vaccinated without a mandate, and they are the same group that disproportionately dies from cervical cancer. He asked what effect those factors had on the models' highest risk populations. Dr. Chessen responded that that issue has less impact in a CE analysis, because many of the vaccine's benefits involve reducing the follow-up costs after screening. But it would affect cervical cancer incidence, and he hoped to add that into the analysis later.
- Dr. Chessen confirmed for Dr. Finger that the averted medical costs were included in the CE analyses. Some of the papers did not provide a breakdown of the benefits, but he offered to get that from the modelers.
- Dr. Gall supported beginning the vaccine's use at age 11 or 12, but added that vaccination for females aged 13-26 who were not previously vaccinated is also critical. ACOG could not support a recommendation for this vaccine only for pediatric use. Just one reason for that was that solely pediatric use would provide no impact on cancer prevention for ~25 years.
- Dr. Sam Katz observed that almost all the studies presented related to the U.S., and asked what modeling had been done for resource poor countries without cancer screening. Dr. Garnett reported a lot of work on that, particularly by Dr. Goldie, under a grant from the Gates Foundation and the WHO. She is collecting data and studying the vaccine's impact in India, Latin America and other resource-poor areas. The results for the U.S. were presented "because that is where we are."
- Dr. Traenor commended this as the most informative session he had ever attended in discussing the pro's and con's of a vaccine. He asked what the assumptions were, in the scenarios of low vaccination rates in women, about the VE of vaccinating men. Dr. Garnett reported that the assumption was of similar effectiveness against acute infection in men as seen in women ─ a very high efficacy.
- Dr. Pickering asked about vaccine availability. Dr. Feinberg reported that Merck had invested significant resources to ensure its availability for all indicated cohorts in the label for the first years of use. Dr. Monteyne reported the same as true for GSK.
- *Bridging* . Dr. Martin Myers asked FDA's opinion of the correlation of immunogenicity between the 9-15 year-old female age group to that in males, as a surrogate marker. Dr. Baylor responded that it was too early in this vaccine application's review to comment on that. Dr. Powell asked why the bridging data could be applied to young adolescent females but not males.
- Dr. Markowitz responded that the 9-15 year old females could be bridged to VE in older females, but there was no such parallel group for the boys.

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- Dr. Barr added, from Merck's perspective, that the 100% VE, slightly higher immunogenicity found in boys, and the same type of hair-bearing, keratinized skin around the genitalia of both sexes, supported male vaccination. That also would provide the benefits of herd immunity to controlling infection.
- Dr. Peggy Reynolds demurred, noting that not only is efficacy not shown for males, but also that females are protected from cervical cancer by transudated IgG.
- Dr. Dubin cautioned that the genital herpes vaccine trial showed differences in gender-based efficacy, despite the similar distribution of genital herpes lesions in men and women to that of genital wart lesions. That could be applicable to the questions about the relevance of bridging.
- But Dr. Barr disagreed, calling that speculation. He added that the objective is not only to prevent cervical cancer, but RRP, genital warts (for which the vaccine is 100% effective on women's external genitalia), and other cancer burdens that HPV can cause. Although the organs are different, the skin is the same, as is the natural history, HPV types, treatment and efficacy. He urged vaccination of males to avoid the limitations of a gender-specific policy and to broaden the vaccine's availability to all.
- Dr. Temte asked about cost effectiveness considering the incremental costs with male vaccination added, and whether that would make it so expensive as to prevent a recommendation. Dr. Chesson could only report that the range of costs per QALY is great across the only two studies that address this question. CDC is trying to figure out now why that is.
- Dr. Schuchat noted that the models assumed the stability of other HPV types. She asked if there was any reason for concern about replacement types, particularly as regards the herd immunity being modeled. Dr. Garnett reported that was included in the analysis. The concerns were that removing the progress to disease can invite replacement by other types; and that this could create a niche for the other types by removing the natural cross immunity. That will be studied in Finland. But evolutionarily speaking, the HPV types are ~10% different in genotype, and 2% different even within types, making them fairly stable. This is an important issue. Additional immunity created by the vaccines, which is not conveyed by natural infection, is also possible and being studied. Dr. Barr added that the HPV-16 vaccine trial showed comparable disease rates caused by the four types. He also noted that women infected with one type are at higher risk for another and thought a replacement phenomenon to be highly unlikely.
- Dr. Renee Jenkins, of the National Medical Association, pointed out that access to this vaccine for eligible children would be through the VFC program, which is already under strain. Dr. Lance Rodewald reassured her, though, that by statute, VFC coverage is mandatory spending and the funding will be available. However, the Section 317 funding is discretionary, and more of a concern.

PUBLIC COMMENT

Dr. Bobbi Gostout, Associate Professor at the Mayo Clinic, attended to represent the Society of Gynecologic Oncologists. She had no vaccine-related conflicts to declare. She stated the importance that the ACIP hear from physicians serving the women who still develop cervical cancer, even in highly screened populations. There are no easy solutions; some women cannot or will not avail themselves of care; some do not understand the importance of screening; and some rely on a Pap test result that turns out to be a false negative. HPV vaccine provides hope

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for all those categories and most promisingly, it would reduce the endocervical cancers that are missed by current screening, as well as the >90% caused by HPV-16 and -18. Those who survive cervical cancer often cannot have children thereafter. It is so disturbing to see these cases, knowing that the field is so close to eliminating the disease. She put the Society of Gynecological Oncologists on record at this meeting in support of action by federal agencies to approve and license the vaccine as soon as possible and to disseminate it as broadly as possible. The SGO supported maximum vaccination of females and, as the science supports it, of males, and urged the ACIP to recommend that the VFC program include this vaccine.

Ms. Chris Armenderez, a psychologist from Minnesota, is also a patient of Dr. Gostout who treated her for invasive cervical cancer. For years, her Pap test results were returned as Class 2. noting "possible cellular inflammation," then accelerated to Class 3+. After a miscarriage that occurred about six month before her diagnosis, she had fairly constant bleeding, including after sex. An endometrial biopsy found severely abnormal cells and she had a D&C, after which her cancer was diagnosed. Before her surgery, she sat up all night holding her sleeping 3-year old son, mourning that if she died early, he would not remember her. Her surgery was successful. She stressed the tragedy that women without access to medical care die of this, and supported implementation of the vaccine so that no one else would have to go through her experience.

Dr. Carolyn Runowicz, President of the American Cancer Society, also strongly supported the ACIP's approval of HPV vaccine. Not only is it historic as the first cancer vaccine, but it can help address cancer's disparity, which disproportionately affects the underserved, uninsured, underscreened, and racial and ethnic minorities. If this vaccine is widely implemented throughout the school system as other vaccines are, that disparity can be affected for cervical cancer. The vaccine offers the power and the opportunity to prevent this disease.

Ms. Amelia Toper, a survivor of cervical cancer, urged the ACIP to make the vaccine available to all individuals, with no age limit. She is a nurse and married with two children, one 18. Although she always followed health guidelines such as annual Pap screening, her cancer was diagnosed in stage 1B. It was removed, but she still worries about recurrence and for her daughter. That angers her, because this is a preventable disease. Despite her post-operative discomfort, she drove 1½ hours to urge the vaccine's recommendation by ACIP. She attended to speak, to protect her daughter and other women. An ACIP recommendation will extend HPV vaccine's availability to all women and every child, male and female.

Ms. Susan Crosby is the President and Executive Director of Women in Government. A national, nonpartisan organization for female state legislators, the WIG works with the legislators to provide information helpful to making difficult policy issues. In 2004, 44 states developed cervical cancer prevention legislation. To date, 37 have passed it, to learn its causes, incidence, mortality, and what each state can do to eliminate cervical cancer. She asked the ACIP to help these women legislators by recommending that the vaccine be made available to all, regardless of their socioeconomic status.

Ms. Moira Gaul, a policy analyst for the Family Research Council, welcomed the vaccine's potential for improving health and preventing deaths. She thanked Merck and GSK for meeting with the FRC to explain their goals for marketing this vaccine. The FRC will follow the

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vaccine's experience to see if it is safe and effective for all, and has found that to be very encouraging so far. The FRC also will follow the activities of the pharmaceutical companies, the federal and state governments, and the medical community as the vaccines are released, especially to determine if there is any impact on sexual activity. They are very concerned that information be distributed to public health, physicians and parents, that HPV will not prevent other STDs, even other HPV types that cause cancer. Recognizing the recent epidemiological studies' finding that the vaccine is most effective at earlier ages, she cautioned the health care community to clearly convey that only abstaining from sexual contact protects from STDs. But since HPV also can come from sexual abuse/assault, or marrying someone infected, the vaccine is a benefit. Since parents should decide about matters of their children's health, the FRC strongly opposed any mandate, including school entry, since HPV is not easily transmitted. Health care providers should discuss the full range of issues affecting health. Counseling on risk elimination strategies to prevent STDs should be developed, to match the risk elimination messages for tobacco, drug and alcohol abuse. The best primary prevention is to limit sexual activity to a single, life-long monogamous relationship, thereby avoiding the physical and psychological effects of STDs.

ROTAVIRUS VACCINE

Data Review, Rotavirus Efficacy and Safety Trial (REST)
Presenter: Dr. Penny Heaton, Merck

> Overview: Overview of Phase III clinical trial study design; safety and efficacy data supporting licensure of Merck's pentavalent human bovine reassortant rotavirus vaccine (PRV).

The FDA approved the safety and efficacy data of Merck's Phase III trial of a pentavalent human bovine reassortant rotavirus vaccine (PRV) and licensed it on February 3, 2006. PRV is an orally administered vaccine that is suspended in a liquid buffer stabilizer. The buffer protects the vaccine from gastric acid and the stabilizer allows refrigerated storage with a 24-month shelf life. It is easily administered directly from the tube to the infant, and has a three-dose regimen compatible with the childhood schedule. The trials administered the first dose at age 6-12 weeks, followed by two more doses at 1-2 month intervals on the 2, 4, 6-month schedule and the 2-, 3-, 4-month schedule. The formulation contains five human bovine reassortants, including the human G1, G2, G3, G4, and P1(8), which constitute >90% of the rotavirus strains in the U.S. and worldwide, and bovine G6 and P7.

The PRV development program was outlined, from the vaccine technology's licensure in the early 1990s through three Phase II studies and three Phase III studies: efficacy and safety trial (006), dose-confirmation efficacy study (007), and lot consistency study (009).

Evaluations. The *efficacy* evaluated in the Phase III studies were VE to prevent rotavirus acute gastroenteritis caused by the vaccine serotypes (G1-4; non-G1-4 strains containing P1; and VE to reduce healthcare encounters for rotavirus gastroenteritis, including hospitalizations, emergency department (ED) visits, and physician office visits. Other than vaccine *immunogenicity*, the study explored antibody responses to concomitantly administered other licensed vaccines, and

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safety relative to serious adverse events (AE), including intussusception. Other AEs of special clinical interest (for any live rotavirus vaccine) were fever, vomiting, and diarrhea.

Study design. The Phase III trials involved 71,799 subjects, 36,000 of whom received PRV and 35,799 received a placebo. The age at first dose was 6-12 weeks and the next two doses were administered every 4-10 weeks, year-round. Case definitions were developed that included ELISA confirmation for rotavirus gastroenteritis and radiographic, surgical, or autopsy diagnosis for intussusception. Active surveillance followed every infant for safety and healthcare encounters for rotavirus gastroenteritis. The parents were called at weeks 1, 2, and 6 after vaccination and then every six weeks thereafter, up to a year after enrollment. Extra calls were made every two weeks during rotavirus season, and children vaccinated during the season were followed through that and the next full rotavirus season.

Vaccine efficacy results. VE against G1-4 rotavirus gastroenteritis was:

- 73.8% against any rotavirus disease, 98% against severe disease.
- Reduction in hospitalizations: 95.8%; in ED visits, 93.7%, in office visits, 86%.
- VE ranged from 68-82% with overlapping confidence intervals, and did not vary according to infant feeding status (i.e., breast fed, breast and formula fed, etc.)
- VE in premature infants (N=2000) of gestational age ranging from 30-35 weeks was similar to that of the overall population, at 70% against any severity of rotavirus gastroenteritis.

*Immunogenicit*y. The statistical criterion for demonstrating non-inferiority for concomitantly administered DT, IPV, Hib, and Hep B was ≤10 percentage points decrease among PRV versus placebo recipients, for the proportion who achieve seroprotection (95% CI). The criterion for pertussis and pneumococcus: ≤2-fold decrease among PRV versus placebo recipients for the ratio of GMT (95% CI). The analysis compared antibody responses to the licensed vaccines co-administered with PRV versus given with placebo, for:

1. Three doses of DTaP and pneumococcal conjugate vaccine, measuring GMTs ~1 month after the third dose (at age ~7-8 months)
2. Two doses of COMVAX® (Hib/Hep B) and IPV, measuring GMT at ~5 to 6 months of age.

Results. The statistical criteria for diphtheria, tetanus, IPV, Hib, hep B, and the pneumococcal conjugate serotypes were met. For pertussis, the statistical criteria for toxoid and FHA were met, but not for pertactin. No cause for that was found. Retesting mirrored the original results, but for additional tested subjects and the combined sample, the criteria for all three compartments were met. There still is no explanation for the initial pertactin failure, but the reanalysis showed that the pre-immunization titers were not a factor.

Conclusions. The data support concomitant administration of PRV with the already-licensed childhood vaccines. The clinical significance of the original lower pertactin titers remains unclear. Additional testing and/or another study to confirm the reanalysis' favorable results is being considered. Data show that two-component vaccines, particularly in post licensure effectiveness studies, show protection against pertussis that is similar to that of multi-component vaccines.

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Safety results for intussusception. In all, REST had 35 investigator-diagnosed cases of intussusception. Two cases were negatively adjudicated and one case could not be adjudicated due to malfunctioning equipment; all were in the placebo group. Thirty-two cases were positively adjudicated; of those, four cases occurred after the child completed the study and again, they were all in the placebo group. Of 28 cases identified in the year follow-up after a dose, 11 occurred with 42 days of the dose, six in the vaccine group and five in the placebo group. Seventeen cases, seven in the vaccine group and ten in the placebo group, occurred outside of that 42-day period but within the one-year safety follow up.

Intussusception case intervals were charted by dose and by day post-dose. The relative risk for dose one was 0.9; that for the 42-day period after any dose was 1.2 (1.6 if adjusted for multiplicity, in a 95% CI of 0.3 to 5.0). The data charted by day showed a sporadic distribution of the cases. There was no clustering of vaccine cases without a similar cluster of placebo cases, and none occurred in the two-week period after Dose 1, the period of greatest intussusception risk with Merck's former rotavirus vaccine, RotaShield.®

AEs of special interest. Fever after each of the three doses was similar in both the vaccine and placebo groups. For vomiting and diarrhea, the small differences between vaccine and placebo groups were small (1.3%) but statistically significant. However, the vast majority of these cases were characterized as mild by the physician.

Conclusion. PRV is efficacious against rotavirus gastroenteritis of any severity and highly efficacious against severe disease. It reduced healthcare encounters for rotavirus gastroenteritis by 96% for hospitalizations, 93% for ED visits, and 86% for physician office visits. Concomitant use data indicate the PRV can be co-administered with DTaP, IPV, Hib, hep B, and pneumococcal conjugate vaccine. PRV is well tolerated with respect to all adverse experiences, including intussusception with some mild, small increases in mild diarrhea and vomiting.

Review of Cost Effectiveness Data

Presenter: Dr. Mark Widdowson, National Center for Infectious Diseases (NCID)

Overview: Updated, expanded results of the cost-effectiveness analysis presented to ACIP in October 2005.

This cost effective analysis was done with a probabilistic model in which a fictitious 100,000 children were followed from birth to age 59 months to estimate the cumulative number of different rotavirus disease outcomes in that period. The same number of outcomes were calculated for this cohort, but vaccinated, at 2, 4, and 6 months. Medical and nonmedical costs of each outcome type were estimated, including the cost of the vaccine program and adverse reactions. The cost effective ratio was calculated from the healthcare-payer perspective (medical costs) and the societal perspective (both medical and nonmedical costs), for cases averted and life-years saved. The resulting distributions for each input to the model were then combined to an output distribution, and all distributions were plotted for a median and a 95th percentile.

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Disease burden inputs assumed at least one episode of clinical rotavirus disease per child by age 59 months, among 75% of the U.S. children (3 million). NCHS provided data on rotavirus-caused diarrhea outcomes which required healthcare over a ten-year period. That was multiplied by a published fraction for rotavirus, to arrive at the annual number of rotavirus disease outcomes per year. Published RV mortality data were used to calculate annual rotavirus deaths.

Rotavirus outcomes ranged from death, hospitalization, hospital outpatient, ED and physician office visits, and care at home, for >3 million cases of rotavirus. The large (5 million enrollees) MarketScan database supplied data for four years of *medical costs*, which were translated to 2004 dollars and then discounted by 3% for the social and healthcare perspectives. The median cost calculated for hospitalization (median of 2 days), for example, was $2962, ranging from $1181 at the 5th percentile to $7426 at the 95th percentile.

Nonmedical costs included days lost from work to care for a sick child ($118/day), travel for health care, extra diapers, special food, child care costs, and for mortality, lifetime productivity lost. The data used for *vaccine efficacy* outcomes (the same five listed above for rotavirus outcome) were adapted from the Rotateq® trial, published in the January *New England Journal.* This trial used a range of efficacy measures, from 65 % for mild diarrhea to 90% against hospitalization and death.

The cost effective ratio was calculated for several program costs: dose of oral RV vaccine, its administration, hospitalization for intussusception (1:50,000 vaccinees, which added 10 cents to the total vaccination cost per child), and outpatient workup for non-intussusception adverse events (an extra 15 cents per child vaccinated). In the absence of a vaccine price, a cost range of $10-$80 was used, plus $10 per dose to administer it, resulting in a range of $30-$240 per child.

Analysis results for cost effective ratios per case of rotavirus averted were charted, from the healthcare perspective and the societal perspective. From the healthcare perspective, the breakeven point was a total cost of $33/dose; anything less would be cost saving. From $33-$66, the vaccine program probably would be cost effective; from $66-$143, cost effectiveness would be unlikely, and above $143, it would not be cost effective. If administration costs are removed, the $66 to vaccinate becomes ~$12/dose. With Merck's $62.50 published list price for the new rotavirus vaccine translating to a total cost per vaccinee of ~$217, the rotavirus vaccine would not be cost effective from a healthcare perspective.

From the societal perspective, breakeven cost is $107 total cost per dose. From $107 to $156, the program would likely be cost saving, but unlikely to be so from $156 to $238; and after $238, it would not be cost saving. The total $107 cost translates to $42 per dose, which again makes Merck's $62.50 price unlikely to be cost saving from a societal perspective. But there was also a 20% chance that it may be cost saving at $62.50/dose.

Charted by life-year saved, the breakeven points mirror those for each case averted. But the rarity of deaths prevented by rotavirus vaccination makes the potential costs per life-year saved much greater, at $400,000 per life-year saved versus $400 per case averted. A separate sensitivity analysis was done to account for 50% of days lost from work, subtracting that from the base-case estimate. Increasing the days off work made the vaccine program more cost

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effective and conversely, less cost effective with less days off work. The breakeven point, including extra days off work, was $52 per dose, still outside the Merck price.

The cost effective ratios for different outcomes at $62.50/dose were charted from the healthcare perspective: $470,729 per life-year saved and $336 per case averted. From a societal perspective, it would $197,190 per life-year saved and $138 per case averted. Results of a sensitivity analysis of the model's inputs were charted, showing the most important to be the cost per hospitalization and per ED visit.

Reduced morbidity in the U.S. due to a vaccine program for the 4 million birth cohort (July 2004) was charted, assuming 70% coverage for the full three doses by age 6 months, and 25% coverage for only one or two doses (half the efficacy). The program would reduce events (hospitalizations, home care, ED/office visits, etc.) by an average of 51%. There would be more reduction of hospitalizations and ED visits than of home care needed, because of the increased efficacy for more severe outcomes. From the medical perspective, at Merck's price, the program's medical costs would be $514 million. But it also would save a substantial nonmedical cost total of $300 million, meaning a final cost from the societal perspective of only $250 million at $62.50 per dose and the same coverage rates.

It is important to remember that vaccines are not necessarily cost saving. A chart demonstrated that the newer vaccines are less cost effective than the older ones. One dose of varicella and the hepatitis B vaccine provide savings, while pneumococcal, meningococcal, pertussis and rotavirus vaccines incur net costs, from both a case saved and QALY saved perspective.

Among the analysis's limitations were that the vaccine's true cost will probably be less than $62.50 for the VFC program, and that private contracts introduce another variable. Initial coverage levels also will likely be much lower thank 70%, which is the DTaP level. While that would not affect the cost effective ratio, it would affect the overall net cost of savings of a vaccine program. Finally, the analysis does not include the psychological costs of anxiety about a sick child or about adverse reactions.

Physician/Provider Surveys on Rotavirus Vaccine Use
Presenter: Dr. Alison Kempe, University of Colorado

> Overview: Rapid turnaround national survey done by CDC of practitioners' attitudes and beliefs about rotavirus vaccine use.

This national survey sought to determine pediatricians' knowledge and attitudes about rotavirus disease, their intentions about recommending a new rotavirus vaccine, and perceived barriers to rotavirus vaccination.

Survey methods were outlined. It was conducted in a sentinel physician network that was randomly recruited from AAP membership, but designed to be representative of the AAP membership overall and of the region of the country, practice location (urban, inner city or not; suburban, or rural), and setting (private, managed care, hospital-based, etc.) A panel of pediatricians developed the survey, which was administered by mail or e-mail in January and

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February 2006. It is still not completed.

Preliminary results. The response rate at the time of the interim analysis was 66%. Respondents and nonrespondents were similar in terms of region, practice setting or location; 55% were male, 45% female; 65% of respondents had >50% of their patients who were insured; 78% percent participated in the VFC program.

- Perceived rotavirus burden: 1) Most common cause of infectious diarrhea in children aged <2 years: 55% strongly agreed; 30% somewhat agreed; 2) most frequent cause of severe diarrheal disease in children aged <2 years: 82% strongly agreed; 3) need for a safe and effective rotavirus vaccine in the U.S., 51% strongly agreed, 37% somewhat agreed.
- Experience with RotaShield:® All the respondents were aware of the problems associated with RotaShield® before its withdrawal from the market, by: 1) administration: 53% administered it routinely; 9% intermittently; 38% had not administered it; 3) experience of intussusception: 12% had patients or knew of patients who had intussusception suspected of an association with RotaShield.® 4) plans to discuss the RotaShield®-intussusception association with patients when discussing the new vaccine: 50% would routinely discuss it; 32% would do so only if it was raised by the parents; 6% would not discuss it; 11% were unsure.
- Intentions to recommend the new vaccine if ACIP and AAP recommend it for routine versus permissive use: 1) Routine use: 50% would strongly recommend it; 34% would recommend; 11% would inform but not recommend; 1% would recommend against it. 2) Permissive use: 33% would strongly recommend, 43% would recommend but not strongly, 19% would inform but not recommend, and 1% would recommend against.
- Speed to implement vaccine use if ACIP/AAP recommended routine use: 51% would begin within six months of the recommendation; 28%, 6-12 months; 7%, 1-2 years; 1%, 2 years. Another 14% were unsure.
- Reasons to wait >6 months: 1) insurance coverage: 90%; ensure no vaccine side effects: 81%; adequate vaccine supplies: 65%; see if other providers use the vaccine: 36%; see if parents accept the vaccine: 20%.
- Barriers to giving rotavirus vaccine: 1) failure of some insurance companies to cover vaccination: definitely, 51%; somewhat of a barrier, 28%; 2) lack of adequate reimbursement for vaccination: definitely a barrier, 42%; somewhat a barrier, 32%; 3) parents' reluctance due to RotaShield® withdrawal: definitely a barrier, 30%; somewhat a barrier, 42%.
- Physicians' concerns about rotavirus vaccine safety: 1) definitely a barrier, 21%; somewhat a barrier, 26%; 2) upfront vaccine purchase costs to the practice: definitely a barrier, 21%, somewhat a barrier, 27%; 3) concern about obtaining adequate supplies: definitely a barrier: 20%, somewhat a barrier, 33%.
- Definite barriers to rotavirus vaccination by ≤15% of respondents: parental concern about vaccine safety in general, 15%; parents thinking rotavirus vaccine is unnecessary, 12%; respondent concerns about adding another vaccine to an overloaded vaccine schedule, 9%; respondents' belief that rotavirus was not a severe disease requiring vaccination, 5%; time needed to discuss vaccine safety with parents, 4%; general administrative burden to the practice, 3%.

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The survey data's limitations include potential selection bias, despite efforts to build a study population representative of the AAP or the AMA, and that the survey measures the intent to vaccinate rather than what physicians are actually going to do.

Conclusion. Most pediatricians (88%) surveyed believed there was a need for a rotavirus vaccine in the U.S. If a new rotavirus vaccine were recommended for routine use, 83% would recommend it, 50% of them strongly. With permissive use, fewer would recommend ─ 77% overall and 33% strongly. A majority, 51%, would begin using vaccine within six months of ACIP/AAP recommendations. Barriers anticipated by respondents included the lack of broad coverage by insurance companies, lack of adequate reimbursement to physicians giving this vaccine, and parental reluctance to vaccinate because of withdrawal of the prior rotavirus vaccine. When discussing new rotavirus vaccine with parents, many would discuss the association with prior vaccine and intussusception, either routinely or if it was raised up by the parents.

Post-licensure Surveillance Plans

Presenter: Dr. Penina Haber, Office of the Chief Science Officer, CDC

The main tools for post-licensure safety monitoring are the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system for reporting vaccine adverse events, and the Vaccine Safety Datalink (VSD), a collaboration between CDC and eight large U.S. health maintenance organizations with an annual enrolled birth cohort of >90,000.

VAERS is a voluntary nationwide reporting system able to detect previously unrecognized or rare reactions. Monitoring for those will be done by CDC and FDA, reviewing daily reports and alerts of all serious adverse events and other medically important conditions. The VAERS main focus in this case will be on intussusception and suspected intussusception, any reports of which will prompt immediate follow-up, and other serious gastrointestinal outcomes. A VAERS analysis of serious reports includes radiology, surgery, or autopsy information and medical records confirmation. The Brighton case definition for intussusception will be applied to verify suspected reports. The reports will be graded and then compared to the background rates obtained from the VSD data.

The VSD's advantages for vaccine safety research are its access to a large and well-defined population, with computerized linkable administrative databases to support controlled population-based studies. The VSD rapid-cycle (real-time) analysis for Rotateq will monitor for possible increased risk of intussusception, and evaluate other prespecified conditions and associations identified from VAERS and from the manufacturer's Phase IV studies.

The post-licensure study will include infants aged 0-12 months who received the Rotateq® vaccine, followed for 40 days after vaccination. Automated outcomes data and chart validation will be in the analysis, and sequential statistical testing will compare rates of intussusception and other conditions seen after Rotateq,® to expected rates.

Merck's Pos-tlicensure Monitoring Plans

Presenter: Dr. Chris Mast, Merck

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Merck is implementing a three-phase or three-component plan for comprehensive pharmacovigilance to monitor vaccine safety: 1) maintenance of a large safety database of ongoing and future clinical studies of Rotateq® among >71,000 subjects, to monitor the safety of this product; 2) two pharmacovigilance activities, one a prospective population-based study assessing intussusception and general Rotateq® safety, and the other enhanced passive reporting through telephone follow-up of all intussusception cases and expedited case reporting to the FDA. FDA also will be apprised of all adverse events monthly, in addition to Merck's quarterly reporting. And, 3) Merck will coordinate and collaborate with CDC and the FDA on these respective pharmacovigilance activities.

Merck's active surveillance plans, approved by the FDA, were summarized. The prospective surveillance study will explore both intussusception and general safety in the same study population. The study population is a large insured population, separate and complementary to the CDC/VSD study. In that, Merck will evaluate all infants (~44,000) receiving Rotateq® (on- or off-label) during the study period. Safety will be assessed for 30 days after each dose, as well as alternate intervals for the secondary analysis.

The post-licensure study will compare the incidence of intussusception among vaccinees to the background rate. The latter will be examined in a baseline study before licensure, to confirm the study's operating statistical assumptions. A sequential design similar to Dr. Haber's description will assess intussusception cases as they occur and continuously monitor during the study period. One objective to be explored is the use of unvaccinated concurrent controls if potential confounding factors can be controlled.

Safety will be assessed descriptively by recording adverse experiences among infants who received Rotateq® in periods after vaccination. Analytical assessment of general short-term vaccine safety will compare post-Rotateq® vaccination adverse events with two control periods. In one, vaccinees will be their own control group, and the other is a historical cohort. All adverse events resulting in hospitalization or ED visits during the study period will be captured. This method has been used for other vaccines, and the results were published.

Discussion included:

- Dr. Lieu raised the cost effective analysis results of $178,000 per life year saved, and $138 per case averted. Another analysis that would be helpful, would be to go on to calculate dollars per QALY. She had quickly calculated a net societal cost, after deducting work loss, of ~$250 million per year and 1.5 million cases averted. She calculated further that if about a day of life is traded to avoid a case of rotavirus, that the vaccine would appear cost effective at $50,000 per QALY saved. Dr. Widdowson reported a life year saved analysis as briefly discussed but not done, because the relatively brief rotavirus episodes would not greatly affect the subsequent QALYs. However, that could be estimated.
- Dr. Campbell asked what the duration of the vomiting or diarrhea was among the 15%-25% of vaccine recipients, so as to understand the impact on parents' time lost from work. Dr. Heaton responded that these episodes, being described as mild, would typically only last 1-2 days.

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- Dr. Kempe conveyed Merck's own surprise that the physicians asked about Rotateq were so generally positive, although they tend to be so about new vaccines in general. They seemed to view Rotateq as a new vaccine
- Dr. Morse asked if parents had been surveyed as well, and if so, if they shared the pediatricians' concerns about safety. Dr. Jim Alexander, of NIP's health communications staff, reported that CDC is doing key informant interviews and focus groups of parents, especially young parents likely to have, or about to have young children, to assess their attitudes about new vaccines.

Rotavirus Vaccine Working Group Draft Proposed Recommendations
Presenter: Dr. Umesh Parashar, NCID

The recommendation options for vaccine use in general were for routine or universal use, permissive, or a targeted strategy to high-risk groups. Considerations discussed by the Working Group included:

- Burden of rotavirus illness in the U.S. in children aged ≤5 years, ~70% (2.7 million) children will have an episode of rotavirus gastroenteritis, resulting in >200,000 ED visits, >400,000 outpatient visits, 55,000-70,000 hospitalizations, and 20-60 deaths annually. Charted cumulative hospitalization rates showed 90% due to rotavirus by age 2 years.
- High-risk groups for severe RV disease include infants with low birth weight, those born to young mothers, and those socially disadvantaged. But these groups comprise only a fraction of overall severe RV cases, so a targeted vaccination strategy would not effectively reduce severe rotavirus disease. Routine or universal immunization of infants with three doses of this vaccine given at 2, 4, and 6 months of age was chosen as the optimum strategy. Dose 1 would be given from 6-12 weeks of age, as done in the clinical trial. That is supported by available safety data. All three vaccinations should be done by 32 weeks of age, with at least a 4-10 week interval between doses.
- NIS data show an 88% uptake of the first DTP dose by 12 weeks of age, then rising in a slow plateau to 98% by age one. So, although having the strict cutoff for 6-12 weeks of age would potentially reduce vaccine coverage by 10%, the Working Group opted to follow the age period supported by safety data from the clinical trial, at least in the initial years of the immunization program until more data are available through post marketing surveillance.
- The vaccine can be administered to infants with transient mild illnesses and can be co-administered with other vaccines given at 2, 4, 6 months of age.
- There are two contraindications proposed by the working group: T- or B-cell deficiency (including infants of HIV-positive mothers, unless the infant is clearly uninfected), since this is a live viral vaccine. The second is serious allergy to any vaccine component or to a previous dose of the vaccine.
- Precautions are stated for infants with moderate or severe acute gastroenteritis at the time of vaccination and infants with moderate or severe febrile illness. In both cases, vaccination should be delayed to recovery, unless the pediatrician fears that the child will not return for vaccination. Infants with pre-existing chronic gastrointestinal disease can be vaccinated, since the risks of the disease are greater. There is no association of this vaccine to intussusception, but infants who have had a prior episode of intussusception should not receive this vaccine. Premature infants can be immunized if they are at least

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six weeks of age, clinically stable, and are being or have been discharged from the hospital nursery. Infants who have recently received any antibody-containing blood products may be vaccinated.

- The small risk of shedding and transmission (after dose 1, by 12%-13%) does not outweigh the risk of transmission from a child with wild rotavirus disease to household contacts, so the infant should be vaccinated. Vaccine should not be readministered to infants who regurgitate a vaccine dose. Limited related safety and efficacy data indicated that, since the vaccine has a high titer, even a partial dose might lead to some immune response and protection.

Discussion:

- Dr. Abramson understood the data-based rationale for the very tight vaccination schedule, but strongly advised that very clear guidance be provided on it, as children will certainly be presented for vaccination both early and late. Dr. Treanor said that guidance for vaccinating outside the window will be developed.
- Dr. Halsey urged a more permissive recommendation for HIV-positive children. Antiviral therapies have greatly reduced maternal transmission of HIV (to only 5%), and immunosuppression is minimal until months after birth. Making HIV status a contraindication will discourage needed studies from being done.
- Dr. Poland suggested that the broader definition of altered immunocompetence in the General Recommendations be applied, and also edited the "theoretical benefits" phrase to be "known benefits outweigh theoretical risks."
- Dr. Heaton clarified that the REST design selected the early 6-12 week window because the intussusception rate is low at that time, which helped them to ensure that any repeated signal of intussusception risk would be detected. Merck has no concern about vaccinating at an older age. A first dose at 13 weeks will still be clinically acceptable. The post-licensure studies will look specifically at age issues and at vaccinating HIV-positive children. They do not expect the latter to be problematic since this group has received live OPV with very few adverse events.
- Dr. Phil LaRussa, of Columbia University, clarified that most HIV-exposed children will have had two negative postnatal tests, one at age ≥2 months, and almost all remain negative to 18 months of age.
- Dr. Deborah Wexler commented on this recommendation's precaution for moderate to severe "febrile" illness, which differs from other recommendations in citing "febrile." She favored consistency unless there is a reason to specify fever.
- Dr. Heaton said that the clinical trial exclusions may not have been sufficient to prevent trial participation by a child with an unrecognized IgA deficiency. And, in terms of shed disease, children with natural disease shed ten- or eleven-fold more virus from natural infection than they do from a vaccine dose.

Dr. Allos moved to accept the proposed recommendations, for a universal recommendation at 2, 4, 6 months, with the minor changes suggested, and Dr. Stinchfield seconded the motion.**.**

Further discussion included agreement that the HIV qualification would be changed from a contraindication to a precaution and that the recommendation would say the vaccine "should be administered between 6-12 weeks of age."

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Vote
Conflict: Drs. Treanor, Poland

In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morse, Morita, Stinchfield, Womeodu, Abramson
Opposed: None
Abstentions: Treanor, Poland

The motion passed.

VFC Resolution
Presenter: Dr. Greg Wallace, NIP

With the ACIP's approved of a general universal recommendation for the rotavirus vaccine, a vote was now needed to incorporated the vaccine into the VFC program. This was done in two parts; to add the rotavirus vaccine to the VFC's list of covered vaccines (to now total 15 vaccines), and then to specify its administration, details of which were lifted directly from the recommendations:

- Administer dose one from age 6-12 weeks, with the routine dosage at 2, 4, and 6 months, with 4-10 week intervals between each dose, and none given past age 32 weeks.
- The standard language about referring to the package insert about dosages was included, as well as that on serious allergic reactions.
- Language on altered immunocompetence was moved to the Precautions section, including that on HIV and other conditions related to immunocompetence.
- "Febrile" was deleted from the language on moderate to severe illness.
- Provider judgment was advised for children with pre-existing chronic GI conditions.
- The intussusception experience of the previous rotavirus vaccine was acknowledged and this vaccine was expected to be helpful for children who have had intussusception. Studies to date were described.

Discussion included:

- Dr. Pickering expressed concern about moving all immunodeficient diseases to the Precautions section, since that would include rare primary immune deficiencies (e.g., T- and B-cell deficiencies, x-linked gamma globulinemia) for which this live vaccine should not be given. However, Dr. Paul Offit commented that although those children can shed virus for long periods, they tend to get mild disease. Even children with severe combined immunodeficiency suffer little from natural infection, and he doubted the vaccine would be of greater risk. He would delay the vaccine only if the child was about to have immunosuppressive therapy such as a bone marrow transplant, and even then the child's age and whether it was rotavirus season would be factors in the decision.
- Ms. Stinchfield pointed out that HIV had already been moved to the Precautions section, not the other primary immune deficiencies. She suggested strengthening the language on altered immunocompetence in the Contraindications section to specify "known T- and B-

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cell immunodeficiency," to protect physicians who may not know by 12 weeks that a child has an immunodeficiency. Dr. Abramson agreed.

- Dr. Halsey addressed the complexity of this question. The AAP has loosened its strictures on giving live vaccines to immune deficient infants. They now provide some flexibility for vaccinating children with conditions such as B-cell immune deficiency disorders, those receiving replacement immunoglobulin, or those with IgA deficiency. There just should be consultation with an immunologist or infectious disease person to evaluate each situation.
- Mr. Kevin Malone, of the Office of General Counsel, confirmed that the VFC language had to be specific before a vote could be taken.
- Dr. Sam Katz objected to singling out HIV, as there is no evidence that rotavirus poses an undue burden to HIV-positive children. In the U.S., children born to an HIV-positive mother will be seen by someone, but that is not the case in Africa, and listing HIV as a contraindication to this vaccine will severely affect them.
- Dr. Baylor pointed out that the vaccine label's precautions include infants with primary acquired immunodeficiencies, including HIV/AIDS.
- Ms. Stinchfield noted that live vaccines such as varicella are given to children with HIV who have a normal CD4 count, and questioned why this live vaccine should be treated any differently than others.
- The language advising against administration after 32 weeks would be changed to "should be given by 32 weeks."

Dr. Pickering regretted that the complexity of the immunology made this decision difficult. Of the four major types of deficiency (T-cell, B-cell, phagocytic, and complement), live viral vaccines can be given to children with the last two, so grouping all four as contraindications is incorrect. But on the other hand, splitting them might make the recommendation too complicated for what is trying to be achieved in a small number of children.

Dr. Wallace agreed to edit the recommendation based on these comments, particularly in the Precaution section to advise seeking the advice of a specialist. With that, and language on altered dosage intervals, he would return for the ACIP's vote in the morning.

ACIP GENERAL RECOMMENDATIONS ON IMMUNIZATION

Revisions to the General Recommendations

Presenter: Dr. Ed Marcuse, General Recommendations Working Group Chair

Overview: Past and new changes to the ACIP General Recommendations document

The ACIP General Recommendations document is its compendium of the information needed about immunization. Its revision every ~5 years is always a challenge, given the rapidity of change (or persisting lack of data) in the field. This revision is expected to be released in September, pending the ACIP's approval on this day, perhaps with additional edits.

General recommendation changes previously presented to the ACIP were:

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Vaccine administration:

- A 5/8" needle is adequate for intramuscular injection; the reference was removed to the 7/8" needle, which is no longer produced.
- There is no need to aspirate prior to vaccine injection
- There is no preferred site for intramuscular injection, but a cautious preference is expressed for the thigh in infants and the deltoid in adolescents and adults.

Storage and handling of immunobiologics:

- The language was strengthened to advise keeping vaccine properly stored to the expiration date (to stop automatic discard of vials opened >30 days).
- The recommendation was strengthened to contact the state health department on the procedure for mishandled or inappropriately stored vaccines. This is controversial, since there are no clear data to guide this decision, and it depends on the vaccine and how it was mishandled. Since expert guidance is needed, the Working Group felt the health department was the first place to check.

Altered immunocompetence:

- A permissive recommendation for the use of varicella and pneumococcal conjugate vaccine after hematopoietic stem cell transplantation in immunocompromised patients was inserted, with a reference.
- A caution was inserted about the use of live vaccines in patients on tumor necrosis factor, alpha inhibitors and other isoantibodies, after related advice from experts that these are analogous to the effect of high dose steroids.

Discussion included:

- Dr. Hull asked rhetorically how a state health department could be expected advise on complex issues like vaccine mishandling if the ACIP cannot. He asked if the NIP could develop a table or formal guideline to help advise this field. Dr. Kroger reported that the revised recommendations will have a table of information for a range of vaccines derived from the respected *Vaccines* by Plotkin and Orenstein. But realistically, most questions are case-based, frustrating any kind of standard reply. Contacting the manufacturer could be the best suggestion. Dr. Kuter reported that Merck has some algorithms potentially helpful to answer the questions of vaccine appropriateness for use.
- State representatives emphatically agreed that guidance is desperately needed. Dr. Kelly Moore, Medical Director of the Tennessee Health Department, developed her state's guidance herself, based on the WHO and Australian guidelines. Ms. Beth Rowe-West, who manages the North Carolina state program, reported requests for judgments at every site visit. NIP cannot be called for guidance about every refrigerator that is too warm or cold, something they hear about "at least twice a day."
- There was some opinion that mis-stored vaccine simply should not be administered, to protect the integrity of vaccines as a whole. But Dr. Abramson raised the problem posed when the mishandling is realized in retrospect. Dr. Moore agreed, reporting common experiences of practitioners who found their vaccine frozen and had to contact thousands of families thereafter. The final decision is made by an adequately informed parent who can require the physician to revaccinate. But, just as fever will not be found without

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taking a temperature, such incidents will not be known unless someone looks at the temperature logs.

- Dr. Salisbury reported the U.K.'s similar experience. The instances of the recommendation being ignored over time, however, are far less than those of a cleaning person who forgot to re-plug the refrigerator on Friday evening. Calling the manufacturers rarely helps, as they generally just advise consulting the package insert, being loathe to risk the liability of any other decision. In his opinion, people just need to make sensible judgments; if the vaccine was not out of the cold chain long, it is a reasonable risk to use it. It is easier to discard it, but that could be just an expensive waste.
- Ms. Lynn Bahta, of Minnesota's health department, disliked the removal of the previous recommendation's text of what to do if a child receives what turns out to be a nonviable vaccine. That removal leaves no national standard at all on which to rely.

Dr. Abramson recommended that this be discussed further in a conference call. He asked those with comments or concerns to email him or Dr. Marcuse about this issue and the changes outlined, which will be addressed again in June.

New Revisions to the General Recommendations since October 2005
Presenter: Dr. Andrew Kroger, NIP

The entire 2002 General Recommendations document was not revised, but significant new changes were made. These have been reviewed by the ACIP liaisons and the Association of Immunization Managers. Most of the major changes came from the ACIP statements revised in the past four years. These include:

- Timing/spacing of newly licensed vaccines.
    - Live vaccines/LAIV: Parenterally administered live vaccines must be deferred after receipt of blood products (and vice versa). The deferral period can range from 2 weeks to 11 months, depending on which product was given first. This interval is necessary because blood products can interfere with replication of parenteral live vaccines. . There are no data on this, but subject matter experts' opinion (CDC, Influenza Branch) is that the antibody response to LAIV will not be affected by circulating antibody, making unnecessary the interval between administration of LAIV and antibody-containing blood products. The new language reads: "Yellow fever, oral Ty21a typhoid vaccine, and live attenuated influenza vaccine are exceptions to these recommendations."
    - A 28-day interval between LAIV and other live vaccines not given simultaneously was recommended by ACIP in 2005.
    - The AAP currently recommends a one -month interval between Tdap and MCV4 not given simultaneously. The new language recommends "No interval between LAIV and antibody containing blood products;" a "four week interval between nasal or injected live vaccines if non-simultaneous," and a "1 month interval between Tdap and MCV4 if non-simultaneous."
- Contraindications and precautions: New vaccines were added to the table: Tdap, TIV, LAIV, MCV4, and MPSV, and their contraindications/precautions were taken from the

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published vaccine-specific recommendations. There are provisional recommendations for Tdap, listing severe allergic reaction and encephalopathy as contraindications. Precautions are: moderate or severe acute illness, GBS, progressive neurologic disorder until the condition is stabilized, and a history of Arthus reaction, causing severe local reactions. For the latter, Tdap vaccination is deferred unless it has been ten years since the previous dose.

- Vaccine administration:
  - Tables were added for the new vaccines' (Tdap, MCV4, MPSV) recommended dose and route. This will include the issue of IM-recommended vaccines given subcutaneously (e.g., meningococcal conjugate vaccine). A suggestion to include combination vaccines will be added, but had not been incorporated when this draft was distributed.
  - A table addresses needle length by age (0-10 and ≥11 years), body mass, and site, as regards intramuscular injections. Different factors determining appropriate needle length for each group are addressed. It calls for the use of at least a 1" needle length for all preadolescents, adolescent, and adults. But that also depends on body mass; if low, there is a risk of hitting bone. This needs to be addressed in more detail.
  - A table on the treatment of anaphylaxis addresses only the IM and oral treatment regimen, for both pediatric and adult patients.
- Altered Immunocompetence. A new table presents the recommendations for vaccination of persons with altered immunocompetence that were presented to the ACIP in October 2005. The table is organized by disease categories parallel to those in the AAP's 2006 Red Book (i.e., primary-secondary conditions also classified by cell-type, such as B- or T-cell deficiencies). The column for "Recommended Vaccines" may be relabeled "Risk-Specific Recommendations By Virtue of Altered Immunocompetence" to avoid the perception that only the listed vaccines should be used for that specific disease. The last column addresses vaccine efficacy and adds comments.
- Special Situations:
  - LAIV and Protein and Protein-Derivative vaccines reactivity. MMR and varicella not administered concurrently to a tuberculin skin test can cause a false negative result. The current (2002) recommendation is, when the vaccine is given first, to delay the PPD/TST for at least four weeks post-vaccination. For LAIV, a live vaccine whose effect on the PPD/TST is unknown, the Influenza Branch subject matter experts recommended treating LAIV like other live virus vaccines, spacing the PPD/TST four weeks later if it is not simultaneous, or performing the PPD/TST first.
  - Severe allergy to vaccine components. The new language clarifies that the preservative thimerosal in vaccines given to children has only been in trace amounts, or not at all, since mid-2001. It also provides the new recommendations for the inactivated influenza vaccine licensed in 2005 for children.
  - Vaccination of internationally-adopted children. In view of the new hepatitis B recommendations, the language for international adoptees now recommends both a surface antigen test and vaccination as primary approaches. With varicella vaccine recommendations, the definition of "immunity" will be taken from the varicella-vaccine-specific provisional recommendations.

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Dr. Kroger asked for the ACIP's approval of these revised recommendations subject to the inclusion of actions at this meeting and minor revisions of language, format and citations.

Discussion included:

- Dr. Hull strongly recommended revision to the statement indicating that since mid-2001, vaccines routinely recommended for infants and have been manufactured without thimerosal. Taken out of context, that sentence has been used to resist state legislation to restrict the use of thimerosal in vaccines. He agreed to provide replacement text.
- Dr. Poland reported being asked about the intradermal vaccinia (smallpox) vaccine, and recommended including that as well. It was not included because it is not a universally recommended vaccine. However, it could be appropriately included to meet the needs of such broader use of these recommendations as by the military.
- Dr. Stan Gall asked about the simultaneous administration, in the postpartum period, for RhoGAM, MMR and varicella. Dr. Kroger responded that the 2002 guidance was not changed in its direction to give MMR after RhoGAM to protect against rubella. He agreed to check the vaccine-specific recommendations on varicella since it is being encouraged for postpartum use and, as Dr. Gall noted, there are a fair number of women who need RhoGAM at that time.
- Dr. Jeff Duchin suggested adding to the international adoptee text a recommendation that family members ensure they are up to date on their own vaccinations.
- Dr. Doug Campos-Outcalt, of the AAFP, asked why the hepatitis B surface antigen recommendation did not include surface antibody inhibition. Dr. Kroger answered that the hepatitis B vaccine-specific recommendations advise use of the surface antigen test for large groups of people considered at high risk, in order to identify carriers. The "large group" includes international adoptees from high-risk countries, so to simplify matters, it was decided to recommend the test for all international adoptees. It was also felt that in view of the lack of records, providing the one dose to all also was advisable. Dr. Abramson commented that a positive surface antibody test would establish the need for vaccination and would be a cost effective way to proceed. Dr. Wexler said that the presence of antibody could be maternal in origin, and not vaccine. For that reason, the child should receive three doses of vaccine unless they have a document recording those doses. But the surface antigen test must be done to identify a carrier. Dr. Kroger added that the vaccine might, although rarely, produce a positive surface antigen test. A footnote may be inserted to advise serology first, then vaccination.
- Dr. Schaffner questioned the necessity of the statement about "potential interference between LAIV and other live attenuated viral vaccines," since LAIV replicates only in the upper airway while the other vaccines are administered parenterally and replicate systemically. Dr. Kroger responded that the new language reassures that there is no concern about LAIV relative to circulating antibody in blood products, nor about LAIV simultaneously administered with another live vaccine. But it does advise the interval when LAIV is not administered simultaneously with another live vaccine. But Dr. Marcuse raised Dr. Schaffner's question again, noting that the ACIP to date has not considered if there should be any spacing for the LAIV or rotavirus live vaccines. He asked if a nonspecific immune response from a parenteral vaccine could prevent a topical vaccine's take, or vice versa. Dr. Plotkin answered that interference could occur for two

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reasons: the introduction of interferon, which could be tested, and an effect on cellular immune response, primarily CD4. Relevant data from the manufacturers on these questions would be good to have. Dr. Jeff Stoddard, of MedImmune, stated that there are not yet any data from the ongoing immunogenicity studies to answer that question, but that would be available soon. In that event, Dr. Marcuse asked if the rule of spacing should be continued until more data are in hand. There were nods all around to that question, indicating agreement.

Public Comment

Mr. Gary Stein, of Families Fighting Flu, related that his daughter Jessica had died of influenza. People always think that "it can't happen to us." That is not true, but individuals can make a difference. For those reasons, he attended to encourage ACIP to recommend annual influenza vaccination for all children. On the next day, ACIP was to discuss including children aged 2-6 in the universal vaccination recommendation. He urged the committee to pass that vote to expand this recommendation. It would be a step in right direction, since many pediatricians do not recommend influenza vaccination now, and ACIP expansion of the recommendation will spur them to do so. He asked that the ACIP act to spare another family the tragedy of losing another child.

Mr. Joe Lastinger, who lost his daughter Emily to influenza, was joined by Richard and Luisa Kanowitz and John Bellovich, who also had lost their children to flu. He called ACIP's recommendation critically important. Had it been in place several years ago, Emily might have been vaccinated and she would be alive today. He understood the concern about the vaccine supply, but he had researched what is available. His impression was, if children to age 6 are included, that would add 20 million children to the population for vaccination. CDC's data indicate that 40% of those are already covered due to their health status or that of a household contact, so in reality, only ~12 million more children would need to be covered. And of those, it is likely that many would not seek the vaccine. Even in his own community, people who knew Emily and what had happened to her still do not vaccinate their children. If only 75% do, that would be an additional 9 million children. The manufacturers expect to produce 120 million doses for the next season. He asked the committee to please consider the millions of children who, based on its decision tomorrow, could be vaccinated next year and saved, or not. If the members are uncertain, he asked them to please think about these particular children, and the hundreds of others who might still be alive today had they been vaccinated.

With no further comment, the meeting adjourned at 6:03 p.m. and reconvened at 8:00 a.m. on the following morning.

FEBRUARY 22, 2006

CDC DIRECTOR'S COMMENTS

Presenter: Dr. Julie M. Gerberding, CDC Director

CDC remains committed to the basic public health issues affecting Americans' daily lives: obesity; chronic diseases such as cancer and cardiovascular disease; tobacco use, injuries, and

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disabilities. But media attention goes to special issues such as terrorism and pandemics, also necessary work, which challenges CDC's ability to keep its portfolio balanced.

An outline was provided of the CDC programs funded by its current $8 billion appropriation, according to program increases, stable funding and decreases. Funding has increased (1600%) since 2001 to build and maintain the Strategic National Stockpile and to respond to terrorism, supported the Vaccines for Children program and work on birth defects global immunization and environmental health.

However, the increase for immunization, when adjusted to the price index (an accounting method for the cost of science), is actually stable funding. While that is something to be grateful for, with increasing numbers of new vaccines and the growth of adult and adolescent vaccination programs, strategies realigning resources or reconfiguring programs will be needed to meet Congress' deficit-reduction budget trends. Additionally, the benefit to other programs, such as the President's proposed budget's inclusion of $93 million for domestic HIV/AIDS testing, is offset by no funding for the public health work that naturally follows testing, such as partner tracing and treatment.

CDC received $3.1 billion of an emergency $7.1 billion supplemental appropriation for influenza pandemic preparedness and response. This will also benefit seasonal influenza response, improving seasonal vaccine supply and development of new antiviral drugs; and it has already improved CDC's rapid alert communications capacity.

These are all part of CDC's strategy to maximize and extend the benefit from categorical investments to much broader applications, by concertedly directing budget resource decisions to support very specific health impact goals. Concurrent stressing of efficiencies in-house has produced a focused, lean and effective structure that earned CDC the OMB's commendation for appropriate resource utilization. These two approaches are being generalized broadly across CDC. Dr. Gerberding thanked the committee, not only for its very hard work to support immunization, but also for wise counsel on such resource allocation issues.

But other programs have lost ground in funding, including occupational safety, injury prevention, TB, STDs, public health research, leadership and management initiatives, business services support, buildings and facilities, and the youth media campaign. Immunization also still faces considerable challenges. More vaccines mean more doses to more people in more age groups and communities. This accelerates the increasingly complex process of delivering them to those most in need, monitoring and evaluating immunization safety, and scaling up all this to match production scale, while maintaining the program's overall credibility and vaccines' safety.

But the challenges fade in the light of such rewarding inaugurations, as addressed at this meeting, of another cancer defeated by vaccine (HPV), and the immense impact the rotavirus vaccine will have to save children lives worldwide.

Discussion included:

- *Vaccine distribution*. A vaccine summit held recently examined seasonal influenza vaccine production and distribution options to close the supply/demand gaps. Production

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will rise to at least 100 million doses of seasonal vaccine, and the market will be driven to create that demand. The problem with vaccine distribution is that CDC does not own the vaccine. Further adjustment with the private sector's distribution system is needed. Last year, it was the smaller purchasers who did not receive vaccine, in part due to Chiron's delayed product release or their own late order. CDC's VFC purchase also commands a lot of the initial supply. One strategy is the join small purchasers into groups to gain more clout. Another is production modernization, but that may take 3-5 years.

- *Vaccine financing systems*. Multiple and perhaps combined solutions will be needed to address the many components of vaccine financing. Only one aspect is risk versus profit (e.g., the egg-based influenza vaccine process, and Viagra versus other therapeutic vaccines). Government purchases also help to ensure a reliable market.
- Dr. Abramson noted ACIP's mandate to examine the safety/efficacy and cost effectiveness of vaccine, but not the funding implications. There is concern about the possibility substantial social inequity that could result from unequal access to the new vaccines. Dr. Gerberding acknowledged that many public health investments, as a matter of policy, have to balance the potential benefits. She hoped to hear more of these concerns and potential resolutions. Dr. Gellin reported that the National Vaccine Advisory Committee (NVAC) has begun to address those issues, which differ from the ACIP's mandate, and they also increase focus on vaccine financing.
- *CDC reorganization.* Dr. Schuchat reported that the Coordinating Center for Infectious Diseases holds three CDC infectious disease centers: the NIP, NCID and NCHSTP. But over the next month, the NIP will transition into a larger activity tentatively being called the National Center for Immunization and Respiratory Diseases, to link vaccine-related work from the laboratory bench through vaccine delivery and immunization services, including influenza activities.

OLD BUSINESS

Resolution to Add Rotavirus Vaccine to the VFC
Presenter: Dr. Greg Wallace, NIP

Dr. Wallace presented the revised resolution, which incorporated the edits from the previous day. It specified that dose one should be initiated for infants aged 6-12 weeks and notes that the last dose should be administered by 32 weeks of age.

Two options were offered to address altered immune status, which was formerly a contraindication to vaccination. This could be moved this to the Precautions section, advising the physician to consider the potential risks and benefits for infants with, for example, lymphoma and other immunocompromised conditions. And, severe immunodeficiency such as severe antibody deficiency or severe combined immunodeficiency could be cited under Contraindications.

Discussion included the implications to Medicaid payment if a child aged >32 weeks receives a third rotavirus dose at an office visit. The committee was reminded that the VFC not a reimbursement program; it only provides vaccine to VFC providers. The members were advised

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to simply recommend on the technical issues. The resolution clearly states that if eligible, the child should receive the vaccine. Any impact on VFC program would have to be addressed by the Office of General Counsel. The VFC auditors will note vaccine administered outside of the recommended time frame, but are unlikely to penalize the practice. Dr. Marcuse asked if the footnote on this could simply be removed from the resolution. But Dr. Seward recommended retaining the age recommendation, given the removal of the "should not be" wording, reassurance that VFC children will be covered at >32 weeks, and that the new wording is consistent with the package insert and ACIP recommendations (which will be revised). Ms. Lynn Bahta agreed, adding that the footnote is instructive to the practitioner.

Dr. Marcuse **moved to accept resolution as presented, but to remove the footnote on the dosing interval.** Dr. Morse seconded the motion.

Vote

In favor: Marcuse, Poland
Opposed: Beck, Campbell, Finger, Gilsdorf, Lieu, Morita, Treanor, Womedou, Abramson

The motion failed.

Dr. Finger **moved to accept the resolution as presented with grammatical corrections.** Ms. Stinchfield seconded the motion.

Vote

In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Poland, Stinchfield, Treanor, Womedou, Abramson
Opposed: None
Abstained: None.

The motion passed.

Additional comment. Dr. Mark Feinberg, of Merck, requested an edit for clarification and completeness. Rather than, as now stated, referring to the vaccine's safety when administered after 12 weeks of age, as based on data from the clinical trial, he suggested text to say "safety or efficacy of the vaccine administered, the first dose administered after 12 weeks of age." However, since this was suggested after the vote, it was not incorporated into the VFC resolution.

Vaccine Storage. Dr. Abramson reported a decision by NIP to meet with the Association for Immunization Managers to discuss possible solutions to the issue of improperly stored vaccine, to help refinement of the ACIP wording. They will discuss what additional information might be available (e.g., from the Australian guidelines or the manufacturers), and potentially needed educational initiatives and research.

Changes to the ACIP General Recommendation

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Presenter***:*** Dr. Andrew Kroger, NIP

Needle length. The wording was revised as suggested on the previous day. The Working Group will continue to discuss table revisions for intramuscular (IM) injection based on age, body mass, and site, to provide all the data sources. **The ACIP accepted this as presented.**

Severe allergy to a vaccine component (i.e., influenza vaccine/thimerosal). With inactivated influenza now the standard recommendation for children, new language was needed:
"Since 2001, inactivated influenza vaccine is the only vaccine routinely recommended for children under two years of age that contains thimerosal as a preservative. Inactivated influenza vaccine also may contain trace amounts of thimerosal that are residual from the manufacturing process. A thimerosal-free formulation of inactivated influenza vaccine for use in children was licensed in 2005. TT, Td, and DT vaccines contain thimerosal as a preservative."

Matters remaining to be discussed were the necessity of a spacing interval with non-simultaneous administration of LAIV and other live vaccines, and RhoGAM immune globulin and varicella; the issues (including cost effectiveness) related to repeated vaccination for international adoptees with unknown hepatitis status, including the conduct of a hepatitis B surface antigen test and a hepatitis B surface antibody test. Language will be added to address vaccination of family members of international adoptees.

Discussion included:

- Dr. Hull suggested just having the table say that vaccines may contain preservatives to maintain their potency and safety, then listing those that might have preservative. There was **general agreement** to that recommendation
- Mr. Phil Hosbach, of SanofiPasteur, reported that Tt and Td also are available with only trace amounts of thimerosal.
- Dr. Baylor asked that the FDA Website be referenced, which will also be useful with new vaccines released in future.

Altered Immunocompetence
Dr. Katz asked a question in reference to the changes needed to Table 11, specifically relabeling of "Recommended Vaccines" column to clarify the vaccines recommended for people with altered immunocompetence. Dr. Abramson clarified, on Dr. Katz' question, that Table 11 would be modified. There may be other edits, but neither Table 11's nor any others were expected to be substantive.

Ms. Stinchfield **moved to approve the ACIP General Recommendations with the modifications presented**. Dr. Poland seconded the motion

Vote

In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Hull, Lieu, Marcuse, Morita, Poland, Stinchfield, Treanor, Womedou, Abramson
Opposed: None
Abstained: None.

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The motion passed unanimously.

VARICELLA ZOSTER IMMUNE GLOBULIN

VZIG Update: Availability of a New Product
Presenter: Dr. Mona Marin, NIP

In 2004, the only U.S.-licensed manufacturer of varicella zoster immune globulin (VZIG) announced their withdrawal from the market. CDC's literature search on possible VZIG alternatives was presented to the Varicella Working Group and, in October 2004, ACIP recommended the use of intravenous immune globulin (IGIV). However, VZIG was preferred for post-exposure prophylaxis of patients at high risk of complications and severe disease. The VZIG supply was expected to last to April, 2006, but will probably be exhausted by March 1.

By July 2005, CDC, FDA and subject matter experts decided that, in view of weak scientific data supporting an alternative method, FDA should encourage new IND applications for immune globulin. Given the impending depletion of VZIG supply, FDA made an IND, Varizig®, available in February under an expanded access protocol. Varizig® is manufactured by Cangene Corporation, Canada. It is a lyophilized, purified human immune globulin preparation made from plasma, with high levels of antivaricella antibodies, immune globulin Class G. When reconstituted, is provides a ~5% IgG solution for IM administration. As an IND, administration requires informed consent.

The Varizig® indication is for patients exposed to varicella, who have no immunity from natural disease or age-appropriate vaccination, and who are at high risk for severe disease and complications. These are the same patient groups who would receive VZIG: those who are immunocompromised; pregnant women; neonates whose mothers developed varicella symptoms from <5 days before delivery to two days after; premature infants of >20 weeks gestation who are exposed as neonates and who have varicella naïve mothers; and those <28 weeks' gestation or who weigh ≤1,000 grams at birth and who are exposed as neonates, regardless of maternal varicella history.

Providers should make every effort to obtain and administer Varizig® to these groups as soon as possible after exposure, and it can be administered as late as 96 hours; it. When that cannot be done, one dose of IGIV can be used as an alternative, at a recommended dose of 400 mg/kg. That is also true for pregnant women, or the physician may choose to closely monitor her for varicella symptoms and begin acyclovir treatment if illness develops. The vaccine comes in 125-unit vials. The recommended dose is 125 units per 10 kilograms of body weight up to a maximum of 625 units (five vials); the minimum dose is half a vial, 62.5 units for patients weighing <5 kilograms. Standard varicella vaccination should follow Varizig® in the absence of any contraindications, but only after an interval of five months after Varizig®. The vaccine is unnecessary if the patient develops varicella after receiving Varizig.®

FFF Enterprises distributes Varizig® under the expanded access protocol. It has received central IRB approval; local IRB approval is not required, but they should be informed of the protocol. If

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they reject the central IRB's jurisdiction, the Varizig® can still be shipped but the local IRB must supervise its administration. In an emergency, Varizig® can be used once without regard to IRB review requirements, to ensure the patient is promptly treated. But that must be reported to the IRB within five working days and the IRB must review any subsequent Varizig® treatment.

Interested pharmacies and healthcare providers can fill out the FFF forms in advance to be prequalified to receive and use Varizig®. When needed, the completed release can be faxed to FFF, which determines patient eligibility and assigns a patient number to those eligible. Or, FFF can provided the product release form upon request to its 800 number, fax or e-mail it back and begin the process. Generally, Varizig® can be provided within 24 hours. This information will be published in the *MMWR*.

Discussion included a report that, aside from the *MMWR* notice, Varizig's® availability will be published in medical journals, and promoted at the conferences held nationwide by the Department of Education and Communication. Details can also be received from FFF. The *MMWR* will also be circulated to professional associations and the ACIP liaisons, and the ACIP members also were encouraged to promote it within their own fields. There is a link to FFF's standard two-page request form on the FDA Website as well. This presentation's slides and all others presented at this meeting were to be posted on CDC's Website within a week.

INFLUENZA VACCINE

Introduction

Presenter: Dr. Ban Allos, Influenza Working Group Chair

The Influenza Working Group has met monthly, and on occasion bimonthly, to discuss vaccine composition changes for the 2006-2007 season; to develop a recommendation on the use of adamantanes (as >90% of the strains are resistant to them this season); to develop a suggested ACIP recommendation related to vaccine tiering, and to suggest an ACIP encouragement to vaccinate children aged 24-59 months this year, that would be expanded to an recommendation the following year.

The working group also discussed the rationale for extending influenza vaccination recommendations to persons at risk for nonhuman influenza (e.g., those working with animals, poultry, or swine and travelers to areas affected by avian flu) as a way to prevent reassortment; this plan was ultimately not adopted by the group. Finally, a universal influenza vaccination policy may eventually be recommended after the working group reviews the existing data and data gaps.

To date, the vaccine's safety, ability to prevent hospitalizations and deaths, feasibility, and economic aspects have influenced expansion recommendations. The working group acknowledged that the proposed expansion of recommendations for influenza vaccination to include children aged 24 through 59 months of age represented a paradigm shift -- one based on prevention of outpatient, ED and pediatrician visits. Future changes to the recommendations may consider the indirect effects of vaccination and prevention of the theoretical risk of reassortment.

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Review of 2005 Influenza Vaccine Summit Meeting.
Presenter: Dr. L.J. Tan, AMA

Overview: Activities and recommendations of the 2005 Influenza Vaccine Summit

Dr. Tan outlined the content of the Influenza Summit referenced by Dr. Gerberding, which was held January 24-25. The Summit's presentations and complete minutes are on the Web site www.ama-assn.org/go/influenzasummit. These summits have been cosponsored by AMA and CDC since 2001 to address influenza vaccine supply issues.

The January meeting involved 112 organizational stakeholders in the pubic/private partnerships related to influenza vaccination (e.g., manufacturers, distributors, professional medical association, pharmacists, health insurance, etc.) Its objectives were to identify vaccine supply, ordering, and distribution issues in the last influenza season; to review any trends revealed by survey data; to develop recommendations on those issues; and, to develop subsequent activities. Among the issues identified were:

- Vaccine supply and distribution. Summit recommendations included: ensure timely information regarding vaccine distribution and supply that is effectively communicated to providers, public, and the media, by all stakeholders in influenza immunization; ensure a transparent vaccine-distribution system that is seen as equitable, with clear, timely, and frequent communication to providers about vaccine ordering and shipment policies; and encourage optimal vaccine usage to avoid vaccine disposal at season's end (e.g., no-return policies; government purchase; tax credits for returned vaccine). The many partners of the Summit supported preseason stockpiles for CDC from multiple manufacturing sources to buffer the effect of a manufacturer's production failure
- CDC tiering recommendations. The summit wrote a letter to ACIP noting that while the recommendations are national, vaccine supply issues are regional, due to regional implementation. The Summit recommends that tiering should only be used when there are issues of vaccine supply and if implemented, a standard but flexible plan should be created for such implementation. Tiering implementation must be consistent across all providers and its removal should depend on regional-level vaccine supplies.
- The vaccine testing and release process needs to be as efficient as possible to help resolve long-term vaccine supply.
- Recommendations to reinvigorate demand included moving toward universal immunization and encouraging research on related data gaps (e.g., research relevant to school-age children aged 6-19). This issue is considered by the Summit as critical to long term stability of influenza vaccine supplies and to reaching the Healthy People 2010 immunization-related goals.
- The impact of vaccine shortages on the performance measurement of institutions (e.g., hospitals, long-term care facilities) has to be acknowledged. If vaccine is unavailable, institutions should not be held to those performance standards.
- Influenza vaccine tracing is needed at all levels, as is a clear definition of the related federal, state, and local government roles in obtaining and distributing vaccine. Legislation to ban thimerosal-containing influenza vaccines and all thimerosal-containing vaccines is being advanced to the state level and the Summit urges that

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partners become involved in legislator education on the science of the issue.

- Improve vaccine demand, especially for the predicted >100 million doses anticipated for the 2006-2007 season. Educate and target high priority populations better; target education on vaccine's cost effectiveness to third-party payers and employers; extend the immunization season; plan for when there is excess vaccine; and, as discussed on the previous day by Families Fighting Flu, give influenza disease a "face."
- The manufacturers should limit partial shipments, especially if there is no shortage. Any partial-shipment policy should be consistent and well communicated to providers. Pre-booking and distribution data for influenza vaccine should be available at least to public health. The providers without vaccine should be identified at the beginning of the season, to ensure that they get vaccine if there are any supply gaps.
- Vaccinate healthcare workers.

Summit accomplishments included:

- Establishment of a vaccine-supply task force to address supply and distribution challenges; the letter to ACIP discussing the inadequacy of the tiering system; expressing support for universal influenza immunization recommendations; and, urging ACIP to promote vaccine use in a timely and clear manner.
- The Summit Communications Working Group and its Executive Committee have begun examining short-, mid-, and long-term vaccine communication needs. A Reimbursement Working Group is analyzing influenza vaccine coverage from the perspective of third-party payers.
- A statement will be issued on the importance of establishing a national adult immunization program.
- The summit is working with CDC, manufacturers, distributors, and partners to identify the data available to better track vaccine and determine how it could be accessed.
- FDA and the manufacturers are being urged to study how vaccine production can be optimized.

The summit is interested in leading development of a partnership to develop a national, coordinated strategy for seasonal influenza, in terms of influenza prevention as well as vaccine production and utilization, to lower its overall morbidity and mortality.

Presentation by National Foundation for Infectious Diseases

Presenter: Dr. Carol Baker, President-Elect

Overview: NFID position on influenza burden on and vaccination need by children with asthma.

Despite years of recommendations to vaccinate children with asthma for influenza yearly, it appears that rates are low (<40%) given that these children are not routinely assessed for the need for vaccination against influenza. Two studies, in a large HMO and an asthma clinic, examined influenza vaccination in children. The former had 10% coverage; the latter, 25%.

In response, the NFID convened a roundtable in November of 2005 with representatives of ~20 major medical and public health groups. After a full day's discussion of the known data about

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influenza and its impact on children with asthma, they arrived at several key messages, which were published in a *Call to Action* that was available at this meeting. Its key messages are:

- Influenza and other respiratory viruses can be deadly for children with asthma. Viral respiratory infections precipitate wheezing in asthmatic children. Influenza is the only vaccine preventable viral respiratory infection. Morbidity is increased in asthmatic children with influenza; they receive more antibiotics and are much more likely to have an outpatient medical visit.
- Asthma puts millions of children at increased risk of morbidity and mortality. Over 6 million American children have asthma and it is an urban epidemic. It is the third leading cause of children's hospitalization and precipitates ~750,000 ED visits by in children aged <15 years. In 2002, 170 children <15 years died of asthma-related causes. In the 2003-2004 influenza epidemic, 45% of the 153 children and adolescents who died from influenza had asthma.

The NFID call for action invites a comprehensive effort to: 1) increase influenza vaccination rates, especially for asthmatic children; 2) add or increase the annual influenza vaccine outreach activities to asthma education programs and treatment guidelines; 3) support practice-based efforts; 4) increase local influenza vaccination rates, and 5) use public health forums to advertise influenza as a vaccine-preventable disease, and the need of children with asthma for the vaccine's protection. ACIP's help in this initiative, by strengthening its own recommendations, will be appreciated by the NFID.

Update on Influenza Antiviral Resistance

Presenter: Dr. Alexander Klimov, NCID

Overview: Recent antiviral resistance and WHO/FDA-recommended influenza vaccine composition for the next season

Adamantanes resistance. Resistance to adamantanes (amantadine and rimantadine) can emerge rapidly as a result of a single mutation in the influenza virus' M2 protein. Over 7,000 human influenza A (H3N2) viruses isolated worldwide were tested at CDC in 2005. An alarming increase in the proportion of viruses resistant to adamantanes was observed in several Asian countries. In previous seasons, the proportion of resistant A/H3 viruses circulating in the U.S. has increased from ~1% (1994-2004) to 12% in 2005.

Recently, more than 200 Type A isolates collected in the U.S. from October through December 2005 were tested at the Influenza Branch, CDC. Most of the tested viruses were of the H3N2 subtype and few were of H1N1 subtype. Of the influenza A(H3N2) isolates, 92.3% had the Ser-31-Asn amino acid change in the M2 protein and were amantadanes-resistant. The proportion of resistance among few H1N1 isolates was found to be 25%.

CDC published a health alert on January 14, 2006, and recommended against the use of amantadine and rimantadine for the treatment or prophylaxis of influenza in the U.S. during the 2005-06 influenza season. The data about resistance of currently circulating viruses to adamantanes were published in the *MMWR* (dispatch) on January 17, 2006 (vol 55, pp. 1-2) and in JAMA on February 1, 2006 (*JAMA*, 2006;295:891-894).

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Vaccine composition for next season. Data collected by WHO collaborating center laboratories (including one at the Influenza Branch) were charted. Influenza A (H1N1) comprised 19% of the circulating strains, mostly in Asia and Africa. Influenza A (H3N2) isolates comprised 45% of the strains, predominating in North America, followed by Asia, Africa and Europe. B/Victoria-like viruses held 27% of the share, with Africa leading, followed by fairly even rates in Europe and North America and some in Asia. B/Yamagata-lineage viruses were the least seen strains (9%). So, the most common (64%) strains circulating were of type A, with H3 dominating, followed by influenza B viruses.

A new antigenic variation of H3 was identified. Also, B/Victoria-lineage viruses became predominant (75%) over B/Yamagata-lineage isolates (25%).

In response, WHO announced on February 15 that the H1 vaccine component would be the same: A/New Caledonia/20/99(H1N1)-like virus. The H3 vaccine component was replaced by A/Wisconsin/67/2005 (H3N2)-like viruses (recommended strains for vaccine production are A/Wisconsin/67/2005 and A/Hiroshoma/52/2005). B/Victoria-lineage strains, B/Malaysia/2506/2004 and a B/Malaysia-like virus – B/Ohio/1/2005 – were recommended as the type B component of the vaccine. FDA's Vaccines and Related Biological Product Advisory Committee (VRBPAC) agreed with the WHO recommendations.

Influenza Surveillance Data Update

Presenter: Dr. Katherine A. Poehling, Vanderbilt University

> Overview: Inpatient and outpatient surveillance data from the New Vaccine Surveillance Network (NVSN) (2001-2004) and published data.

CDC's NVSN is a population-based, laboratory-confirmed influenza surveillance network in the counties of Rochester, New York; Cincinnati, Ohio; and Nashville, Tennessee. The influenza burden among children aged ≤5 years was surveyed among in-patients in three counties over four influenza seasons, who were admitted for ARI or fever. Out-patient surveillance was done in the same three counties from 2002-2004. This was done in the only pediatric ED in the three counties, and in 1-3 outpatient clinics per county. Cases for both groups were confirmed by PCR or viral cultures.

A preliminary sub-analysis was done of NHIS parental reports nationally, indicating that 5% of children aged 6-23 months are at high risk, as are ~10% of children aged >2 years. For both, the primary high-risk condition is asthma, which is diagnosed twice as much in children aged >2 years than in the younger children (10.6% versus 5.2%, respectively). The mean rates of lab-confirmed influenza-related hospitalizations were calculated per 1000 healthy children and then for low- and high-risk children, for three age groups: 0-5 months, 6-23 months, and 2-5 years of age. The results were as follow.

Hospitalization rates are high in children aged 0-23 months, at 4.5/1000, versus 0.9 for 6-23 months (0.65 for low-risk and 5.38 for high-risk) and 0.3 for age 2-5 years (0.25 and 0.75 for

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low- and high risk, respectively). *Conclusion:* Those data support the current recommendation and, since these rates decrease with age, a universal recommendation may not be supported.

Outpatients. For the 13-week influenza season, outpatient (clinic and ED) visit rates were calculated using data from the NVSN and the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Medical Care Survey (NHMCS) survey. The rates were similar in the mild 2002-2003 season. But in 2003-2004, the rates were about three times higher for the high-risk group, although comparable between all children and those at low risk. The published Tennessee data of 19 influenza seasons (Neuzil et al, *NEJM* 2000) showed and average of ~90-100 outpatient visits per 1000 children aged 2-4 years, and ~80/1000 among those aged 5-9 years. For those children aged ≥2 years, ~80% were prescribed antibiotics. *Conclusion.* The outpatient data indicate rates potentially sufficient to encourage or recommend vaccination of healthy children aged 24-59 months. Other than direct effects, the expanded vaccination may produce herd effects. Influenza surveillance should include older children and adults to monitor related policy effects.

Discussion included:

- This preliminary analysis could not explain why a smaller effect emerged from high risk conditions among both out- and in-patient visits by children aged 2-5 years. It could be that the higher vaccination rates being seen include those higher-risk children.
- The two B lineages are of different genetic and antigenic groups; human serology data on the anti-hemagglutination antibody level of the Yamagata lineage indicate a >50% difference to B Victoria.
- Dr. George Peter suggested, as this type of analysis moves to older-age groups of children, to consider using the potentially sensitive marker of school absenteeism for earlier outbreak detection.
- Dr. Nichol complimented Dr. Poehlingh on the data for children age <5. She hoped ACIP would fully recommend vaccination for that age group in spring or summer, especially if abundant doses are available. She also supported Dr. Baker's suggestion to improve attention to children at higher risk. That could be accomplished by enhanced ACIP recommendation language, and/or publication of a Notice to Readers in the *MMWR.* She added that high risk adults aged <65, whose immunization rates also are low, might be added.
- Dr. Lieu agreed and reported a similar cost analysis being done by her and Dr. Lisa Prosser to advance vaccination of children aged 2-18 years. These data will well supplement that work, which suggests that universal vaccination would be very cost effective and good policy.
- Dr. Tan reported that an AMA task force is examining supply and distribution issues for short-term contingencies and to reach the long-term goal of increasing demand. From both that analytical perspective and philosophically, the AMA supports universal immunization recommendations.
- Dr. Temte reported analysis of Wisconsin's sentinel surveillance data, indicating surprisingly high percentages of children age 0-4 years presenting to clinics for ILI. They do not progress to hospitals or EDs, but are conveying influenza to all their contacts.

Key Issues/Changes Proposed for the 2006-07 Influenza Recommendations

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Presenter: Dr. Nicole Smith, CDC Influenza Branch

The changes proposed for the next season's influenza recommendations were to:

- Change the vaccine composition as described, to two new strains for the influenza A (H3N2) virus and influenza B vaccine components. The influenza A (H1N1) virus component remains unchanged.
- Recommend against the use of adamantanes this season.
- Change wording on vaccine tiering to advise against prioritizing without a vaccine supply delay or decrease, and to prepare for contingencies if a disruption to the vaccine supply occurs.
- Recommend vaccination to prevent illness among an expanded group of young children, encouraging vaccination of children aged 24 through 59 months of age. The Influenza working group will present data in October regarding whether other age groups should be considered for inclusion among the groups for whom annual influenza vaccination is recommended.
- Additional edits to these recommendations reiterate the importance of two doses for children not vaccinated previously, and emphasize that influenza vaccine should be offered throughout the season. Other updates on the influenza vaccine products, coverage level changes, and references will be included in the revised statement.

Options presented to ACIP for the influenza-related recommendations, with pros and cons, were:

1. Continue the current recommendation to annually vaccinate children 24 through59 months of age with high risk conditions, or if the children are household contacts of high risk persons. Change the wording on tiering and recommend against the use of adamantanes, and the additional edits. *Advantages:* This option is potentially the most feasible; it allows for a continued focus on efforts to improve the vaccination coverage levels of existing priority groups and it provides an opportunity to see if the vaccine supply is stabilized. *Disadvantages:* This option continues the risk-based recommendations for children aged $\geq$24 months, and it does not take advantage of expected increased vaccine supply, which could be used to help vaccinate more people, including children 24 through 59 months of age.

2. Option 1, plus <u>encourage</u> annual vaccination of children aged 24 through 59 months beginning in 2006-2007; defer the full recommendation until the Working Group presents their analysis in October about the potential inclusion of other ages in the recommendation. *Advantages:* This option incorporates a broader understanding of the true burden of illness; it may help to reduce the risk of influenza-related complications for all children aged 24 through 59 months (not just among those children who have high risk conditions); and it gives the vaccine manufactures advance notice of the potential need for increased vaccine production in 2007-08, while not producing a huge immediate increase in vaccine demand. *Disadvantages:* The use of encouragement language presents a less-clear recommendation that may confuse parents, providers, and payers; the evidence in support of routine vaccination is not as strong as for other high risk groups; this approach sets a precedent of using ambulatory care visits as a measurement of burden of disease; and, if there are vaccine supply delays or interruptions, this option could strain the vaccine supply available to reach young children.

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3. Option 1, plus recommend annual vaccination of children aged 24 through59 months of age beginning in 2007-2008. *Advantages*: The same advantages as Option 2, except that a recommendation is more likely to be implemented and therefore a greater reduction in the risk of influenza-related complications for all children 24 through59 months of age might be expected. *Disadvantages:* Same as Option 2.

4. Option 2, plus encourage routine vaccination of household contacts and out-of-home caregivers of children aged 24 through 59 months beginning in 2006-2007. *Advantages:* This option should raise the awareness of the importance of influenza vaccination and the concept of protecting others; it is consistent with other recommendations for vaccinating household contacts and caregivers; it takes advantage of the expected increase in vaccine supply to reach household contacts and caregivers; and it may increase the public's demand for influenza vaccine, thereby offering manufacturers an incentive to increase their production of influenza vaccine. *Disadvantages:* Same as Option 2.

Discussion:

- Mr. Phil Hosbach reported sanofi pasteur's plan to make 50 million doses of influenza vaccine which should be enough to cover the extra children covered. Sanofi's production also could be increased by 1-2 million doses if necessary.
- In response to a question by Dr. Joseph Bresee, of the Influenza Branch, all of the ACIP members indicated that they agreed with the language on amantadanes and tiering changes.
- Dr. Gilsdorf asked if 50 million doses would be enough. Dr. Smith reported that National Immunization Survey data from the first two years of the recommendation encouraging influenza vaccination. The proportion of children 6 through 23 months of age who were reported as being fully vaccinated against influenza increased from 4.4% in 2002-03 to only 8% in 2003-04, but children in this age group who received one or more doses of influenza vaccine increased from 7.2% to 17.5%, respectively. National Immunization Program staff have developed preliminary estimates indicating that an additional 5.3 million healthy, 24-59 month-old children who are not household contacts of high risk persons would be covered by the proposed change. Behavioral Risk Factor Surveillance System data indicate that ~39% of these children would have been previously vaccinated, and, therefore would only require one dose of influenza vaccine per year (compared to two doses for previously unvaccinated children in this age group).
- There was an inquiry regarding whether vaccinating older children could reduce the disease burden in the 0-6 month-old group through herd immunity; Dr. Smith was unsure of the data and noted that the working group was planning to present a review of the data at the October ACIP meeting. In the meantime, Dr. Smith highlighted that the ACIP was currently being asked to consider the direct benefits of reducing the risk of influenza-related emergency department and outpatient visits among children 24 through 59 months of age.
- Although no formal Vaccines for Children Program (VFC) resolution could be voted upon until there is a full ACIP recommendation, a permissive VFC resolution would allow the use of influenza vaccine for any VFC eligible child, regardless of his/her age. Dr. Wallace reminded the committee of the complexities of the influenza vaccines'

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different formulations. SanofiPasteur produces a pediatric formulation of the influenza vaccine that is approved for use among children 6 through 35 months of age. During the last two years, sanofi has not distributed all of its doses of this product. The vaccine produced by sanofi for children 3 years of age and older is also used by adults and, therefore, there is competition among the different age groups for that presentation. The Chiron-produced influenza vaccine can be used for children 4 years and older, but they have had some production issues during the last two years. FluMist, the live attenuated influenza vaccine produced by MedImmune can be used for healthy children 5 years and older.

- Andrew McNight, of GlaxoSmithKline, reported their plan to produce 20-30 million doses of influenza vaccine for the American market this next season (2006-07). The vaccine will be licensed for persons ages ≥18 years in the U.S., but is licensed abroad for use in persons ≥6 years of age. Eventually, GSK expects to produce influenza vaccine for the U.S. that will be approved for younger age groups.
- Dr. Poland confessed to being bothered by "creeping incrementalism." Bicycle helmets are recommended, knowing there are not enough, as are annual mammograms without enough facilities to do them. Already, 40,000 people die annually of a vaccine-preventable disease. And, with the development of resistance to adamantanes, use of antivirals for treatment of influenza is less of an option. Health care workers are frustrated with the additional groups added every year and the "ticking clock" of pandemic influenza threatens co-infection and reassortment. Dr. Poland declared that now is the time for ACIP to be bold and to recommend influenza vaccination for all Americans; the recommendations could be phased in over time. No other strategy would so well galvanize all involved, from the manufacturers to governments. It would point out the high risk target groups while also clearly articulating the vaccine's rationale at the community and population levels. He suggested a universal recommendation could be phrased as follows: "Annual influenza vaccination is encouraged for all Americans to reduce morbidity and mortality, work and school place disruption, and infection. It also aids pandemic preparedness, phased in over time. There also are specific age and condition recommendations for groups who should receive priority for vaccine."
- Dr. Ben Schwartz, of the National Vaccine Program Office, reported on the October 2005 meeting on readiness for a universal influenza vaccination recommendation. The attendees agreed t hat there is a large burden of illness associated with influenza and that the overall effectiveness of influenza vaccine is not optimal and varies by season depending upon the circulating strains and vaccine match. Workshop participants acknowledged information gaps remain on the indirect effects of vaccinating some populations (e.g., incomplete data on the benefit of school children to reduce disease among family members and the elderly), and on the effectiveness and safety of repeated annual vaccinations. For example, some data indicate decreasing effectiveness among some children with cystic fibrosis. The cost effectiveness of influenza vaccination depends on several factors, including vaccine cost and the population being targeted, and feasibility was raised by immunization managers. Ultimately, the meeting participants reached consensus to move toward a universal recommendation, but recommended that implementation occur in stages over time to avoid unintended consequences and to have time to fill the information gaps.

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- Dr. Jacques Morena, of the Immunization Safety Office, urged that if ACIP were to recommended more studies and data to support a universal recommendation, it should also recommend the funding to do so.
- Dr. Baker strongly recommended extending the recommended age group fro vaccination to 59 months of age (Option 3) and urged ACIP to skip encouragement language in favor of a direct recommendation. She argued that the option would ensure that influenza vaccination for children 24 through 59 months of age would be covered by private health plans and VFC, that pediatricians would adopt the practice, and that currently unvaccinated asthmatic children would be vaccinated along with children. Dr. Neuzil agreed with Dr. Poland, with a feasible incremental approach. If monitored with the New Vaccine Surveillance Network, the public health infrastructure also could be established so that eventually, the effectiveness of the influenza vaccination recommendations for older children and adults could be evaluated.
- Dr. Jim Turner, of the American College Health Association, also agreed with Dr. Poland's proposal, which Dr. Turner had recommended 4-5 years ago. He offered another variation on the proposal: rather than saying "persons at high risk of complications should consider getting the vaccine," just saying "persons should consider…"
- Dr. Walter Orenstein opposed using the word "encourage," because it does not help clinicians dealing with private insurers nor does it set a clear standard of care. He advised ACIP to either make a recommendation or not, rather than issue an "encouragement," and he preferred that the recommendation be issued sooner rather than later. Dr. Orenstein pointed out that there already is a permissive recommendation to vaccinate the whole population, and 40-50% of the 2-49 year-old age group is already covered by existing recommendations. Whatever is decided, he suggested that the ACIP signal that influenza's mortality and morbidity are unacceptable, and that strategy changes will periodically be reviewed, right up to considering full universal vaccination.
- Dr. Wexler, of the Immunization Action Coalition, commented that the influenza vaccine is already recommended for 66% of the population. Since only 90 million doses are used (by half the population), the current approach clearly is not working well. Risk-based (e.g., for asthmatic children) recommendations are hard to implement and do not help families of 11-12 year-old children who die from influenza. She advised simply saying "The vaccine can be given to anyone who wants it." She suggested that this approach would give health care providers the responsibility to offer the vaccine or to tell their patients about its availability (rather than having to ask for it), as was done for meningococcal vaccine before a full recommendation was issued.
- Ms. Elisa Kanowitz, mother of Amanda, who died March 1, 2004, was very encouraged thatACIP was considering expanded recommendations. She supported the full recommendation, urging the committee members to "avoid analysis paralysis." According to Ms. Kanowitz, the data are good, and more children like Amanda, Emily, and Jessica will die by next year. With more than enough vaccine next year, it should be recommended for the whole population.
- Dr. Poland asked if the morbidity for the 2-5 year-old group was different from that of adult risk groups. Dr. Neuzil noted that Dr. Poland was raising an important point that had not been clearly addressed. Dr. Neuzil reported that morbidity is measured differently among children and adults, but one analysis of outpatient visit data found that

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the results were almost identical to age 15, beginning at >2 years of age. According to Dr. Neuzil, the hospitalization data are probably the best proof of the higher rate of severe complications associated with influenza among those aged <5 years compared to those aged 5-49. But the rates in those aged <5 is driven a lot by children under 2 years of age.

- Dr. Poland commented that, if the risk is the same, why parse out pieces of it? Dr. Abramson raised the feasibility issue as one reason. For example, access to children aged to 5-6 years is pretty good, and how to implement the recommendation in stages is part of policy considerations.

Dr. Poland offered an Option 5, or Option 3+, to recommend vaccination for all Americans. Essentially, this proposal was Option 3 to recommend annual vaccination of children aged 24-59 months, beginning in the 2006-2007 season, and encouraging everyone to get vaccine. "Annual influenza vaccination is encouraged for all Americans to reduce its related morbidity and mortality, work and school place disruption, and infection. It also aids pandemic preparedness, phased in over time. There also are specific age and condition recommendations. These groups should receive priority for vaccine."

Further discussion occurred which included Dr. Beck's clarification that there were two alternatives on the table, which did not include full recommendation, but recommended vaccination for those aged 24-59 months and encouraged vaccination for everyone else (i.e., universal), with the latter phased in. In his opinion, this effort was part of the strategy to move toward universal vaccination that was not committing ACIP to a time line, but was providing a goal to move toward.

Dr. Lieu moved to recommend influenza vaccination for children aged 24-59 months, beginning immediately. It was assumed that vaccination of their household contacts and out-of-home caregivers was also included in this motion. Dr. Allos seconded the motion. In a friendly amendment, **Dr. Poland moved an addendum to encourage all to be vaccinated for influenza as part of a strategy to achieve universal immunization**. This was seconded by Dr. Allos.

Dr. Gilsdorf asked the state health department representatives how the proposed recommendation would be received. Dr. Moore, of Tennessee's health department, asked that the universal implementation be divided into pieces to avoid exceeding the vaccine supply, having to tier the recommendations, and struggling to reach the high risk populations. Dr. Morita agreed; Massachusetts' situation would be the same.

Dr. Lieu reiterated the original motion **to recommend vaccination for children aged 24-59 months.** No second was required as it had already been done.

Vote
Recommended influenza vaccination for children aged 24-59 months

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

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Abstained: None

The motion passed.

Dr. Poland **moved to state that annual influenza immunization is encouraged for all as part of a strategy to achieve universal immunization.** Again, no second was needed.

Discussion:

- Dr. Lieu supported the sentiment, but found the encouragement confusing, and remained concerned that it may disrupt state agencies' work.
- Dr. Treanor was opposed, because it implied that ACIP had made a decision for universal vaccination in the absence of a discussion of data supporting the proposal, which he felt needed to occur.
- Dr. Marcuse supported the sentiment, but he was reluctant to use "encouraged." To achieve credibility, he wanted the discussion of a statement about a universal immunization vision to include vaccine efficacy and safety data; provider and consumer education; and, more information on efficacy and on herd immunity effects from vaccinating preschool versus school-aged children.
- Ms. Beth Rowe-West, of North Carolina, voiced her own and other program managers' familiarity with the use of the word "encouraged" by now, and their support of universal vaccination. Dr. Moore, of Tennessee's immunization program, also commented that the health departments would do less to implement this proposal than the private sector. She reported that in Tennessee, the health department provides only administers 10% of the influenza vaccinations; the private sector gives 90%.

Dr. Tan stated the AMA's support of the language proposed. But to move the discussion along, he suggested, rather than saying "as part of an evolving strategy to move towards universal vaccination," saying "as part of an evaluation of a universal immunization strategy." He noted that his suggestion would loosen the language somewhat, but still allow encouragement of annual influenza immunization for all. Dr. Poland accepted that amendment and seconded it.

Further discussion noted that the concept of moving toward a universal influenza vaccination recommendation was not new; it was published in the *MMWR* ACIP influenza statement a few years ago, before Chiron had its production problems. There was lingering concern that next season's influenza vaccine supply would be insufficient to meet the need for a full recommendation, and that even "encourage" implied that ACIP had reviewed all of the pertinent data.

Vote
Encouraging annual influenza immunization part of a strategy to achieve universal immunization

In favor: Allos, Campbell, Finger, Poland, Stinchfield, Treanor, Womeodu
Opposed: Beck, Gilsdorf, Marcuse, Lieu, Morse, Morita, Abramson.

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Dr. Abramson voted no because that intent can simply be made part of the statement. He also remembered that recusals had not been checked. Dr. Treanor was uncertain if he had a conflict or not, as he had done a clinical study for ID Biomedical, which is now owned by GSK. Dr. Pickering stated that Dr. Treanor's vote would be removed, but even without the recusal, the motion would have failed because it had failed to receive a majority of the votes.

The motion failed.

Dr. Marcuse summarized that there was clear enthusiasm for the concept, only division on its expression. Dr. Poland felt that he had achieved conceptually what he wanted. He remained unpersuaded by the fears expressed regarding the complexity of the current recommendations, and commented that if safety concerns are valid, the last vote should be revisited. His desire was to see ACIP move beyond its annual reactive role, and to state a laudable public health goal that all would support.

Dr. Abramson summarized that the next statement would acknowledge that ACIP is working toward the goal of annual universal influenza vaccination in the U.S. He was not concerned about safety, but about other issues that all needed consideration. Dr. Poland agreed with that approach. Dr. Halsey cautioned ACIP about its recommend to discontinue the use of adamantanes for fear that the recommendation could prompt the manufacturers to stop making them. Dr. Halsey noted that adamantanes may be effective for other influenza strains. Dr. Abramson welcomed that point.

Dr. Poland moved to state that a strategy of universal influenza immunization is being evaluated by the ACIP. The motion was seconded by Dr. Lieu. Dr. Stinchfield suggested placing a sentence near the end of the statement, to the effect that anyone who wants influenza vaccine should receive it.

There was a vote on the statement, including tiering and incorporating Dr. Halsey's point that the recommendation against the use of adamantanes is based only on current virologic susceptibility, which may change over time. The motion had already been seconded

Vote
On the statement, including tiering and incorporating note that the recommendation against adamantanes' use is based only on current virologic susceptibility, which may change over time.

In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Lieu, Morse, Morita, Poland, Stinchfield, Treanor, Womeodu
Opposed: None
Abstained: None (there was no conflict involved in these aspects)

The motion passed.

VFC Changes Relevant To Influenza Vaccine
Presenter: Dr. Greg Wallace, NIP

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In past years, VFC only covered children at high risk and their contacts, and vaccine was left over even in years of shortage. Current changes to the VFC recommendation were:

- A permissive recommendation for vaccine use among all those VFC-eligible children aged 6 months through18 years of age, with priority given to routine high risk groups when supplies are limited, and with the addition by ACIP in 2005 to add those with compromised respiratory function.
- The first high risk group, 6 through 23 month-olds, will now say 6through 59 month-olds.
- Contacts will change from those of children aged <2 years to children aged <5 years.
- The language for LAIV will be added to the statement, "All healthy children age 5 through 18 years with priority when supplies are limited to…" the contacts listed for TIV.
- All currently licensed vaccines will be listed in the footnote.

Discussion included:

- Vaccination will also be recommended for contacts of those children aged 24 through59 months.
- Dr. Poland asked if there were any new data on anaphylactic reactions due to chicken allergy, since that evidence was found to be outdated for MMR. No one had that information; the influenza working group will look into it. If it cannot be determined for this year, it will be addressed next year.

Dr. Finger **moved to approve the VFC resolution with the changes described.** Dr. Poland seconded the motion.

Vote

In favor: Allos, Beck, Campbell, Finger, Gilsdorf, Lieu, Morse, Morita, Poland, Stinchfield, Treanor, Womeodu, Abramson
Opposed: None
Abstained: None (there was no conflict involved in these aspects)

The motion passed.

Update on HHS Pandemic Influenza Planning
Presenter: Dr. Bruce Gellin, Director, NVPO

A national strategy for pandemic influenza was released by the President on in November 1, 2005, and the Department of Health and Human Services (HHS) pandemic influenza plan was released the next day. The implementation preparedness plan for activities across the federal government will soon be released. Preparedness activities for seasonal influenza and pandemic are aligned.

Of the $7.1 billion proposed for pandemic preparedness, $6.7 billion was for HHS. Congress provided $3.3 billion in December, and the President's budget for 2007 proposed another $2.3 billion for this coming year (the second year of funding of the original budget plan).

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Federal Roles.

- The largest aspect of preparedness is the creation of a stockpile in bulk of 20 million courses (2-doses) of vaccine against the most likely pandemic threat, by February of 2006 (currently there are 8 million doses of H5N1 vaccine, at 90 mg/dose).
- Creation of a domestic influenza vaccine manufacturing capacity sufficient to produce 300 million courses within 6 months of a pandemic onset is being examined; as is increasing egg-based capacity and accelerating cell-based production capacity, retrofitting existing manufacturing facilities for emergency influenza vaccine production, accelerating the development of dose sparing techniques (e.g., adjuvants, immune stimulants, delivery technologies), and developing a broad spectrum influenza vaccine.
- A Request for Information (RFI) was posted on January 30, 2006, regarding efforts to expand existing egg-based influenza vaccine manufacturing facilities, to build new facilities, to convert existing manufacturing facilities that produce FDA-licensed vaccines and biologics to produce influenza vaccines, and to advance the development of recombinant-based influenza vaccines. Responses are due in February.
- The goal of the Strategic National Stockpile (SNS) of antivirals is to be able treat 25% of the U.S. population with antivirals (75 million treatment courses), reserving another 6 million for containment uses. There is full funding for 50 million doses and to subsidize the states' 25% of the remaining treatment courses.
- An RFI was posted last year, and some responses have been received, to develop new prophylactic or therapeutic agents to prevent or treat influenza virus infection. With the resistance to adamantanes, only neuraminidase inhibitors are left as treatment. The treatment criteria include shelf life, efficacy, bioavailability or half life, and, oral or parenteral delivery.
- More than 100 subject matter experts at CDC are working on pandemic preparedness.

State roles. The states were allocated $350 million in the recent emergency pandemic influenza appropriation passed by Congress in December. Each state will receive at least $500,000, with additional funds allocated by population. New York City, Chicago and Los Angeles County will receive supplemental grants. The balance of the $250 million appropriated will be awarded later in 2006 based on progress and performance. States and municipalities will use these funds to accelerate and intensify current planning efforts for pandemic influenza and for plan exercises.

Other FY06 budget priorities include expansion of FDA's regulatory science base, enhancing the SNS (with personal protective equipment, ventilators, etc.), increasing CDC's influenza lab capacity, expanding domestic biosurveillance and situational awareness, advancing the development of rapid diagnostics, and expanding education and risk communication activities. In addition, the U.S. contribution of global pandemic preparedness is $334 million.

NIH/NIAID H5N1 Update

Presenter: Dr. George Curlin, NIAID/NIH

Trials. Of NIH's current >100 ongoing active clinical trials, >33% are exploring a pandemic strain vaccine. Vaccine options include inactivated vaccines similar to TIV, live vaccines similar to LAIV, and inactivated vaccines with novel adjuvants and routes of administration. Inactivated

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vaccine has a proven technology and the largest manufacturing capacity, and its licensing would be simpler. Multiple doses probably will be required.

Safety/Efficacy. Past experience with H5 vaccine development includes the response to the initial Hong Kong outbreak. The Hong Kong H5-based vaccine is predictive for the current vaccine trials (i.e., higher doses give a better response, but all doses give some response.) Second-dose data are needed. The current trial of the rgA/Vietnam1203/04 (H5N1) vaccine involves healthy adults ages 18-64 years in a prospective, randomized, double blind study. Two intramuscular (IM) doses are given at a 28 day interval. The antigen range is broad, from 7.5 to 90 mcg, and the end points are safety and immunogenicity (neutralization titer of 1:40). To date, the vaccine has been well tolerated, producing some neutralizing responses at all doses, but the highest doses gave the best response (a 45–90 mcg dose was "acceptable").

Immunogenicity. Several strategies are being explored to overcome poor vaccine responsiveness: administering a priming dose, incorporating adjuvants, and using alternate administration methods including intradermal (ID) vaccination. In Europe, 30 mcg doses of the H5 formulation have been found effective with an alum adjuvant, but in normal interpandemic vaccines used at NIH, the alum has poorly enhanced immunogenicity. The current study (DMID 05-0217) is a dose ranging study on a constant alum vaccine formulation among healthy adults. The MF59, a proprietary adjuvant in use, has been promising.

Route of delivery. Intradermal vaccination was studied previously, comparing 15 mcg delivered IM versus 6 mcg delivered ID. The latest study compares 3 mcg and 9 mcg ID. No difference was seen in the previous study in those persons aged 18-60 years, but the IM delivery was much more effective than ID in those persons aged >60 years.

Formulation. Studies of live attenuated vaccines are also underway, and some cold-adapted H5, H7, and potentially pandemic strains have been developed. These vaccines are of interest because they are highly immunogenic in susceptible populations (although correlates of protection need to be defined); they can potentially be used at low doses, and their induction of mucosal immunity might reduce transmission. They also may offer some cross protection. However, they are not licensed in all population groups; more safety data are needed; as are correlates of immunity that could be extended to the elderly. Other concerns involve issues of transmission and reassortment.

The experimental pandemic vaccines include nasal inactivated vaccines, cross-protective peptides and epitopes, virus-like particles, alternative live vaccines, vectored approaches, and DNA vaccines. But the current critical question in the search for a pandemic vaccine is whether the H5 hemagglutinin is intrinsically less immunogenic in humans. Its biological mechanism is unclear. NIH is awaiting Australian data which reportedly indicate a good vaccine with an alum adjuvant, based on the Vietnam strain.

The vaccine development pipeline to date includes:

- Sanofi pasteur and Chiron have submitted the current vaccine trial data for publication. Higher doses generated acceptable response. There are data on healthy adults and ancillary populations are already under study.

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- Sanofi pasteur's vaccine trials have completed enrollment in the elderly study, and enrollment is underway for the children's study. Sanofi pasteur's H5N1 vaccine with adjuvants is being studied among healthy adults (DMID 05 0127) and older adults (DMID 05 0141).
- Chiron's H5N1 M59 was very immunogenic with the H9 strain. They are awaiting an import license to begin trials.
- A booster dose to the current two-dose H5N1 vaccinees with the sanofi pasteur H5N1 vaccine is being done to assess its benefit.
- Also planned, but on hold, is a study to add the H5N1 to the routine annual vaccine for healthy adults.

Discussion included a question of how far in advance a vaccine can be developed before the virus has been identified as a pandemic strain; whether the 20 million vaccine doses for the stockpile will be developed before then; and, if so, what was expected of the vaccine's efficacy. Dr. Curlin responded that the Vietnam strain, which has spread to Eastern Europe and Africa, is apparently fairly stable. The hope is that this virus will sufficiently protect from any new strain, should a pandemic occur. Dr. Gellin added that the annual influenza vaccine formulation also is based on the most recent strain, hoping that this would provide cross-protection to any strain deviation. But should a new strain emerge, a new vaccine would have to be developed. This situation is occurring currently, where a prototype vaccine is now being developed using one selected clade of the two current H5N1 clades. Slightly less than 8 million doses have been manufactured this year by sanofi pasteur and Chiron; the pandemic vaccine cannot be manufactured until production of the annual strain ends. As a result, commercial scale manufacturing of the pandemic strain will have to wait until next fall. But with increased manufacturing capacity, the prepandemic vaccines perhaps could be made while the companies produce the annual vaccine.

TETANUS-, DIPHTHERIA TOXOID, ACELLULAR PERTUSSIS VACCINES

Report from the Pertussis Working Group

Presenter: Dr. Dale Morse, Pertussis Working Group Chair

Overview: Review of ACIP Pertussis recommendations

The ACIP recommended protecting adolescents aged 11-18 years against pertussis in June 2005, by giving one dose of Tdap rather than Td. The Tdap dose was encouraged even if the Td had already been given. An interval of >5 years between Td and Tdap also was encouraged, but shorter intervals could be used. In October 2005, the Working Group discussions of a recommendation for adults aged 19-64 years produced the following suggestions:

1. Adults aged 19-64 years should receive a single dose of Tdap, in place of the next Td, to reduce pertussis among adults and reduce transmission of pertussis to infants. An interval <10 years since the last Td can be used for booster protection against pertussis. The safety of an interval as short as ~ 2 years between Td and Tdap is supported by a Canadian study.
2. Adults who have or will have close contact with an infant <12 months of age (e.g.,

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parents, grandparents, childcare providers, health-care workers) should receive a single dose of Tdap at an interval shorter than 10 years since the last Td, to protect against pertussis. Ideally, they should be vaccinated ≤1 month before close contact with the infant. (Cocooning)

3. Interim guidance regarding pregnancy was: "Women should receive a dose of Tdap in the immediate post-partum period if they have not previously received Tdap."

On this day, the Working Group presented the issues related to Tdap use among health care workers and adults aged >64 years. In June, presentations are scheduled on the issues related to the use of Tdap among pregnant women (adolescents and adults), and an ACIP statement on that will be proposed.

The purposes of Tdap vaccination of adults are to:

1. Protect them from pertussis morbidity.
2. Decrease pertussis exposure to persons at increased risk of severe pertussis and its complications, especially infants aged <12 months and adults with co-morbid conditions.
3. Reduce the cost and disruption of pertussis in institutional settings.
4. Reduce the reservoir of pertussis.

Considerations related to these objectives are that Tdap is licensed as a single-dose vaccine. Its duration of immunity wanes at ~5-10 years after vaccination and infection, which makes the need for a ~10-year Tdap booster probable. Finally, the vaccine could cost ~$20 more than Td. Tdap is expected to be effective in stopping transmission, but how that will be shown in the population is unknown. Currently, Td coverage among adults aged 19-64 years is low, at only~55%-67%, and is ~42% among in those aged >65. Tdap is not licensed for use in those aged >65 due to a lack of data to support that.

The Working Group advised ACIP to recommend Tdap at a short interval after the last Td for healthcare workers with direct patient contact in hospitals or ambulatory care settings, and to allow permissive use of Tdap among adults aged >64 years, even thought this is an off-label use.

Manufacturer Updates

- *sanofi pasteur* Dr. Michael Decker reported that Sanofi Pasteur is revising study protocols to provide data in ~3 years that will support licensure of Adacel™ with no upper age limit. Study enrollment is under way in Germany to assess Adacel™ given as the sixth consecutive dose of acellular pertussis vaccine; the five previous doses were given as Tripedia®. A similar Adacel™ study will be done with U.S. and Canadian cohorts as soon as they age to the lower age limit for Adacel™, expected in ~1 to 1½ years. A safety study of repeated Adacel™ administration will be done in a population that first received Adacel™ ~4½ years ago to provide an evaluation of the safety of re-administration after a 5-year interval.
- *GSK.* Dr. Friedland reported post-marketing studies are underway of Boostrix® co-administered with MCV4. GSK is working with FDA to expand the licensed indication for Boostrix® beyond aged 18 years of age. A study of six consecutive doses with Boostrix® has been completed and is described in the package insert.

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Tdap Use Among Adults Aged >65 Years
Presenter: Dr. Katrina Kretsinger, NIP

Overview: Review of the scientific rationale for permissive-use of Tdap among adults >65 years of age, the current standard of care, considerations from the program perspective, and proposed wording. Older American adults have the highest tetanus case incidence and mortality; improving vaccination against tetanus and diphtheria is important.

Vaccine. Adacel™ (Tdap), made by sanofi pasteur is licensed for use among persons from age 11 to 64 years as single-dose booster immunization against tetanus, diphtheria, and pertussis. ACIP recommended Tdap use in that age group. Adacel™ also is the only Tdap licensed for use from age 19-64, as GSK's Boostrix® is licensed for ages 10-18. There are no prelicensure safety or immunogenicity studies for Adacel™ use among adults >65 years (older adults) who in 2002 comprised 12% of all Americans (~36 million).

Pertussis disease burden. No prospective population-based study data exist on pertussis incidence among older adults, but pertussis is probably under-reported, as it is among younger adults. In a serosurvey of 100 adults aged ≥65 years tested every four months for three years,,10 developed *B.pertussis* infection as measured by antibody rise, and half of those infected developed cough illness (Hodder *CID*. 2000;31:7-14).

Data of the National Notifiable Disease Surveillance System (NNDSS) from 1996-2004 were examined. In that period, 894 cases of pertussis were reported among older adults; of these 8% were hospitalized and x-rays indicated that 12% had pneumonia, a higher rate than that reported for adults or adolescents. Four patients died, all of whom had co-morbidities.

A 1992 pertussis outbreak in a Dutch religious institution had a 53% attack rate of laboratory-confirmed clinical pertussis in its older residents, four of whom died from pertussis-associated causes (Mertens, *Eur J Clin Micro*. 1999; 18:242-247). The attack rate in a 1985 Wisconsin nursing home outbreak was 36% (Addiss, *JID*. 1991; 164:704-10).

Pre-licensure safety and immunogenicity data among adults 19 to 64 years of age were examined (in the absence of prelicensure data for older adults). Also reviewed was preliminary data of an Austrian study of Tdap administered with IPV among older adults, and VAERS reports.

- *Td506.* The principal Adacel™ safety and immunogenicity study Td506, randomized persons aged 11-64 years to receive either sanofi pastuer Td or Tdap (both have the same diphtheria and tetanus toxoid quantities). Data were gathered for four pre-defined age groups (11-17, 18-28, 29-48, 40-64), as well as from an ad hoc subset of adults aged 60-64 years.
- *Td506 safety data* were charted for local reactions (pain, erythema and swelling) for the four age groups from vaccination to 14 days later. Reports of pain decreased with the recipients' increasing age, rates of erythema and swelling were constant, and fever rates were generally lower for adults than adolescents. Serious adverse events (AE) were followed for six months, and were 1.9% for both Td and Tdap recipients. The U.S.

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Adacel™ prelicensure safety studies had two serious adverse events that were possibly related to Tdap; both resolved without sequelae.

- Unpublished *Austrian Tdap*-IPV combination vaccine (Repevax™) immune-response study data were reviewed. Repevax™ has the same Tdap composition as Adacel.™ The study enrolled 252 healthy adults aged 59-91 years; all had had Td boosters but no pertussis vaccine. They received one dose of Repevax™. Pre-defined immunogenicity and safety endpoints were not primary study objectives. Written AE reports were solicited 5 weeks after vaccination (recall that in Td506 AEs were solicited at 14 days after vaccination. The Austrian cohort on average were older (59-91 years) than the Td506 cohort (48-64 years), and had about half the AE rates found in Td506. Comparison of the two studies should be interpreted with caution because these studies were conducted under different protocols, by different investigators, and using different evaluation criteria.
- *VAERS* is a national, passive surveillance system for reporting adverse events following vaccination. No disproportionate rate of adverse events among older adults is reported after Td and TT among older adults compared with younger adults (Lloyd JC et al. *Vaccine* 2003; 21). Reports of Guillain Barré Syndrome (GBS) and extensive limb swelling are rare after Td in older adults.
- *Immunogenicity to tetanus and diphtheria toxoids after Tdap.* Immune responses to tetanus and diphtheria toxoids were reviewed separately from immune responses to pertussis antigens because the serologic correlates of protection for tetanus and diphtheria are defined, Tdap was seroprotective against tetanus and diphtheria and the booster-responses met the noninferiority criteria for Td among adults aged 11-64. Presented tables showed unpublished data for adults aged 60-64 years, demonstrating the same high seroprotection for Tdap as for Td. Although the response to tetanus and diphtheria toxoids was adequate from age 49-65 years, antibody responses to both toxoids declined with advancing age.
- *Immunogenicity to pertussis antigens after Tdap.* Serological correlates of protection for pertussis are not well accepted. The Tdap (Adacel™) licensure for 11-64 year-olds was based on inferred efficacy from the boosting response in adults with serologic bridge to the immune response to three doses of DTaP among Swedish infants.
- Pre- and post-vaccination geometric mean titers (GMTs) from older adults in the Austrian study of Tdap-IPV were compared with results from the ad hoc subset of adults aged 60-64 years from Tdap arm of the U.S. principal pre-licensure study (Td506). Both studies showed older adults had an immune response to pertussis antigens. In the principal pre-licensure trial Td506, the GMTs by age category showed that levels of filamentous hemagglutinin and pertactin remained relatively constant with increasing age, but levels of pertussis toxoid and fimbriae 2 and 3 declined with increasing age.

In summary, the pertussis burden among older adults is not well defined but likely substantial. No U.S. trials of Tdap have been conducted among older adults, but other related data do not suggest safety concerns; AE rates are similar or decline with increasing age. Based on results among aging younger adults, tetanus and diphtheria immunogenicity are likely to be similar after Tdap and Td for older adults, but data specific to this group are lacking.

The *rationale for permissive use of Tdap* include the following: use of Tdap is consistent with

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and would reinforce the existing standard of care for the recommended tetanus and diphtheria decennial booster, Tdap would provide pertussis protection standard for care for older adults who are in contact with infants (e.g., grandparents or be healthcare workers), and Tdap would allow programmatic flexibility and provide guidance for clinicians.

The *disadvantages of permissive use of Tdap* include the increase in cost over the cost of Td for older patients, and that its use would be off label. In the past, the ACIP has made off-label recommendations for special populations and vaccine situations, such as use of *Haemophilus influenzae* type b conjugate vaccine for immunocompromised adults, and use of DTaP at age 12 months (given a 6-month interval) for a child unlikely to return for the 4th dose scheduled at 15 to 18 months of age. Some past ACIP vaccine recommendations included routine use among older adults when the vaccine was licensed without upper age restriction (e.g., influenza vaccine, Td, and PPV-23).

The working group proposed permissive use of Tdap among older adults, to be accompanied by information describing available safety and immunogenicity data, and information to ensure that the standard of care for tetanus and diphtheria are maintained through use of either Td or Tdap. The working group also proposed that ACIP include a specific recommendation for additional studies on Tdap safety and immunogenicity among older adults as a basis for any future recommendation.

Proposed recommendation. The suggested wording was as follows:

> "Tdap is not licensed for use among adults >65 years of age. The safety and immunogenicity of Tdap among adults >65 years of age were not studied during U.S. pre-licensure trials; data from clinical trials among older adults are limited (see section, Tdap among Older Adults). Clinicians can choose to administer Tdap to adults >65 years of age for protection against pertussis in addition to protection against tetanus and diphtheria.
>
> "Recommendations for use of Tdap in adults >65 years will be updated as new data become available.
>
> "All adults, including adults >65 years of age, should receive a dose of tetanus toxoid- and diphtheria toxoid-containing vaccine every 10 years for protection against tetanus and diphtheria, and as indicated for wound management."
>
> (Areas of future research related to Tdap and adults): "... Studies are needed to establish the safety and immunogenicity of Tdap among adults aged >65 years to support an evidence-based recommendation for use of Tdap among older adults…"

Discussion included points in favor of permissive use of Tdap in older adults:

- Dr. Plotkin appreciated, to general agreement, the cocooning strategy of protecting infants by vaccinating parents and grandparents.
- Dr. Schaffner advised against limiting Tdap by age group, which risks further confusing internists and the public. Although the issues of safety and immunogenicity need to be

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addressed, he thought them unlikely to be substantive, and few internists would hesitate to give Tdap to patients aged 66 as well as 64.

- Both Dr. Decker and Mr. Hosbach said ACIP's decision would not affect their plan to study Tdap in older adults. They anticipated it will require 2-3 years to complete the study and obtain FDA licensure.
- Dr. Tan liked the permissive language and favored letting physicians choose, especially since the following text states that recommendations will come, pending data.

Points opposed to permissive use of Tdap in older adults included:

- Dr. Baylor commented that this recommendation varies from the FDA-approved label, which was based on the available data. He noted that studies have begun or are ongoing in these populations, and data will be available sooner rather than later. Additionally, the proposed recommendation is generic for Tdap, not a specific product. The GSK product is licensed only to age 18, a big difference to age 64. (Dr. Kretsinger noted that the recommendation for adult Tdap use only applied to one product, Adacel,™ and that this is clearly stated in the adult recommendations.)
- Dr. Abramson commented that ACIP only has recommended off-label when there was no chance of getting the needed data, something not the case here. Dr. Lieu agreed.
- Dr. Pickering commented on the very small number of participants in the studies, none of whom were in the full targeted age group, and the great difference in the U.S. and Austrian studies. He found the recommendation to be too subjective. He agreed with other comments that the studies are being done and clinicians already can vaccinate this older age group against pertussis if they so choose.
- A permissive use statement would not tell internists they shouldn't use the vaccine but rather that it would state that evidence supporting use of the vaccine among older groups is not available. Regardless, discomfort with a "recommendation" contrary to FDA licensure remained, Further, few studies provide evidence that older adults are an important source of pertussis for infants, which leaves the benefit of vaccinating older adults hypothetical for cocooning. Similarly, few or no studies provide evidence that older adult care providers are a source of pertussis for infants in child daycare.
- Neither Td nor Tdap is paid for by Medicare for preventive care.
- Dr. Pickering recalled the DTaP/Hib vaccine discussion when permissive off-label use of DTaP/Hib was released. He indicated that if a statement like this had been released, hundreds and maybe thousands of children would not have been properly immunized again Hib.
- Dr. Jeff Duchin, of NACCHO noted that the pertussis burden of disease is not significant in older adults, nor a large factor in transmission, negating any urgency to recommend at this time.

Alternatives suggested were:

- Dr. Campbell suggested deleting the last sentence of "Clinicians can choose to administer…" and the next two paragraphs about updates and the decennial booster. She proposed adding, "We recognize that vaccinating this population will likely be important to full implementation of a cocoon strategy."
- Dr. Wexler suggested saying, "While not specifically recommended by ACIP for use, or licensed by FDA at this time, clinicians can choose to administer…"

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- Dr. Temte urged caution, especially in view of ACIP's development of evidence-based classifications for its recommendations. He had heard no data on rates of transmission between grandparents and infants; and the pending product is for adolescents, the highest transmission group. Clinicians have the right to treat as they see fit, but they look to ACIP for evidence-based guidance.

Dr. Finger **moved to amend the proposed recommendation language by striking the sentence beginning with the word "Clinicians..."** The motion was seconded by Dr. Campbell.

Dr. Morse reported the Working Group's minor concern about safety in this age group, and wish for more of a science base of exposed children. But they concluded that the sentence does not really matter, since physicians can vaccinate anyway as soon as it is licensed.

Dr. Allos observed (and Ms. Stinchfield agreed) that if the "clinicians…" sentence is dropped, the recommendation would read more like a caution against using the vaccine in people aged >65. Waiting to weigh the benefits and risks may do more harm. She suggested saying, "The ACIP would like to recommend use of this vaccine in those aged >65, but cannot do so until data are available. That is anticipated in ~2 years." That would convey this as an option to physicians about the newborn as well as to grandparents.

Vote
To approve the amended recommendation text.

In favor: Campbell, Finger, Gilsford, Lieu, Marcuse, Morita, Abramson
Opposed: Morse, Poland, Stinchfield, Womeodu
Abstained: None

The motion carried.

Tdap Use Among Healthcare Workers
Dr. Tejpraptap Tiwari, NIP

Overview: Rates of pertussis among health care workers, transmission in health care settings; related costs.

Protecting the 8-10 million U.S. healthcare workers from acquiring and transmitting infectious diseases is a public health goal. Adult pertussis morbidity is substantial and includes cough for ≥3 weeks for 80%-100%. It can cause urinary incontinence in ~39% of women, rib fractures in ~4% of adults, and syncope in ~3%. Although data describing the incidence of pertussis among health-care workers are limited, a few studies have been conducted. Four were outlined:

1. Of 93 pediatric hospitals surveyed in 1994 by Lane et al (*ICHE* 1997;18:400), 90% of the 62 respondents reported cases of pertussis within the past 5 years. Of those, 11% reported one or more physician contracted pertussis after exposure to a patient; data on other health care workers was not reported.

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2. Deville et al (*CID* 1995; 21(3):639) reviewed conducted annual serosurveys for pertussis from 1984-1989 in a tertiary care hospital. Fifty-one health-care workers were infected (based on elevated anti-PT titer) for a mean annual rate of 8%, and range from 4%-16%. Re-infection was common. The rate of symptomatic pertussis was not reported.
3. Wright et al (*ICHE* 1999; 20[2]:120-3) conducted a serosurvey of 145 health-care workers in a 660-bed tertiary care hospital from 1992 to 1994. Sera were obtained from emergency department (ED) personnel and resident physicians. The rate of symptomatic infection was 40%. Recent infection occurred among 7.6% of ED personnel and 2% of residents. The annual incidence of pertussis among ED personnel was 3.6/100 person-years and among residents was1.3/100 for residents.
4. De Serres G.(*J Infect Dis* 2000;182:174) found a 1.7-times increased risk of pertussis among health-care workers in Quebec compared with the general population. Eight percent of adult pertussis cases from July to December 1998 were among health-care workers, even though health-care workers comprised only 5% of the adult population

Health-care worker role in transmission. CDC data indicate that a wide range of positions among health-care workers acquire or transmit pertussis, but they have in common direct contact with patients and direct contact with other healthcare workers. The two primary factors that foster transmission are delayed diagnosis and treatment in the source case, and late implementation of control measures. The intensity of contact has varied by setting. Outbreaks in each were described, for hospitals' pediatric and adult settings, ambulatory care pediatric and adult settings, and a long-term residential care facility for developmentally disabled adults. A table of reported pertussis outbreaks in pediatric settings (13 studies) showed three outbreaks beginning with a health care worker; two beginning with infant to health-care worker, and 8 beginning with an infant with pertussis. Although 7 pertussis outbreaks in adult-care settings had health-care workers for all the index cases, in three of four long term care residential facility outbreaks patients were the index cases in three, and the index case was not identified in one.

Six studies of health-care workers with pertussis in pediatric hospitals showed cases transmitted by health-care workers before the illness was recognized. The majority of secondary cases were among health-care workers. However, secondary cases among infants occurred and resulted in substantial morbidity, e.g., an infant with hospital-acquired pertussis required mechanical ventilation for >2 weeks and required another 2 months of hospitalization. When pertussis was recognized, investigation identified a large number of contacts who required post-exposure prophylaxis. In one outbreak (Martinez et al) the number of cases and contacts was so large that the hospital chose to give chemoprophylaxis to 3179 employees. Four studies (Jankelovich, 2006; CDC, 2005; Friedman, 2005; and McCall, 2002) described health-care workers and patient exposures in adult-care settings that began with a single health-care worker; secondary cases were prevented by existing control measures.

Costs. Pertussis control guidelines (CDC/HICPAC, *MMWR* 2003; HICPAC, *AJIC* 1998; CDC 2000) advise hospital infection control practitioners identify close contacts, provide post-exposure prophylaxis, test and treat symptomatic employees and patients, and furlough symptomatic employees for the first five days of treatment. These activities are labor intensive and costly. The charted costs of outbreaks at three hospitals (general, general with adult and pediatric beds, and pediatric) ranged from $64,000 to $106,000 in direct costs; from $3500 -

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$21,000 in cost per case; $97-$144 per exposure. Indirect costs for personnel hours lost ranged from $11,000 to $68,000, and $97-$180 in per case. Total costs ranged from $75,000-$174,000.

Cost-Benefit Analysis of Tdap Vaccination of Health-Care Workers
Presenter: Dr. Ismael Ortega-Sanchez, NIP

> Overview: Analysis of potential cost savings from preventing pertussis among vaccinated health-care workers, without change in control practices (given that Tdap's effectiveness to prevent subsequent transmission from vaccinated health-care workers is unknown).

Pertussis in health-care workers and nosocomial pertussis outbreaks are a special concern in health-care settings because transmission can occur to patients vulnerable to severe pertussis. Vaccinating health-care workers will prevent the morbidity of pertussis. In addition, vaccinating health-care workers may 1) reduce pertussis infections and outbreaks in hospitals, 2) decrease transmission and prevent secondary cases, and thereby reduce outbreak size and duration, and 3) reduce the infection containment costs. The last includes case- and contact tracing, post-exposure prophylaxis, and/or treatment of hospital-acquired pertussis cases

To determine if cost savings might be possible from a program to vaccinate health-care workers against pertussis, a probabilistic model was used assuming 1000 hypothetical health-care workers with direct patient contact, followed for ten years. Probability distributions were specified for key parameters using a range of values, and varied simultaneously using Monte Carlo simulations. Results were reviewed for the following outcomes: number of nosocomial pertussis exposures; vaccination-produced net costs or savings from prevented pertussis, according to a hospital perspective. Health costs and benefits were calculated in 2004 dollars with a 3% discount rate. Net costs (or savings) accrued to the vaccination program and benefit-cost ratios were estimated.

Model assumptions: The model assumed 1) no change in post-exposure control measures, including antimicrobial prophylaxis, and 2) an annual turnover rate of 16% of the 1000 health-care workers, and 20% of the original cohort left by year 10. To maintain a stable population in the model, those leaving each year were assumed to be replaced by new, mostly unvaccinated healthcare workers. In the model, 66% of health-care workers were vaccinated at the beginning of the first year. Since some health-care workers who were vaccinated would leave, to maintain protection levels would require vaccination of new health-care workers at the beginning of each year. This progression was outlined on a decision analysis chart, which also included possible vaccine failure, and subsequent exposures.

The literature provided values and ranges for the annual rate of *B. pertussis* infection in health-care workers, the proportion of these infections that would be symptomatic, the number of hospital contacts exposed by each symptomatic health-care worker, and infection control costs per exposure. The cost estimates were comprehensive, including contact tracing, laboratory work, antimicrobial treatment and health-care worker furloughs. The literature provided data on vaccine efficacy and coverage, adverse events, vaccine cost, as well as the mean values for employee turnover rates, etc.

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Algorithms used to calculate the annual number of pertussis exposures prevented, or not, per 1000 healthcare workers, with- and without a vaccination program were described. Exposures were defined as the number of patients and health care workers in the hospital who had direct contact with the persons with pertussis. The number of exposures prevented was the proxy for the number of cases prevented.

Results. After the Monte Carlo simulations of the number of exposures resulting from health-care workers ill with pertussis, we selected the median number of exposures and approximated a confidence interval using the 5th and 95th percentile simulation values. With the Tdap vaccination program in health-care workers, we estimated that a median of 93 (46%) of annual exposures would be prevented, with a range of 13-310 exposures (5th and 95th percentiles). The calculated net containment costs saved in a ten year period (cost of infection control less vaccination costs, both discounted) was $94,981 per 1000 health care workers, with a range of a negative $52,882 (5th percentile) and a positive $534,807 (95th percentile). The benefit-cost ratio of a Tdap vaccination program from a hospital perspective was a $2.38 return for every dollar invested in the vaccination program for health-care workers ($0.36-$10.86).

Sensitivity analyses. A multivariate regression analysis was done over the range of simulation estimates to gauge the analysis' sensitivity for pertussis exposures prevented and the benefit-cost ratio. The statistically significant variables in order of their influence over the model outcome were the number of exposed health-care workers, the incidence of pertussis among health-care workers, employee turnover and cost of the vaccine (both with a negative influence), vaccine coverage and efficacy, and containment costs.

A line graph demonstrated the impact of symptomatic rates and the incidence of *B. pertussis* infection on the benefit-cost ratio. Net vaccination cost-benefits were achieved at a 6.7% incidence rate, if ≥15% of health-care workers are symptomatic, at 3.6% incidence rate if ≥28% of health-care workers are symptomatic, and at 2.5% incidence rate if ≥40% of health-care workers are symptomatic.

Threshold analyses were done to determine breakeven values for ten variables, of which three were highlighted: vaccine cost per dose, number of contacts exposed, and the health-care worker turnover rate. If other factors were not changed, net savings from a vaccination program were possible if, for example, the number of exposed contacts per health-care worker was ≥ 2.5 rather than 8.73 as in the base-case, if the health-care worker turnover rate was >100% rather than 16% as in the base-case, or if the vaccine cost was $84 rather than $30 as in the base-case.

Limitations of the analysis included the use of exposures as a proxy for potential cases, possibly limited generalizability of the results, the assumption of an inverse correlation of vaccine effectiveness and coverage with the number of exposures and outbreaks, an assumed constant ratio of health-care workers-to-beds, and an assumed constant hospital occupancy rate. The model's strengths included 1) the assumed turnover rate and continuous vaccination reduced the relevance of prolonged vaccine effectiveness, and 2) the probabilistic modeling and threshold analyses identified key uncertainties for future research.

Conclusions were that:

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- A Tdap vaccination program in health-care workers could have substantial impact in reducing hospital-acquired pertussis morbidity by reducing the number of annual exposures (-46%).
- The benefits (or savings) from a Tdap vaccination program could be sizable for hospitals even after covering program costs (the benefit-cost ratio could be >1).
- Health and cost outcomes are highly sensitive to the number of persons exposed in the hospital per each symptomatic health-care worker, the annual rate of *B. pertussis* infection in health-care workers, and the proportion of workers who become symptomatic.

Discussion included:

- The vaccine cost per dose was for vaccine only, not the program. Dr. Marcuse noted the far greater cost of a program, to which Dr. Ortega-Sanchez agreed. But even with an $84 total cost, there could be benefit to the hospital. Dr. Hull added that the vaccination would be added to systems already in place to deliver other vaccines, so the increment would be far less than that of a new program.
- Ms. Stinchfield noted that Dr. Tiwari's tertiary care hospital slide indicated 40% of adults are symptomatic with *B. pertussis* infection. That could include nasal carriage, but asymptomatic persons do not transmit.
- The base case incidence in health-care workers was based on the serological studies presented, which came from in-house serologic analysis of antibody titers to determine the annual infection incidence range of 4%-16%.
- Dr. Lieu commented that the presentations inferred a "slam-dunk" recommendation decision. She asked for any areas of controversy. Dr. Murphy identified two: the weak national data on incidence rates, among health-care workers, although outbreaks are well defined; and the unknown level of transmission prevented in vaccinated health-care workers. The vaccine may be efficacious against disease, but even a mild cough or respiratory symptoms may transmit.

Proposed Tdap Recommendations

Presenter: Dr. Trudy Murphy, NIP

Overview: Rationale for recommending Tdap for health-care workers with short interval after the last Td; draft proposed recommendation.

The rationale to recommend one dose of Tdap for health-care workers at short interval after the last dose of Td, rather than the General Recommendations' ten-year interval, involves science, standard of care, and programmatic aspects.

Science. Data indicate substantial morbidity of adult pertussis, and health-care workers with direct patient contact are likely to be at increased risk. Tdap prevents pertussis in adults. The current standard of care supports Tdap vaccination of health-care workers because pertussis immune health-care workers will decrease exposures and secondary cases in both pediatric and adult-care settings. Tdap's safety was demonstrated in a Canadian adolescent study that included intervals as short as 2 years after the last Td booster. However, no data indicate the duration of

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protection against pertussis in adults, or whether Tdap vaccination of health-care workers will be an effective strategy to prevent transmission.

Standard of Care. The standard of care supports Tdap vaccination of health-care workers. ACIP already recommends worker vaccination to prevent the transmission of vaccine-preventable diseases in health-care settings, and ACIP already recommends that adults receive a single dose of Tdap to replace the next decennial Td. ACIP has also recommended that adults in contact with infants receive a Tdap dose at short interval after the last Td, to protect the adult from pertussis and to prevent transmission of pertussis to the infant

Programmatic issues. Facility infrastructure readily allows implementation of a Tdap vaccination program for health-care workers, as done for other vaccines such as influenza. The costs of vaccination will be offset by reduction in infection control activities and medical leave, and by increasing vaccination rates. A single, simple ACIP recommendation can cover both pediatric and adult-care settings, and the health care workers can be prioritized for vaccination (e.g., according to infant- or direct patient contact). However, the vaccine will be an incremental increase in expenses for facilities that now offer Td to their staff, and a larger expense for those that do not. The necessary education and vaccination program will incur substantial cost, and the short interval from the last Td will increase implementation costs in the short term, since more health-care workers will be eligible for this vaccine than would be the case for a simple replacement for the next scheduled Td decennial booster. Finally, the guidelines for post-exposure prophylaxis of vaccinated health-care workers will require review, as they were developed when adults were not vaccinated for pertussis.

Proposed recommendation. The proposed text to recommend Tdap vaccination for health care workers was:

> "Health-care workers who work in hospitals or ambulatory care settings and have direct patient contact should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap.
>
> "Although Td is routinely recommended at intervals of 10 years, an interval as short as 2 years from the last dose of Td is recommended for the Tdap dose among health-care workers (see recommendation for "Short Interval between Td and Tdap").
>
> "These health-care workers include but are not limited to physicians, other primary care providers, nurses, aides, respiratory therapists, radiology technicians, medical and other students, dentists, social workers, chaplains, volunteers, dietary and clerical workers.
>
> "Other health-care workers (i.e., who do not work in hospitals or ambulatory care settings, or who do not have direct patient contact) should receive a single dose of Tdap according to the routine recommendation for use of Tdap among adults, if they have not previously received Tdap.
>
> "These workers are encouraged to receive the Tdap dose at an interval as short as 2 years from the last dose of Td (see recommendation, "Short Interval between Td and Tdap").

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"Vaccinating health-care workers with Tdap will protect them against pertussis and is likely to reduce transmission to patients, other health-care workers, household members and persons in the community.

"Priority should be given to vaccination of health-care workers who have direct contact with infants aged <12 months (see recommendation, "Prevention of Pertussis among Infants Aged <12 months by Vaccinating their Adult Contacts")

"Hospitals and ambulatory facilities are strongly encouraged to provide Tdap for health-care workers and to use approaches that maximize vaccination rates, e.g., education about the benefits of vaccination, convenient access, and the provision of Tdap at no charge.*

Discussion included:

- Ms. Stinchfield suggested adding nursing students to the list.
- Dr. Finger proposed saying that "… hospitals and ambulatory care facilities should provide …" rather than "are strongly encouraged to.."
- Dr. Gilsdorf suggested inserting text indicating the potential cost saving, to lower CEOs' pain from the suggestion that the hospital pay for it.
- The influenza statement provides a precedent for ACIP to say a facility "should" pay for the vaccine, even for populations that are not poor. The new HICPAC/ACIP health-care worker statement recommends that health-care workers' recommended vaccines be purchased for them, as does OSHA's requirement for health-care workers' hepatitis B vaccine. Dr. Carolyn Bridges added that a recent California study demonstrated a strong association between having a vaccination paid for and its uptake by health-care workers.

Dr. Abramson summarized the general consensus to parallel the influenza statements' recommendation that hospital and ambulatory care facilities "should provide," rather than being "strongly encouraged to provide", vaccination. Further discussion included:

- Dr. Myers noted that this would leave out nursing homes, hospices, EMS services, etc. He suggested using the influenza guidelines terminology of "health care personnel" as a catch-all, rather than distinguishing between facilities. Dr. Murphy reported that as discussed by the Working Group, but rejected due to the scarcity of information on nursing homes. The nursing homes' professional association also opposed it because of high turnover. She also reminded the committee that these health-care workers will be covered by the general adult Tdap recommendation. This wording was for catch-up pertussis vaccination of health-care workers in acute care facilities. Nonetheless, Dr. Myers advocated for ACIP's boldness, as Dr. Poland had earlier, to further avoid potential deaths among the elderly.
- Dr. Duchin asked if any studies are planned to better define understanding the vaccine's efficacy in this setting. He was particularly interested since the ACIP has not recommended a change the current outbreak control and post-exposure prophylaxis protocols, which incur a significant cost to healthcare facilities. He also asked how transmission from unrecognized asymptomatic, or mildly symptomatic, health-care workers could be detected. Dr. Murphy responded that funding has been applied for to

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underwrite such studies. NIP would be glad to share its protocol with any facility, and greatly desires such data.

Dr. Allos **moved to accept the recommendation with the edits discussed (i.e., saying "should provide" rather than "strongly encouraged to provide", adding nursing students and ambulatory/acute care settings to the recommendation.**

When Dr. Murphy reported that the definition of "acute care setting" is variable between adult care physicians and pediatricians, Dr. Poland **made a friendly amendment to define "ambulatory care settings" in a footnote.** Ms. Stinchfield seconded that motion.

Vote
To accept the proposed recommendation with edits.

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

The motion passed. Dr. Murphy stated that the ACIP recommendation for health-care workers would be presented to HICPAC for a consensus statement.

HERPES ZOSTER (SHINGLES) VACCINE

Storage/Handling of Herpes Zoster Vaccine
Presenter: Dr. Greg Wallace, NIP

Overview: Issues of cold storage for herpes zoster, varicella, LAIV, and combined measles, mumps, rubella, and varicella vaccine (MMRV)

The herpes zoster (HZ) vaccine up for licensure requires freezer storage. Three other current vaccines do so as well: varicella, proQuad™ (MMR-varicella) and live-attenuated influenza vaccine (LAIV). All must be stored at -15◦ C (5◦ F). Varicella can be stored at 2º-8º C for up to 72 hours before reconstitution, as may LAIV for ≤60 hours before use. At room temperature, varicella holds its minimum potency of 1350 PFU for only 30 minutes after reconstitution. MMRV vaccine many not be stored at 2º-8º C for any period of time, and must be discarded after reconstitution if not used within 30 minutes. LAIV vaccine cannot be refrozen after thawing

The requirement to store vaccines in the freezer leads to storage errors for both freezer-stored and refrigerator-stored vaccines. To determine if a freezer storage requirement poses a problem, CDC conducted two surveys of providers (>700) and practices (221). They found in both that 17%-18% of freezers are too warm at any given time *(Am J Prev Med* 2002;23(4):246-253; *Pediatrics* 2001;107(6):3100-104). CDC's guidelines advise turning the thermostat of standard household-type refrigerators to the coldest setting to maintain a -15º C temperature, but that could make the refrigerator too cold. Careful monitoring is needed. The refrigerator thermostat controls the volume of air going into the freezer, although freezers control their own temperature. Some refrigerators have temperature zones that vary.

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With freezer storage for some vaccines, the old dormitory-style refrigerators are no longer acceptable. About 30% of standard refrigerator freezers used to store varicella vaccine were too cold, and for inactivate vaccines, too-warm storage is less of a problem than too-cold storage. HZ vaccine users will include providers inexperienced in simultaneously maintaining vaccines in a refrigerator and a freezer. If they are not a VFC site, the lack of inspections will leave that uncorrected without a concerted education campaign by the Academies and the professional societies.

Dr. Barbara Kuter, of Merck, reported their extensive education campaign when varicella vaccine was first released. That included putting information on the outside of the shipment box, on the vaccine vial itself, and additional information in the box. They plan the same activities for the zoster vaccine. Dr. Kelly Moore, of the Tennessee Immunization Program, reported their extensive experience with mishandled varicella vaccine that must be discarded yearly. They recommend the small dorm-size, freestanding counter-high freezers, which cost ~$400-$500, to maintain the cold temperatures needed by varicella without compromising the refrigerated vaccines.

Survey of Internists/Family Care Practitioners About Herpes Zoster Vaccine

Presenter: Dr. Allison Kempe, University of Colorado, Rocky Mountain Prevention Research Center

CDC and the Vaccine Policy Collaborative Initiative conducted a survey of internists and family care practitioners, randomly sampled to represent the ACP and AAFP national associations, as well as geographic regions, locations (urban, rural suburban), and setting (private practitioners, etc.). They were surveyed in two sentinel provider networks in November/December 2005, to determine:

- The perceived burden of Herpes Zoster (HZ) and Post-Herpetic Neuralgia (PHN) in primary care practice
- The practitioners' intentions for recommending a new HZ vaccine if it is recommended by ACIP
- Perceived barriers to HZ vaccination.

The survey was administered over eight weeks by Internet or mail, based on the provider's preference. The Internet and mail protocols were both described. The initial contact information included an informational paragraph about the clinical trial of the new herpes zoster vaccine (Oxman et al, *NEJM* 2005). The survey was pilot-tested in community advisory panel composed of internists and family medicine physicians from across country.

The response rate was 62% (N=272) for general internal medicine (GIM) practitioners and 76% for those in family medicine (FM, N=328). Email surveys conducted by a Web-based survey company were selected by 66% of the respondents. FM and GIM characteristics did not differ appreciably, with ~80% in a private practice setting, although most family medicine physicians were in rural areas. Survey results were as follow for disease burden:

1. *Number of zoster patients seen* in the last year, with- and without PHN (combined GIM/FM data): without PHN, a median of 3 each for patients aged 50-59 and ≥60 years; and 1 and 2 patients, respectively, with PHN. Both groups were immunocompetent.

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2. *Median visits to treat*: 2 with PHN, 4 without; referred to sub-specialty: None, 74% without PHN, 36% with it; referred 1%-9% of patients: 22% and 41%; and referred ≥10% of patients: 4 % and 23%, respectively. The specialties were ophthalmology (24%), dermatology (6%). Neurology (32%), and pain management (40%).
3. HZ and PHN cause *significant burden of disease* in my older patients: 35% strongly agreed; 46%, somewhat; 19% somewhat or strongly disagreed.

Responses on vaccine use and recommending it were:

4. *Vaccine use is warranted* for the burden of HZ and its complications in patients. GIM: strongly agreed: 15% for those aged 50-59 years; 40% for those aged 60 to 79, 38% for >80; FM: 17% for age 50-59 years; 29% for 60-79 and 28% for >80.
5. *GIM likelihood to recommend HZ vaccination:* ≥75% were very likely or somewhat likely for the two older groups and the severely debilitated; 76% were only somewhat likely or unlikely to vaccinate those 50-59 years old.
6. *Likelihood of FM to recommend HZ vaccination*: The proportions of responses were similar to the GIM group, except they were more likely to recommend for the younger (50-59) age group, and their rate differences between likely and unlikely were less broad than the GIM group.

Only 15% responded to an open-ended question about groups the physicians would consider off-label use among. They listed patients overtly or functionally immunocompromised; those with chronic disease; those less able to tolerate shingles, or with shingles history, especially if severe; those who had varicella during infancy, immigrants; those who could infect others; healthy persons aged < 50 with varicella history; and healthy children and adults susceptible to varicella

Barriers to vaccination were asked, according to definitely a barrier — somewhat of a barrier — not a barrier (N=595). Among the questions and responses were:

- Reimbursement/financing issues: Definitely a barrier, GIM, 31%, FM: 44%, average 38%; somewhat of a barrier, 38%; not a barrier, 24%.
- Patients unwilling to pay if not covered: 37% - 43% - 20%.
- Up front vaccine purchase costs: 30% - 35% - 35%.
- Patients will not think they need this: (23% - 45% - 33%.
- Insufficient information about duration of protection: 22% - 40% -38%
- Insufficient information about safety: 17% - 35% - 48%

Barriers identified by <10% of providers included freezer storage; physician concern about safely administering a live attenuated virus to patients with chronic medical conditions; ineligibility of many patients if FDA retains the trials' contraindicated groups; and contraindication for use among immunosuppressed patients. Others included unknown varicella disease status by patients not living in the U.S. for the past 30 years or foreign-born, and the potential for accidental vaccination of a child.

Summary of findings:

- About 80% of FM and GIM providers strongly or somewhat agreed that HZ and PHN cause a significant disease burden in their older patients.
- A significantly higher percentage of physicians strongly agreed to a higher burden for

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patients aged 60-79 years, versus 50-59 years, to sufficiently to warrant a vaccine (FM 29% versus 17%; GIM 40% versus 15%).

- Overall, both FM and GIM providers were very- or somewhat likely to recommend HZ vaccination for all age groups, but significantly more would do so for patients aged ≥60 than those 50-59 years (FM 78% versus 60%, GIM 79% versus 57%).
- The major perceived barriers to vaccination were financial (the top 3; inadequate reimbursement, up-front costs, patient unwillingness to pay), followed by patients not perceiving the need and insufficient information about duration of protection and safety.

Shingles Prevention Trial, Zostavax®

Presenter: Dr. Paula Annunziato, Merck

Overview: Epidemiology/medical need of HZ, severity and burden (medical and non-medical) of disease; study population for ZOSTAVAX® and Shingles Prevention Studies; ongoing and planned activities.

ZOSTAVAX® would be the first intervention to prevent HZ and its complications, including PHN. Its efficacy and safety was demonstrated in a pivotal study of participants aged >60 years. FDA is reviewing its license application now.

Herpes zoster epidemiology The increase of HZ incidence with advancing age was clearly charted by decade, with almost half (46%) occurring after age 60. PHN is the pain that persists after resolution of an HZ rash. It occurs in 10-20% of HZ patients, but in ≤30-50% of those aged >60. Estimated prevalence is ~500,000 cases in the U.S., with new incidence of 100-200,000 annually.

A study of pain severity (Katz J, Melzack R, *Surg Clin N Amer* 1999;79:231-52) was reported by patients with painful syndromes. The pain scores of zoster and PHN were exceeded only by those for abdominal hysterectomy and acute headache. HZ and PHN pain scores surpassed those for childbirth, fibromyalgia, chronic cancer and musculoskeletal pain.

Disease burden. HZ causes 50-60,000 related hospitalizations annually (average stay of 5-7 days) in the U.S., 12-15,000 of them with a primary HZ diagnosis. Yearly, about 3 million HZ-related ambulatory care visits occur, averaging 3 visits per episode, and 33% involve at least one visit to a specialist. But HZ patients with pain for ≥90 days have >10 visits on average. The non-medical burden in the U.S. includes work and productivity loss, preliminarily estimated at an average of 3-7 days per HZ case. That equates to >600 to 750 thousand work days lost annually in the 50-59 year old category alone. Quality of life is severely affected in terms of physical, functional, social and psychological status.

Zostavax® clinical development program. The Zostavax® clinical trial enrolled >20,000 participants, mostly Caucasian, gender balanced and aged 30-99 years, with a variety of underlying medical conditions (except for altered immune status or past HZ history). The largest study in this program was the Shingles Prevention Study (SPS).

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Shingles Prevention Study (SPS). This was a double-blind, placebo-controlled, multi-center trial at 22 sites from November 1998 to April 2004. A collaboration between the VA, NIH, and Merck, it enrolled 38,546 subjects ≥60 years of age who were age-stratified (from 60-69 and ≥70 years. Nine of ten subjects had ≥1 underlying medical condition. The subjects were randomized equally between ZOSTAVAX® or placebo. The ZOSTAVAX® was administered at its potency just prior to expiration, to ensure a conservative conclusion. Monthly telephone follow-up was done to identify HZ cases and to monitor adverse events (AE), and all subjects were actively contacted at the study's end.

The most frequently reported prior medical conditions were arthritis and hypertension, followed by a prostate disorder, allergic reaction, GI disorder, hypothyroidism and hypercholesterolemia. Many other conditions were also, but less frequently, reported. VE was assessed by HZ incidence, PHN incidence, and zoster pain burden. The latter combined the incidence, severity and duration of zoster-associated pain.

Results were as follow:

- *Incidence of zoster,* compared to placebo, was reduced by 51.3%; PHN incidence dropped by 66.5%, and zoster pain burden of illness dropped by 61.1%.. Interestingly, VE differed against HZ according to age strata, being higher in the younger 60-69 year-old age group (63%) versus those >70 (38%). VE against PHN and zoster pain burden of illness was similar between the two age groups. The greater VE for the younger age group appears to be from prevented HZ cases and their subsequent PHN and other complications. For the older age (>70) group, the vaccine benefits are HZ cases prevented and pain amelioration for breakthrough cases.
- To assess VE among more frail persons, the subjects' baseline QALY scores related to functional limitations due to health status were assessed. About half the SPS subjects had at least some limitation in their functional status, defined among ~10% as moderate or severe. VE against HZ was well preserved in those groups, at ~50% among persons with self-rated mild, moderate, or severe limitation. The VE for PHN was similarly well preserved; the VE in these subgroups was ~60%, close to the 67% overall study VE. A similar ~60% VE against zoster pain burden of illness also was seen in these subgroups.
- *Duration of protection*. The study subjects were followed for an average of 3.1 years (some for ≤5 years) to assess VE. The data showed it to be well preserved through year 4, but data are still too few to be conclusive. However, a trend was apparent for high VE after the first year of vaccination: 62% for HZ, 85% for PHN, and 79% for herpes zoster burden of illness. The VE rises after year 1 to be very stable on all three end points.

Safety. The ZOSTAVAX® safety data were built on the extensive VARIVAX® safety database of 56 million doses distributed since licensure in 1995. A clinical evaluation compared the >20,000 subjects vaccinated with ZOSTAVAX® to >19,000 placebo controls. The large cohort and trial database allows study power sufficient for even some uncommon adverse experiences (i.e., 97% power to detect events at 1.8 /10,000 frequency and 80% power to detect 0..8/10,000). Across eight Zostavax® studies to date, the vaccine has been well tolerated.

- *Adverse events* reported in the SPS were recorded and assessed during the trial and in the safety follow-up period to day 42. SAEs were evenly distributed between the number and percentages of patients across the vaccination groups (i.e., 255 in the Zostavax® group,

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254 in the placebo group). An AE monitoring sub-study provided vaccine report cards for nonserious adverse experiences, which also were followed through the study for hospitalizations for any reason. That sub-study showed a difference in the number and percent of subjects who reported serious AEs (SAE), at 0.64 subjects in the Zostavax® group and 0.41 in the placebo group, which was statistically significant. But the reverse was also true, almost exactly, in the slight difference between the subjects who did not receive the vaccine report card, which balanced out the overall cohort. The Zostavax® group reported 191 SAEs and the placebo group reported 213.

- The reported SAEs included five serious ones possibly related to vaccine: two in the Zostavax group (asthma exacerbation and a case of polymyalgia rheumatica) and three in the placebo group. Mortality was balanced between the two groups. The SAEs were listed by groups and were balanced overall. The most frequent was cardiovascular-related symptoms, at 0.4%, followed by general body- and central nervous system, and digestive systems, at 0.2%. For CVS, the smaller adverse event monitoring sub-study reports split, at 20 in the Zostavax® group and 12 subjects in the placebo group; for CNS, 12 in the Zostavax® and 6 in the placebo group. There was no clustering of similar events.

SPS non-serious events included:

- Local injection reactions were vastly higher in the Zostavax® group: at 48.3% versus 16.6% in the placebo group, but that is not unexpected in such a vaccine study. Systemic AEs overall were well balanced between the two groups, although there was some elevation in events of vaccine-related headache episodes. These were fairly low in frequency but were statistically significant, at 1.4% in the Zostavax group and 0.9% percent in the placebo group. All other vaccine-related events, including hospitalizations and deaths, were balanced between the two groups
- *Inadvertent vaccination*: There were no seronegative subjects found in the SPS. Two protocols looked specifically for this in adults; Zostavax® 003 and Varivax®
- *Rash*. Since Varivax® carries a small vaccine-associated rash risk, that was explored for Zostavax.® Analysis determined the post-vaccination rash rate to be much lower than that for Varivax®, with ~0.3% of subjects reporting one to day 42 after vaccination. Of those, only two had lesions containing the vaccine Oka strain VZV. However, those two subjects were not from the SPS, but from earlier studies. No PCRs done in the SPS to detect herpes zoster identified the Oka strain of VZV.

Study 49. Even in the tropical counties where 003 was conducted, only 21 of 1000 screened were seronegative. Protocol 49 also was an international study, which found only 17 of 142 aged >30 who were varicella seronegative. So, no related safety issues were found upon vaccinating these subjects, but it is very rare to find them.

Ongoing/Planned ZOSTAVAX® activities include the VA's continuation of its durability of efficacy study among in SPS subjects (persistence sub-study in 12 of 22 sites that should go out to ten years). Placebo groups' participants are being offered Zostavax® vaccination. Two clinical trials are ongoing; one a bridging study during the transition from frozen vaccine to a refrigerated formulation, and the other a study of concomitant administration of Zostavax® with inactivated influenza vaccine.

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In anticipation of licensure, a risk-management plan is in place to conduct postmarketing surveillance for adverse events, expand the already existing VZV identification program to allow PCR analysis of submitted clinical specimens, and expand the pregnancy registry to include subjects who received Zostavax.®

Summary. The extensive ZOSTAVAX® clinical database includes >40,000 subjects enrolled in the clinical trail program, of whom >20,000 were vaccinated. The vaccine was shown to prevent HZ (VE=51%), PHN (VE=67%), and reduce HZ pain burden of illness (VE=61%). Zostavax® efficacy persists for four years postvaccination, to date; further data are hoped to be released soon to extend that outer range. The vaccine elicits a VZV-specific CMI response and has a an excellent safety profile

There was no discussion following this presentation.

Public Comment.
Dr. Collette Curtis is an anesthesiologist at Emory University hospital who also works in pain management. She reported, of the many PHN patients seen, the particular debilitation among the elderly population. The pain has been described as like being burnt from within, and there is little that can be done for it. She recounted one story, to demonstrate how extreme the pain is, of a 70 year-old man who developed PHN in his thoracic dermatome. There were no openings to see him, until later that day, his son called demanding that he be seen, because he was at the kitchen table with a gun to his head, threatening to shoot himself. With our aging population, she expected to see many more developing PHN, and strongly supported vaccine development to prevent it.

Dr. Harry Strothers is a family physician and geriatrician, and is on the faculty of Morehouse School of Medicine. He agreed with Dr. Curtis about the personal aspect of PHN. The great difficulty of this condition, as opposed to other pain syndromes, is that it does not respond well to pain medications, and the patients become quite desperate. Added to that is that many have other problems, such as being immunocompromised, which make them even more debilitated and less likely to leave their bed for physical therapy to keep them ambulatory.

ACIP EVIDENCE BASED RECOMMENDATION CLASSIFICATIONS
Presenter: Dr. Daniel Fishbein, NIP

Overview: Background and discussion of the process, major changes (already presented and new)

The classifications of evidence on which to base ACIP recommendations have been in development since October 2003. Preliminary methods were first presented to the ACIP in February 2005, when the committee suggested that the evidence-based process be piloted on two ACIP recommendations. Continued work reviewed and adapted the evidence-based methods of the U.S. and Canadian Preventive Services Task Forces, the U.S. Task Force on Community Preventive Services, and the Oxford Centre for Evidence-Based Medicine.

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ACIP vaccination recommendations are unique in their two major components, value to individuals and to community health. Although not every recommendation has community health implications (e.g., no transmissibility), both need to be clear when they are present. The pilot project has helped develop a method useful to modify the recommendations to five analytical steps for the ACIP process:

1. *Develop an analytic framework.* An analytic framework was outlined for the committee. Its steps were similar for both individual and public health, addressing vaccine usefulness, safety, effectiveness and efficaciousness, economic implications, and other vaccination considerations of an ACIP recommendation. For communities, the framework considers whether vaccinating a large number of individuals prevents transmission. The rabies vaccine recommendation was used as an example of one of a few recommendations that need not be evidence based. There are no non-ACIP dosage regimens and it is administered intradermally. That is not approved in the U.S., but the vaccine saves lives worldwide. The statement would have two components: prophylaxis with rabies vaccine for pre- and post-exposure, with five doses of vaccine and human rabies immune globulin in addition to wound cleansing.

2. *Search for and collect the evidence*. The Working Group is searching for and collecting evidence through MEDLINE and the Cochrane library, bibliographies of relevant studies, and consultation with subject matter experts to find older or unpublished literature. Additional searches, data sources (e.g., VAERS) , or inclusion criteria are being specified by each vaccine working group. For rabies, a single study was found that used the ACIP-approved regimen, but for a vaccine no longer licensed in the U.S. (Wyeth's human diploid cell rabies vaccine). They included studies of other biologics not currently U.S.-licensed to gather efficacy and effectiveness data as an evidence base for rabies treatment. The data scarcity forced the use of data on intermediate (elicit an antibody response) as well as final health outcomes.

3. E*valuate the quality of the evidence.* A level of evidence is being assigned based on the design of the study reviewed. The quality of study execution is assessed by examining six categories of potential threats to internal validity: the population and intervention description; the sampling done; exposure and outcome measurements; the data analysis; the interpretation of results; and others. A rating of "good" involves no or one study limitation; "fair" involves 2-4 limitations and "limited" involves more than 5 limitations. For rabies, a postexposure table was provided as an example, for the simple rabies nerve-tissue brain vaccine and for the human diploid cell vaccine. Determining the quality of the evidence and the magnitude of the effect was the most challenging aspect of the exercise, and the ACIP's input was requested. The absence of community data was clearly represented by the one-armed (individual health effect) analytic framework for rabies vaccination. Additionally, there are almost no related economic data with which to calculate the cost effectiveness for the ACIP's postexposure treatment advice. The Working Group is developing CE models for common scenarios faced by clinicians, with the help of Dr. Martin Meltzer, and a model will be created to calculate the benefit of the annual investment in rabies postexposure prophylaxis, despite multiple unknowns.

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4. *Summarize the evidence*. The evidence is summarized on separate tables for each key aspect of efficacy and effectiveness, safety, and economics. The quality of the aggregate evidence is determined by looking at (1) design hierarchy and (2) quality of execution for all studies together. Finally the magnitude of effect is established by the combined outcomes and effect measures for all the reviewed studies.

5. *Convert the evidence into an overall recommendatio*n. The Working Group plans to use four evidence groupings: 1) Immunization is not recommended for the target group; 2) consider individually recommendation; 3) immunization is not recommended for the target group; and 4) evidence is insufficient to make an overall recommendation.

Several points in this process prompted vigorous discussion:

- Again, for rabies: although pre-exposure prophylaxis is critical in the animal kingdom, it has little application for humans, and the human treatment has virtually no community health component. And the question became, with no final health-outcome studies using the ACIP-approved vaccine regimen, on what evidence basis can the ACIP vote?
- One considerations debated by the Working Group was whether vaccination should be provided for free, which studies show improve uptake.
- Implementation of recommendations is already known to be difficult outside of the routine childhood vaccination schedule. Should the ability to implement be a consideration? Also in terms of implementation, what can a busy clinician do? They are already too busy to implement even a fraction of the most strongly recommended preventive services.
- How are off-label recommendations to be handled in an evidence-based protocol (e.g., an ACIP recommendation for a narrower range of a target population)? Fitting that into the model is not easy, nor is the fit of permissive language.

Next steps: The methods paper will be completed and presented at the June ACIP; the evidence-based rabies recommendation will be presented in June or October, and then followed by the evidence-based zoster recommendation.

Discussion included:

- Dr. Marcuse anticipated that the options (recommend; option; do not recommend; or no evidence base to be used) will ultimately require stratification as well. For example, would universal influenza immunization have equal weight to other recommendations, such as hepatitis B or measles?
- There is no set formula being developed to go from the design hierarchy and the quality of execution to a letter grade. Rather, the Working Group expects that the working group developing a statement/recommendation will suggest final recommendations, but the decision will still rest on the ACIP's judgment.
- Mr. Beck asked what value there is for an economic analysis that finds no cost effectiveness, as defined by the measures used for a community program. Dr. Fishbein answered that, while many interventions in the Community Guide may be cost saving, there are others that are not cost saving but are still relatively cost effective in terms of quality adjusted life years. He offered to explain this further after the meeting.
- Dr. Martin Myers wondered how this would affect the ACIP's harmonized

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recommendations with its partner organizations. Dr. Marcuse found it to harmonize beautifully with the AAP's evidence-based system and to be easily translatable.

- Dr. Pickering asked how this analytic framework compared or fit to others in use, and how well the ACIP's might be accepted by other organizations. Dr. Fishbein responded that the AHRQ is developing guidelines for the American College of Physicians to endorse the evidence-based recommendations of other organizations. Since the basis is evidence, there well could be some cross-endorsement. He was confident that this framework would fit the ACP's needs. He also shared a chart of the USPSTF grading system to show its compatibility with the ACIP's potential new system:

- Dr. Martin Myers

USPSTF	ACIP?
A Intervention **strongly** recommended	} Immunization recommended
B Intervention recommended	
C No recommendation for or against intervention	Consider individually
D Intervention not routinely recommended	Immunization not recommended
I Evidence insufficient to recommend for or against.	Evidence insufficient to make an overall recommendation

wondered how this would affect the ACIP's harmonized recommendations with its partner organizations. Dr. Marcuse found it to harmonize beautifully with the AAP's evidence-based system and to be easily translatable.

Closing comments.

With Dr. Abramson's thanks and no further comment, the meeting was adjourned at 4:03 p.m.

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

_____

Jon Abramson, MD, Chair

_____

Date

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Attachment : Attendance

Name	Organization
Dr. Shefer Abigail	Centers for Disease Control and Prevention
Jon S. Abramson MD	Wake Forest University School of Medicine
Kanowitz Adam	Families Fighting Flu
Samuels Alicia MPH	American Cancer Society
Rue Alison	Centers for Disease Control and Prevention
Kanowitz Alissa	Families Fighting Flu
Dr. Thierry Allavoine	Sanofi Pasteur Msd
Jennifer Allen	Merck & Co., Inc.
Ms. Friedman Allison MS	Centers for Disease Control & Prevention
Dr. Kempe Allison MD, MPH	University of Colorado Health Sciences Center
Ban Mishu Allos	Vanderbilt University
Norma Allred	CDCP NIP
Dr. Bandell Allyn Pharm.D.	Medimmune
Dr. Cohn Amanda	National Immunization Program
Mrs. Welsh Amanda	GlaxoSmithKline
Miss Whatley Amanda MPH	Centers for Disease Control and Prevention (Division of Global Migration and Quarantine)
Togba Amelia	Personal
Ms. Parker Amy MSN, MPH	Centers for Disease Control and Prevention
Pollack Amy E. MD, MPH	Columbia University
Dr. Chevez Ana MD MPH	Emory University
Dr. Chevez Ana E MD, MPH	Emory University
Dr. Dayton Ana E. MD	Constella Group
Mr. Padmanabhan Anant	SG Cowen
Dr. Calugar Angela MD, MPH	NIP/CDC
Ms. Makepeace Angelica RN, BSN	St. Joseph"s Hospital of Atlanta
Ms. Isenhower Anne	American Cancer Society
Dr. Schuchat Anne MD	Centers for Disease Control and Prevention
Paula W. Annunziato M.D.	Merck & Co., Inc.
Dr. Mounts Anthony M.D.	Centers for Disease Control and Prevention
Mr. Wisniewski Anthony	MedImmune, Inc.

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William Atkinson	National Immunization Program, CDC
James M Baggs	Centers for Disease Control and Prevention
Carol J. Baker	American Academy of Pediatrics
Dr. Jiang Baoming PhD	CDC
Ms. Bardenheier Barbara MPH, MA	CDC
Eliav Barr M.D.	Merck Research Laboratories, Merck & Co., Inc.
Michelle Basket	CDC
Dr. De Vos Beatrice MD	GlaxoSmithKline Biologicals
Robert L. Beck	Robert L. Beck: ACIP Voting Member
Sloat Ben MPH	Georgia Division of Public Health
Dr. Schwartz Benjamin	National Vaccine Program Office
Joan Benson MD, MPH	Merck & Co., Inc.
Stuart Berman	Centers for Disease Control and Prevention
Stevenson Beth MPH	Centers for Disease Control and Prevention
Anderson Bethany	National Immunization Program, CDC
Pollard Bette	Centers for Disease Control and Prevention
Achal Bhatt	CDC/NIP/ISD
Dr. Phelps Bill PhD	American Cancer Society
Kaafee Billah	MedImmune, Inc.
Gostout Bobbie MD	Society of Gynecologic Oncologists
Andrew Bowser	AB Writing and Editing, Inc. (media)
Damian Braga	sanofi pasteur
Teresa Lynnette Brammer	Centers for Disease Control and Prevention
Camp Brendan	Centers for Disease Control and Prevention
Rutland Brent	sanofi pasteur
Joseph Bresee	Influenza Branch, CDC
Mr. Katzowitz Brian	Children"s Healthcare of Atlanta
Dr. McAlvin Brian MD	Emory University
Edward W Brink	CDC/National Immunization Program/Program Operations Branch
Karen R. Broder	National Immunization Program, CDC
Dennis Albert Brooks	Merck & Co., Inc
Kristin Brown	CDC-NIP (contractor through SAIC)
Dr. Gellin Bruce MD, MPH	Department of Health and Human Services
Judith R. Campbell M.D.	Advisory Committee on Immunization Practices

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Scott Campbell	CDC
Doug Campos-Outcalt	American Academy of Family Physicians
Maria Victoria Cano	Centers for Disease Control and Prevention
Mr. Garcia-Tunon Carlos	Morgan Stanley
Ms. Henderson Caroline	Emory University
Dr. Bridges Carolyn MD	CDC
Dr. Deal Carolyn	National Institutes of Allergy and Infectious Diseases, NIH
Dr. Runowicz Carolyn MD	University of Connecticut Health Center
Christine Casey	Centers for Disease Control and Prevents
Dr. Hanlon Cathleen VMD	CDC
rupprecht charles	cdc
Thompson Charlis	CDC/NIP
James E. Cheek	Indian Health Service
Ana Elena Chevez	Emory University
Bo-Hyun Cho	National Immunization Program
Dr. Coffey Chris MD	Ross Clinic
Dr. Shibutani Chris MD	JPMorgan - Healthcare Research
Gause Christine PhD	Merck & Co., Inc.
Miss Stephen Clarencia	MedImmune, Inc.
vellozzi claudia md, mph	cdc/nip
Dr. Lewin Clement	Acambis
Stephen L. Cochi	Centers for Disease Control and Prevention
Kathleen Coelingh	MedImmune Vaccines
Dr. curtis colette M.D.	Emory University Hospital
Estivariz Concepcion MD	National Immunization Program, Centers for Disease Control and Prevention
Lenore Cooney	Cooney Waters
Nancy J. Cox	Centers for Disease Control and Prevention
Mr. Heit Craig	Cooney/Waters Group
Suhr Cristen MPH	Centers for Disease Control (Contractor)
George Tams Curlin	National Institutes of Health
Dr. Jorgensen Cynthia DrPH	CDC
Miss Knighton Cynthia	Centers for Disesase Control and Prevention
Mr. Babcock Dale	National Immunization Program

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Dr. Morse Dale MD, MS	New York State Department of Health
Dr. Guris Dalya MD, MPH	CDC
Mr. Braga Damian	Sanofi pasteur
Dr. Gordon Daniel MD	Sanofi Pasteur Inc
Dr. Payne Daniel PhD	Centers for Disease Control
Natalie J. Darling	CDC
Dr. Salisbury David CB	Department of Health
Dr. Schofield David Pharm D	GlaxoSmithKline
Jill Davila	CDC - LHI
Xiaohong Davis	CDC/DVRD/Influenza
Anna DeBlois	Association of State and Territorial Health Officials
Shelley Deeks	Public Health Agency of Canada
Dr. Kruzikas Denise PhD	GlaxoSmithKline
Penelope H. Dennehy M.D.	American Academy of Pediatrics
Ms. Gaffoglio Diane	Nancy Lee & Associates
Dr. Simpson Diane MD, PhD	National Immunization Program
Dr. CAMPENS Dirk	GLAXOSMITHKLINE BIOLOGICALS
Mr. Dalrymple Donald "Dack"	Dalrymple & Associates, LLC
Humphrey-Franklin Donelle	Public Health
Dr. Rickert Donna DrPH	Centers for Disease Control
Jag Dosanjh	GlaxoSmithKline
Mr. Kilgus Duane	Centers for Disease Control and Prevention
Gary Dubin	GlaxoSmithKline Biologicals
Eileen Dunne	CDC
Mr. Gwozda Ed	GlaxoSmithKline
Reed Eddie MD	DCPC, NCCDPHP, CoCHP, CDC
Dr. Yamada Eileen	Immunization Branch, California Department of Health Services
Dr. Perry Elaine MD	Merck and Co., Inc.
Elbasha Elamin	Merck & Co., Inc
Goss Elizabeth	Ropes & Gray
Unger Elizabeth PhD, MD	Centers for Disease Control and Prevention
Mr. Weintraub Eric	CDC/OCSO/ISO
Dasbach Erik PhD	Merck Research Laboratories
Grau Erik	sanofi pasteur

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Burns Erin	Influenza Branch, Centers for Disease Control and Prevention
Ms. Joseph Eugenia	parents
Gary L. Euler	Centers for Disease Control and Prevention
Geoffrey Evans M.D.	National Vaccine Injury Compensation Program, Health Resources and Services Administration
James Everette Evans	Sound On-Site, Inc.
Dr. Soud Fatma PhD, RN	Immunization Safety Office
Mark B. Feinberg MD, PhD	Merck & Co., Inc.
Mr. Han Feng	Henry Schein, Inc
Reginald Finger	ACIP member (no affiliation)
Daniel B. Fishbein	CDC
Amanda Foley	GlaxoSmithKline
Stephen M. Ford	Military Vaccine Agency
Stephan L Foster Pharm.D.	ACIP Liaison Representative - APhA
Dr. Lebel Francois	MedImmune Inc.
Dr. Malinoski Frank	MedImmune, Inc.
Dr. Clark Fred PhD	The Children"s Hospital of Philadelphia
Mr. Wyand Fred	American Social Health Association
Leonard R Friedland	GlaxoSmithKline
Miss Sylvina Frutos	GlaxoSmithKline
Jeffrey Fu PhD	Merck & Co., Inc.
Dr. Xu Fujie MD, PhD	Centers for Disease Control and Prevention
Stanley A. Gall M.D.	The American College of Obstetricians and Gynecologists
Sandra Gambescia	Centers for Disease Control and Prevention
Demetria Gardner	Centers for Disease Control and Prevention
Paul M. Gargiullo	Centers for Disease Control and Prevention; National Immunization Program; Epidemiology and Surv eillance Division
Mr. Stein Gary	Families Fighting Flu
Diana Gaskins BSN, MSN	Division of Public Health, Georgia Immunization Program
Mr. Porges Geoff PhD	Sanford C. Bernstein
Dr. Garnett Geoffrey PhD	Imperial College London
Dr. Porges Geoffrey	Sanford Bernstein
Jeff George M.D.	New York,
Jeffrey George	TDG Inc.

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Peter Georges MD	Brown Medical School
Ruth Gilmore	Georgia Immunization Program
Janet R. Gilsdorf	University of Michigan
Dr. Mootrey Gina DO, MPH	Centers for Disease Control and Prevention
Roger Glass	CDC
John W. Glasser	Centers for Disease Control and Prevention
JIll Gordon-Evans	Sound On-Site, Inc.
Michelle G. Goveia	Merck Research Laboratories, Merck & Co., Inc.
Jesse Earl Greene	South Carolina Department of Health and Environmental Control
Amy Groom	Indian Health Service
Dr. Herrera Guillermo MD, MBA	CDC
Jill G. Hackell	Wyeth
Neal Arthur Halsey	Johns Hopkins University
Danielle Halstrom	GlaxoSmithKline
Claire Hannan	Association of Immunization Managers
Mr. Chesson Harrell PhD	Centers for Disease Control and Prevention
Dr. Strothers Harry MD, MMM	Morehouse School of Medicine
Richard M. Haupt M.D.	Merck & Co., Inc.
Penny M. Heaton	Merck Research Laboratories
Dr. Baggett Henry MD, MPH	Centers for Disease Control and Prevention
Teresa M. Hesley	Merck & Co., Inc.
Beth F. Hibbs	CDC OD OSCO ISO
Mark Hirth	Merck & Co., Inc
Barbara J Howe	GlaxoSmithKline
Dr. BOGAERTS Hugues	GLAXOSMITHKLINE BIOLOGICALS
Dr. Harry Hull	Minnesota Department of Health
Harry Frazer Hull	Minnesota Department of Health (member ACIP)
Gina Hunt	Merck & Co., Inc.
Dr. Jevaji Indira MD	Health Resourses and Services Adminstration
Bruce L. Innis M.D	GlaxoSmithKline
Dr. Chan Ivan	Merck Research Labs
Dr. Alexander James Jr.	CDC
Kelly James	Goldman Sachs
Dr. Pellissier James	Merck Research Laboratories

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Ransom James	NACCHO
Mr. Singleton James	National Immunization Program, CDC
Mr. Harrison James R. MAPA	CDC/CCID/National Immunization Program
Ms. Agosti Jan MD	Bill & Melinda Gates Foundation
Dr. Gidudu-Nsubuga Jane MD,MPH	Immunization Safety Office, Office of the Chief Science Officer,CDC
Ms. Quinn Jane	GlaxoSmithKline
Dr. Seward Jane MBBS, MPH	CDC
Dr. Zucker Jane MD, MSc	New York City Department of Health and Mental Hygiene
Ms. Skidmore Janet	Merck & Co., Inc.
Shirley Jankelevich	South Carolina Department of Health and Environmental Service
Dr. Hong Jason PhD	Sanford C. Bernstein
Mr. Schwartz Jason MBE	University of Pennsylvania Center for Bioethics
Bauman Jay	MedImmune, Inc.
Mr. Hackman Jeff	MedImmune, Inc.
Dr. Chodakewitz Jeffrey MD	Merck & Co.
Dr. Cooper Jeffrey MD	Cooper Pediatrics, PC
Dr. Duchin Jeffrey MD	Public Health Seattle & King County
Dr. Silber Jeffrey	Merck & Co., Inc.
Mr. Stoddard Jeffrey MD	MedImmune, Inc.
Ms. Huntington Jennifer	Emergent BioSolutions
Mrs. Lastinger Jennifer	Families Fighting Flu
Tai Jennifer MD	Vanderbilt University School of Medicine
Ms. White Jennifer	Ketchum
Ms. Zavolinsky Jennifer MHS, CHES	Every Child By Two
Mr. Shelton Jerry RPh	Merck Vaccine Division
Mr. Blanton Jesse MPH	Centers for Disease Control and Prevention
Ms. Leung Jessica	National Immunization Program
Ms. Xi Jian	GlaxoSmithKline
Hackell Jill MD	Wyeth Vaccines Research
Dr. Buffington Joanna	Centers for Disease Control and Prevention
Kearney Joanne	Solvay Pharmaceuticals
Mr. Lastinger Joe	Families Fighting Flu
Dr. Modlin John MD	Dartmouth Medical School

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Mr. Vittas John	Families Fighting Flu, Inc.
Dr. Douglas, Jr. John M. MD	Centers for Disease Control and Prevention, National Center of HIV, STD & TB Prevention, Divison of STD Prevention
David Rue Johnson MD, MPH	sanofi pasteur
Tanya A. Johnson	Oak Ridge Institute for Science and Technology (ORISE)/CDC/National Immunization Program (NIP)
Mary Suzanne Johnson-DeLeon	Centers for Disease Control and Prevention
Dr. Bocchini, Jr. Joseph M.D.	American Academy of Pediatrics
Dr. Heyse Joseph	Merck Research Laboratories
Mr. Sullivan Joseph	Merck & Company, Inc.
M. Patricia Joyce M.D.	Centers for Disease Control
Mrs. Magner Judith	GlaxoSmithKline Pharmaceuticals
Miss Rusk Judith	Infectious Diseases in Children and Infectious Disease News
Dr. Shindman Judith	sanofi pasteur Limited
Dr. Schmidt Judy EdD	CDC NIP EIPB
Ms. Gee Julianne	Centers for Disease Control and Prevention
Ms. Schafer Julie MPH, MS	Office of the Secretary, Department of Health and Human Services
Laurie Kamimoto	CDC
Ms. Mason Karen MPA	National Immunization Program
Mrs. Townsend Karen RN	Georgia Chapter American Academy of Pediatrics
Ms. Sapsis Kari MPH	National Immunization Program-CDC
Mr. Iqbal Kashif	NIP/CDC
Dr. Poehling Katherine MD, MPH	Vanderbilt University Medical Center
Dr. Neuzil Kathleen MD,MPH	PATH
Ms. Harbour (Felton) Kathryn	Centers for Disease Control and Prevention
Dr. Kohl Katrin MD, PhD, MPH	Centers for Disease Control and Prevention
Mark Katz	Centers for Disease Control and Prevention
Samuel Lawrence Katz	Infectious Diseases Society of America
Mrs. Dougherty Kelley	Merck & Co., Inc.
Ms. Green Kahn Kelly MPA	American Cancer Society
Conzen Kendra	CDC Div Global Migration and Quarantine
Mr. Bart Kenneth MD, MPH, MSHPM	Department of Health and Human Services, National Vaccine Program Office
Mr. Dennison Kenneth	Wyeth Pharmaceuticals
Dr. Schmader Kenneth	Duke University/Durham VA Medical Centers

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Dr. Ault Kevin MD	Emory University School of Medicine
Dr. Hazelwood Kimberley Pharm D	Public Heatlh
Dr. workowski kimberly md	centers for disease control and prevention
Maureen Kolasa	Centers for Disease Control
Katrina Kretsinger	National Immunization Program, CDC
Armendariz Kris	Society of Gynecologic Oncologists
Mrs. Charlotte Kroft	GlaxoSmithKline
Barbara J. Kuter Ph.D., MPH	Merck & Co., Inc.
Dr. Anderson Larry MD	DVRD, NCID, CDC
Philip S. LaRussa	Columbia University
Ms. Leidel Laura	Centers for Disease Control and Prevention/Office of Director/Immunization Safety Office
Miss Richardson Laura	Influenza Branch-CDC
Mrs. Johnson Laurie	Centers for Disease Control and Prevention
Len Lavenda	sanofi pasteur
Herschel W. Lawson	Centers for Disease Control and Prevention
Charles W. LeBaron	NIP
Dr. Bennett LEE	SANOFI PASTEUR MSD
Marie-Michele Leger	American Academy of Physician Assistants
Laura Leidel	Centers for Disease Control and Prevention
Ms. Cooney Lenore C	Cooney/Waters Group
Roland A. Levandowski M.D.	National Institutes of Health
Tracy Lieu	Harvard Pilgrim Health Care and Harvard Medical School
Anna M. Likos	Centers for Disease Control and Prevention
Dr. Alexander Linda PhD	Digene Corporation
Ms. Russell Lola	CDC, OD Media Relations
Mr. Thomas Lonnie	Henry Schein Incorporated
Adriana Lopez MHS	Centers for Disease Control and Prevention
Dr. Gavin Loretta MPH, PhD	Division of Reproductive Health, CDC
Suchita A. Lorick	CDC/NIP/ISD
Douglas R. Lowy M.D	National Cancer Institute, National Institutes of Health
Beverly J. Lybrand	Merck & Company, Inc.
Ms. Bahta Lynn RN	Minnesota Department of Health
McIntyre Lynne	Centers for Disease Control and Prevention

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Dr. Otten Mac MD	CDC, NIP
Andrew Macknight	GlaxoSmithKline
Susan Patricia Malone	Coastal Health District 9-1
Dr. Patel Manisha MD	Centers for Disease Control and Prevention
Susan E. Manning	CDC
Edgar K. Marcuse MD, MPH	Children"s Hospital and Regional Medical Center
Cortese Margaret	CDC
Ms. McGlynn Margaret	Merck & Co., Inc.
Watkins Margaret	CDC
Ms. Murray Marie	SoWrite
Lauri Markowitz	Centers for Disease Control and Prevention
Tanner Wilson Marsha	Society of Gynecologic Oncologists
Ms. Doroshenk Mary MA	American Cancer Society
Mrs. Eiken Mary	Society of Gynecologic Oncologists
Ms. Mulholland Mary	National Immunization Program
Dr. Staat Mary M.D., MPH	Associate Professor of Pediatrics, Cincinnati Children"s Hospital Medical Cente
Dr. Lindegren Mary Lou MD	CDC
Christopher Mast	Merck Research Laboratories
Eric Edward Mast	Centers for Disease Control and Prevention
Dr. Esona Mathew Ph.D	CCID/Centers for Disease Control and Prevention
Mr. Garrett Matt	Wyeth Vaccines
Mr. David Matthew MD	Independent
Hogben Matthew PhD	Centers for Disease Control and Prevention
Dr. Ciarlet Max	Merck & Co., Inc.
Dr. El Sherif May MD	Centers for Disease Control and Prevention
Mary McCauley	National Immunization Program
William Paul McKinney	University of Louisville School of Public Health and Information Sciences
Lindley Megan MPH	National Immunization Program/ Centers for Disease Control & Prevention
Wharton Melinda	National Immunization Program, CDC
Ms. Arvay Melissa	CDC
Miss Habel Melissa	CDC, Division of STDP, BIRB
Lynne Mercedes	Georgia Division of Public Health

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Dr. Decker Michael	sanofi pasteur
McNeil Michael MD	CDC
Dr. Pride Michael PhD	Wyeth Research
Tidwell Michelle RN, BSN	Georgia Chapter American Academy of Pediatrics
Amy B. Middleman MD, MPH, MS Ed	Baylor College of Medicine
Christina M. Mijalski	Centers for Disease Control, National Immunization Program
Elaine R. Miller	Centers for Disease Control and Prevention (CDC)
Tucker Miriam E.	Pediatric News
Ann Moen	Centers for Disease Control
Ms. Gaul Moira MPH	Family Research Council
Dr. Marin Mona MD	CDC
Dr. Saraiya Mona MD, MPH	CDC
Martha C. Monroe	Centers for Disease Control
Kelly Lynn Moore MD, MPH	Tennessee Department of Health
John S. Moran	Centers for Disease Control and Prevention
Julie Morita	Chicago Department of Public Health
Dale Morsr M.D.	New York State Department of Health
Linda S. Murphy	Centers for Medicare & Medicaid Services
Trudy Murphy	Centers for Disease Control and Prevention
Martin G. Myers	National Network for Immmunization Information
Dr. Cox Nancy PhD	Centers for Disease Control and Prevention
Ms. Fasano Nancy	National Immunization Program CDC
Ms. Roach Nancy	n/a
Mrs. Stoback Nanette	sanofi pasteur
Ms. Revzina Natalya MD	Centers for Disease Control and Prevention
Dr. Monika Naus	on behalf of Public Health Agency of Canada; British Columbia Centre for Disease Control
Mr. Agran Neal	Sanford Bernstein
Deb Neivert	MedImmune
Thomas M. Netzer	Merck & Co., Inc.
Kristin Lee Nichol	Department of Veterans Affairs Medical Center
Dr. Liddon Nicole	Centers for Disease Control and Prevention
Karen H Nielsen	GlaxoSmithKline
Ms. Dahill Noreen	GlaxoSmithKline

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Dr. Baylor Norman Ph.D.	Food and Drug Administration
Glen Nowak	Centers for Disease Control and Prevention
Dennis J. O"Mara	Immunization Services Division, National Immunization Program, CDC
M. Carolyn O"Mara	Centers for Disease Control and Prevention, Health Marketing, Creative Services
Paul Allan Offit MD	The Children"s Hospital of Philadelphia
Peter R. Paradiso	Wyeth
Umesh Parashar	CDC
Smith Parker	Parker Smith Photography
Mr. BAROLLIER Pascal	GlaxoSmithKline
Wortley Pascale	CDC
Manisha Patel	CDC, NIP
Dr. Offit Paul MD	The Children"s Hospital of Philadelphia
Mrs. Rose Paula	GlaxoSmithKline Pharmaceuticals
Christine Pearson	Centers for Disease Control and Prevention
Michele Pearson	Centers for Disease Control and Prevention
Dr. Nuorti Pekka MD, DSc	Centers for Disease Control and Prevention
Haber Penina MPH	CDC
Mrs. Heaton Penny MD	Merck & Co., Inc.
Mr. Sprigg Peter	Family Research Council
Diane C. Peterson	Immunization Action Coalition
Mr. Hosbach Philip	sanofi pasteur
Dr. MONTEYNE Philippe MD, PhD	GlaxoSmithKline Biologicals S.A.
Ms. Arthur Phyllis	Merck & Co Inc
Larry K. Pickering	Centers for Disease Control and Prevention
Cheng Po-Yung Ph.D.	CDC/NCID/DVRD/I/ES
Gregory A. Poland	Mayo Clinic and Foundation
Alicia Postema	CDC/CCID/NCID/DVRD/Influenza
Keith R. Powell	American Academy of Pediatrics, Committee on Infectious Diseases
Dr. Kutty Preeta MD, MPH	Centers for Disease Control and Prevention
Dr. Eidex Rachel PhD	Centers for Disease Control and Prevention
Mrs. Hlay Rachel	GlaxoSmithKline
Aaron Thomas Rak	CDC, NIP, ISD

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Dr. Strikas Raymond M.D.	National Immunization Program
Ms. Werth Rebecca	GlaxoSmithKline
Dr. Turcios Reina	Centers for Disease Control and Prevention
Dr. Jenkins Renee R. MD	Howard University
Margaret Rennels	GlaxoSmithKline
Margaret B Rennels	GlaxoSmithKline
Mr. Dinovitz Richard	Wyeth Pharmaceuticals
Dr. Dixon Richard M.D.	Centers for Disease Control and Prevention; NCHM; DPPP
Dr. Franka Richard PhD.	Centers for Disease Control and Prevention
Kanowitz Richard	Families Fighting Flu
Dr. Salmon Richard DO	Children"s Healthcare of Atlanta at Scottish Rite
Mr. Nelson Rick	National Immunization Program/CDC
Donna Rickert	Centers for Disease Control and Prevention
Dr. Helfand Rita	CDC
Dr. Itzler Robbin PhD	Merck Research Laboratories
Mr. Morlend Robert	Centers for Disease Control
Mr. Oliver Robert	Wyeth Pharmaceuticals
Perry Robert M.D.	Centers for Disease Control and Prevention
Dr. Steinbrook Robert M.D.	New England Journal of Medicine
Mr. Cuca Roberto	JP Morgan
Dr. Womeodu Robin MD	Methodist University Hospital
Lance E. Rodewald M.D.	National Immunization Program, CDC
Von Roebuck	Centers for Disease Control and Prevention
Dr. bernier roger phd	nip
Dr. Levandowski Roland MD	National Insitutes of Health, National Insititue of Allergy and Infectious Diseases
Dr. Rodriguez Romeo	CENSIA (SS)
Mr. Hibshoosh Ron	Goldman Sachs JBWere
Mr. Van Duyne Ron	Immunization Information Systems, NIP, CDC
Ms. Dhara Rosaline MA.,MPH	CDC
Dr. Tiernan Rosemary MD, MPH	Division of Vaccines, Center for Biologics, FDA
Sandra W. Roush	CDC/NIP/ESD
Beth Rowe-West	DPH-DHHS-NC Immunization Branch
Dr. Patricia Saddier MD, PhD	Merck Research Laboratories

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Turner Sam	Ropes & Gray
Dr. Katz Samuel MD	Duke University Medical Center
Dr. Dos Santos Chaves Sandra MD	Centers for Disease Control and Prevention
Tammy A. Santibanez	National Immunization Program
Dr. Jeanne M. Santoli MD, MPH	CDC NIP
Ms. Landry Sarah	GlaxoSmithKline
Ms. Spurgeon Sarah	New England Healthcare Institute
Mona Saraiya	CDC
Debbie Saslow PhD	American Cancer Society
Carlos Sattler M.D.	Merck & Co., Inc.
William Schaffner MD	Chairman, Department of Preventive Medicine, Vanderbilt University School of Medicine
Florian Schodel M.D	Merck Research Laboratories
Anne Schuchat	Centers for Disease Control and Prevention
Dr. Schmid Scott PhD	Centers for Disease Control and Prevention
Ms. Shapowal Sharon	GlaxoSmithKline Pharmaceuticals
Kate M. Shaw	CDC
David K Shay	CDC
Dr. Leader Shelah PhD	Medimmune
Tom Shimabukuro	CDC/NIP
Alan J. Sievert M.D., M.P.H.	American Academy of Pediatrics-Georgia Chapter
Dr. Staprans Silvija PhD	Emory University Vaccine Center
Thomas W. Skinner	CDC
Eric T. Skjeveland	Merck Vaccine Division
Barbara A. Slade M.D.	Centers for Disease Control
Ianthia Smith	Kaiser Permanente
Dr. Jean Clare Smith	Medical Officer, Assistant to the Director for Immunization Policy, NIP, CDC
Nicole Michelle Smith	Centers for Disease Control and Prevention/Influenza Branch
Pamela Srivastava	Centers for Disease Control
Ms. Hoffman Stacey	Centers for Disease Control
Dr. Plotkin Stanley MD	Sanofi Pasteur
Ms. Steele Stefanie	CDC
Renna Stephanie	National Immunization Program

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Dr. Cochi Stephen MD	Centers for Disease Control and Prevention
Mr. Yoo Steve	Sanford Bernstein
Dr. Gordon Steven MD	Cleveland Clinic Foundation
Dr. Rosenthal Steven MD	FDA/CBER
Mr. Vignau Steven	Merck & Co., Inc.
Patricia (Patsy) Stinchfield CPNP	Children"s Hospitals and Clinics of Minnesota
Shannon Stokley	Centers for Disease Control and Prevention
Raymond A. Strikas M.D.	CDC NIP
Stacy Stuerke	Merck Vaccine Division
Mrs. Crosby Susan	Women In Government
Ms. Garfield Susan	Digene Corporation
Dr. Lett Susan MD	MA Dept Public Health
Dr. Reef Susan MD	CDC, NIP
Ms. Van Aacken Susan	National Immunization Program
Ms. Watkins Susan	Sanofi pasteur
Ms. Matter Susanna	Leerink Swann
Ms. LAW Suzette	Centers for Disease Control and Prevention
Dr. Gregg Sylvester	Merck & Co., Inc.
Litjen (L.J) Tan	American Medical Association
Ms. Malik Tasneem	CDC/National Immunization Program
Jonathan L. Temte MD/PhD	American Academy of Family Physicians
Ms. Rutledge Teresa BA	Centers for Disease Control and Prevention
Andrew Kroger Thaddeus	Centers for Disease Control and Prevention
Dr. Allavoine Thierry	SANOFI PASTEUR MSD
Dr. Uyeki Tim MD, MPH, MPP	Centers for Disease Control and Prevention
Mr. Wang Tim	UBS Securities
Mr. Obara Timothy	GlaxoSmithKline
Tejpratap S. P. Tiwari MD	Centers for Disease Control and Prevention
Dr. Shimabukuro Tom MD, MPH, MBA	CDC/NIP
John Treanor	University of Rochester
Monica Trigg	Georgia Immunization Program
Ms. Watson Tureka L.	McKing Consulting Corporation
James C. Turner MD	American College Health Association
James P. Tursi M.D.	GSK Biologicals

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Mr. Jodhpurkar Uday	Sanofipasteur
Elizabeth R. Unger	Centers for Disease Control and Prevention
Thomas M. Vernon MD	Consultant to Vaccine Companies
Dr. Benard Vicki	CDC
Peter Vigliarolo	Cooney Waters Group
Mr. Ahonkhai Vincent M.D.	GlaxoSmithKline Pharmaceuticals
Charles Vitek	CDC (National Center for HIV, STD, and TB Prevention)
Cara Vivarelli-O"Neill	Merck & Co., Inc
Mr. Garrett W. Matthew	Wyeth
Gregory S. Wallace	Centers for Disease Control and Prevention
Teresa R. Wallis	Centers for Disease Control and Prevention
Dr. Orenstein Walter MD	Emory University
Elisabeth A. Ward	Georgia Division of Public Health
Barbara May Watson	Division of Disease Control, Immunization Program, The Philadelphia Department of Public Health
Dr. Hachey Wayne DO, MPH	Department of Defense
Donna L. Weaver	National Immunization Program, CDC
David Webster	Webster Consulting Group
Bruce G. Weniger MD	CDC
Deborah L. Wexler MD	Immunization Action Coalition
Mark Alan Whitaker M.D.	America"s Health Plans
Marc -Alain Widdowson	Centers for Disease Control and Prevention
Eddie L. Wilder	CDC, NID, ISD
Dr. Thompson William PhD	OCSO/Immunization Safety Office
Dr. Vecino William MD	MKGNY
Amy Wishner	PA Chapter, American Academy of Pediatrics
Charles (Skip) Wolfe	National Immunization Program
Eileen L Yee (Lau)	Centers for Disease Control and Prevention
Elizabeth York	GlaxoSmithKline
Laura Jean York	Wyeth
Dr. Moore Zack MD	Emory University
John M. Zahradnik	sanofi pasteur
Fangjun Zhou	NIP

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