CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL IMMUNIZATION PROGRAM

RECORD OF THE MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

June 29-30, 2005

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

Acronyms Used In This Report

AAFP	American Academy of Family Practitioners
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
AIM	Association of Internal Medicine
AMA	American Medical Association
ASCUS	Atypical Squamous Cells Of Undetermined Significance
ASTHO	Association of State and Territorial Health Officers
BCR	Benefit Cost Ratio
BRFSS	Behavioral Risk Factor Surveillance Survey
CDC	Centers for Disease Control and Prevention
CER	Cost Effectiveness Ratio
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment Network
CSTE	Council of State and Territorial Epidemiologists
CMI	Cell-Mediated Immunity
COID	Committee on Infectious Disease (AAP)
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DTaP	Diptheria, Tetanus, Acellular Pertussis (vaccine)
ED	Emergency Department
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
FHA	Filamentous Hemagglutinin (antigen)
FIM	Fimbirae (antigen)
GMC	Granulocyte Macrophage Colony
GMT	Geometric Mean Titer
gp	Glycoprotein
GSK	GlaxoSmithKline
HBIG	Hepatitis B Immune Globulin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus (Vaccine)
HC2	Hybrid Capture 2 (HPV test)
HICPAC	Hospital Infection Control and Prevention Advisory Committee
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HPV	Human Papilloma Virus
Ig	Immune Globulin (IgA, class A; IgG, class G)
IPV	Injected Polio Vaccine
LPA	Lymphocytic Proliferation Assay
MBPHL	Massachusetts Biologics Public Health Laboratory
VAPP	Vaccine Associated Paralytic Polio
VAERS	Vaccine Adverse Event Reporting System
VASP	Varicella Active Surveillance Project
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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MINUTES OF THE MEETING
JUNE 29-30, 2005

JUNE 29, 2005

A meeting of the Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention's (CDC) National Immunization Program (NIP) at the Atlanta Marriott Century Center Hotel in Atlanta, Georgia, on June 29-30, 2005. The meeting agenda was posted on CDC's Website. The meeting was convened at 8:13 a.m. by ACIP Chairman Dr. Myron Levin, who welcomed all in attendance (see Attachment #1).

OPENING COMMENTS

New ACIP Executive Secretary Dr. Larry Pickering made several announcements:

- The OMB issued a bulletin of its peer review policy, which requires peer review for all scientific information disseminated by a federal agency. The policy is posted on the DHHS and was available in print at this meeting. Comments on the policy are due June 16.
- He welcomed Dr. Andrea Gelter, the new liaison representative from the American Association of Health Plans and outlined the meeting's seating arrangements (members in the center, liaisons and ex-officios surrounding them).
- The ACIP home page is www.cdc.gov/acip and the e-mail address is acip@cdc.gov.
- ACIP workgroups scheduled to meet were those to address influenza, the harmonized immunization schedule, human papilloma virus, MMRV, meningococcal vaccine, and adult immunization.
- The next ACIP meeting will be on October 26-27, 2005, at the Century Center Marriott.
- ACIP Protocol: The quorum of ACIP members must be maintained to conduct committee business. The ACIP charter allows the Executive Secretary to temporarily designate ex officio members as voting members in the absence of a quorum (eight members) of members qualified to vote. If voting, the ex-officio members are asked to disclose any potential conflicts of interest. Meeting time is reserved for public comment at scheduled intervals, but may also occur during open discussion if a speaker is recognized by the Chair. ACIP members with potential conflicts of interest are asked to disclose all vaccine-related work and financial interests, and to refrain from any discussion or vote that is related to such matters. When needed, however, limited waivers of such conflicts of interest are granted to enable the members to provide their expertise to the Committee. Waivers may be issued, for example, to members who also conduct clinical vaccine trials or serve on a Data Safety Monitoring Boards (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 the conflict nor in related votes. They may discuss, but not vote on matters related to that company's vaccines.
- The agenda included time for public comment, but the Chair can also recognize such speakers at other times, time permitting.

- Dr. Pickering presented an award to Dr. Levin, whose membership in the board was terminating, and expressed great appreciation of his leadership. Dr. Levin, in turn, expressed his appreciation of the ACIP as an input vehicle for the voice of the public and the vaccine manufacturers in setting policy; for the CDC staff's dedication to the nation's health; and for the ACIP members' year-round work on vaccine issues. He expressed personal satisfaction that such work has eliminated so many previously common infectious diseases. He personally thanked all involved in this work on behalf of his four grandchildren, who will never suffer such vaccine-preventable diseases. During the course of the meeting he thanked and presented awards to other members leaving the committee, Mr. John Salamone and Dr. Guthrie Birkhead.

The members and liaisons then introduced themselves (see Attachment #1). Those reporting potential conflicts of interest were Dr. Levin (research support from GlaxoSmithKline [GSK], Merck, and Merck's DSMB), Dr. Greg Poland (grants from Chiron, VaxGen, and Merck DSMB), and Dr. John Treanor (research support from Protein Sciences and MedImmune, Novartis DSMBs). Dr. Tracy Lieu reported receiving research support from the NIP, and no conflicts.

AGENDA ITEMS

PERTUSSIS

Pertussis Workgroup Update: Tdap Adolescent Recommandations
Introduction: Dr. Jonathan Abramson, Pertussis Workgroup Chair

> Overview: Multi-agency Workgroup review of replacement of DT with Tdap; membership; discussions of recommendation options, particularly regarding interval timing for diphtheria and tetanus containing vaccines, including MCV4.

There are now two FDA-approved vaccines, Boostrix®, manufactured by GSK Biologicals, and Adacel™, manufactured by sanofi pasteur. Presentations at this meeting reviewed the epidemiology of pertussis in adolescents, Tdap vaccines, safety of adolescent Tdap related to Td and adolescent MCV4 vaccines, and safety surveillance. Proposed recommended use of Tdap among adolescents aged 11-18 years were to be offered, with contraindications, precautions, and special situations discussed, for a vote on recommended inclusion of Tdap in the VFC program. On the following day, adult pertussis epidemiology and potential strategies for prevention and control would be offered.

Pertussis in Adolescents and Tdap Vaccines
Presenter: Dr. Margaret Cortese, NIP

> Overview: Reported pertussis incidence 2000-04 cases; clinical features/morbidity; outbreaks; economic studies of an adolescent vaccination program; survey of physician acceptance of such a program; Tdap indications; U.S.-licensure rationale; formulations; pivotal immunogenicity and safety studies of Boostrix® and Adacel.™

Charted reported pertussis cases were shown in a rapid decline from the prevaccine era, but increasing since the 1980s. Despite a likely underestimation of cases due to low physician

awareness and availability of diagnostics, 8000 adolescent cases were reported in 2004. Sixteen states reported >100 cases and six states reported incidence of >25/100,000 population from 2000-2004. Enhanced surveillance in Massachusetts consistently showed high rates among adolescents, as did routine surveillance in several other states. The new recommendations will add monitoring 0f the vaccine's impact on pertussis with new active surveillance sites in Massachusetts and Minnesota, as well as safety monitoring.

Pertussis presents serious clinical features in adolescents. Data indicate paroxysmal cough and difficulty breathing and sleeping among >70%; post-tussive vomiting among about half, and weight loss and whoop in about a third of studied adolescents with pertussis. About 2% nationally are hospitalized and about 2% of those with pneumonia. More serious events such as seizures and unconsciousness occur in <1%. Prolonged duration of coughing (>9 weeks) is the most disturbing feature. In Massachusetts, most (60%) of cases were among those aged <16 years, and most were detected in school outbreaks.

The Massachusetts data suggest that an adolescent vaccination program would: 1) significantly reduce incidence in adolescents and 2) reduce the B pertussis reservoir, therefore potentially reducing its incidence in other age groups. Economic data presented to ACIP in February supported this as likely to be cost effective (depending on incidence and vaccine cost). Additional data from a physician survey presented in February indicated likely acceptance of an adolescent Tdap vaccination schedule at age 11-12 years. Two sites (in Massachusetts and Minnesota) have been chosen to monitor the impact on pertussis disease, pending implementation of such a program. Boostrix® and Adacel™ pivotal trial data were presented, as were the criteria for inclusion and exclusion.

Boostrix®. Licensure was based on noninferiority of the tetanus and diphtheria toxoid components' efficacy compared to Td for seroprotection as well as antibody booster levels. A comparison of the formulations for Td, Boostrix® and Infanrix® showed Boostrix® to have a reduced tetanus and diphtheria content and about a third of the pertussis antigens, pertussis toxin, FHA, and protactin. Immunogenicity criteria were met compared to Td. In the absence of a correlate of protection, immunogenicity for pertussis was shown through a serologic bridge to the German infant efficacy trials after a DTaP primary series, producing an 89% efficacy. Booster responses to each of the pertussis antigens were also assessed and found acceptable.

The overall safety profile was noninferior compared to Td, with comparable reports of injection site redness, swelling, and increase in arm circumference; as well as headache, fatigue and GI symptoms after vaccination. While reported rates of Grade 2 or 3 pain were higher for the Boostrix® group, there was no difference for Grade 3 pain alone. No Arthus reactions or serious adverse events related to vaccination were reported.

Adacel™ The Adacel™ and Daptacel® formularies were compared, showing Adacel's™ reduced diphtheria and pertussis toxin content. All the immunogenicity criteria were met for adolescents compared to tetanus and diphtheria antibody responses after Td. Serologic bridging to the Sweden 1 infant efficacy trial showed booster responses for each pertussis antigen. Similarly, the overall safety profile was noninferior to that of Td. Rates of injection site pain, erythema, swelling, and moderate or severe injection site pain were similar, although the *Boostrix™* group reported more injection site pain. Frequency of fever or other selected systemic events (e.g., headache, tiredness, body aches) was comparable. Although there was

more fever >100.4º F in the Adacel™ group, the frequency was comparable between the two groups. Again, adolescents had no Arthrus reactions or serious adverse events related to vaccination.

Use of Diphtheria and Tetanus Toxoid Containing Vaccines In Adolescents Aged 11-18 Years.
Presenter: Dr. Trudy Murphy, NIP

> Overview: Background for the discussion of minimal intervals between DTaP, Td, Tdap, and MCV4 in light of a theoretical risk of increased adverse events. (There is no evidence of increased risk at present for DTaP, Td, or MCV4.)

The pediatric diphtheria and tetanus toxoid vaccines recommended for infants and children are DTaP and DT; the conjugate vaccine protein carriers (tetanus, diphtheria or CRM197) are Hib and PCV7. The latter contains CRM-197, a nontoxic, mutant diphtheria toxin that induces antibody to diphtheria toxin, especially among children who have already received a primary series of vaccine. Currently, adolescents have received DTwP or pediatric DT; in a few years, they will have received acellular pertussis. Each of the three D- and T-containing vaccines have relatively large toxoid doses for greater priming of immunity, and the *haemophilus* conjugate vaccines also have diphtheria and tetanus toxoid carrier proteins.

The tetanus/diphtheria toxoid vaccines recommended (or under consideration) for adolescents are Td and the currently-licensed Tdap that is under consideration for recommendation. Adult Td and Td acellular pertussis vaccines have a reduced diphtheria toxoid content to decrease the rates and severity of local adverse events. MCV4, the conjugate tetravalent meningococcal polysaccharide-protein conjugate licensed in January 2005 and recommended for age 11-12 years (high school entry), has diphtheria toxoid as the carrier protein for each of the four meningococcal polysaccharides: A, C, Y, and W-135. No conjugate vaccine is indicated for immunization against diphtheria or tetanus, although variable immune responses are induced against the carrier proteins.

The Pertussis Workgroup reviewed the tetanus and diphtheria contents of T- and D- containing vaccines. Toxoid quantities are reported in Lf, (lime flocculation, or limit of flocculation, units) which are the milligrams of protein nitrogen and purity. Although these Lf values are rarely comparable between laboratories, pediatric tetanus formulations have 5-10 Lf and adolescent formulations have 2-5 Lf. The levels for pediatric and adolescent diphtheria toxoid are 6-25 Lf and 2-2.5 Lf for adult vaccines. The MCV4 content in unknown, but sanofi pasteur's Td is ~8 mcg and MCV4 is ~48 mcg, suggesting that MCV4's diphtheria toxoid content may be similar to that in pediatric DTP and DT vaccines.

In 1985, ACIP advised that "…Td rather than DT is the agent of choice for immunization of all patients 7 years of age and older, *because side effects from higher doses of diphtheria toxoid are more common in older children and adults*… tetanus toxoid should be given with diphtheria toxoid as Td every 10 years. If a dose is given sooner as part of wound management, the next booster is not needed until 10 years thereafter. *More frequent boosters are not indicated and can result in an increased occurrence and severity of adverse reactions…"* (Italics added) The objective became to protect adolescents from diphtheria, tetanus, pertussis and meningococcal without increasing adverse events. Since a carrier protein-induced immune response can change with conjugation and the MCV4's higher diphtheria toxoid content may not equate to enhanced

immune response, the Workgroup reviewed sanofi pasteur's three safety/immunogenicity adolescent trial data.

- *Td506*: Tdap compared to Td; >500 subjects in each arm. *Results:* Diphtheria toxoid GMC after Td and after Tdap was comparable at ~7-8 IU/ml.
- *MTA-12*: Simultaneous, concomitant or sequential use of Td and MCV4; >450 healthy 11-17 year-old subjects in each arm; randomized to two Td+MCV4 and Td+placebo. *Results:* GMC after Td plus MCV4 was 120.9 IU/ml; after Td, the GMC was ~8 IU/ml, and that after MCV4 given 28 days later, it was 16.9 IU/ml. .
- *MTA-02:* Evaluation of a subset of subjects who received MCV4; > 400 subjects in each arm were provided the diphtheria toxoid sera. *Results:* Diphtheria antibody level in the subset of subjects receiving MCV4 was 46.5 IU/ml.

Currently, 2-3 doses of the highly immunogenic tetanus toxoid are protective. Diphtheria is slightly less immunogenic, but both protect (at a level >1 IU/ml) for >10 years after boosters, and with boosters, >20 years further. Older children, adults, and young adults produce more robust antibody responses to both toxoids than do older adults. (Cheuvart B et al. *Vaccine* 2004;23:336). Although there are no systematic studies of antibody levels in tetanus cases nor any method to measure toxin levels, the literature indicates that tetanus immunity probably lasts at least 20 years for the vast majority of individuals who have had ≥5 doses, perhaps even 25-30 years for many.

Adverse events. Local adverse events are mild to moderate and self-limited in 1%-80% of primed children and adults after routine TT vaccination and among 5-80% after diphtheria toxoid. More severe local reactions resulted from impurities in older toxoid preparations and after receiving Td, more than after TT. Reactions also occurred after subcutaneous rather than intramuscular injection, larger doses of toxoid, and from multiple doses at short intervals or when high levels anti-tetanus toxoid are present. More severe local reactions for diphtheria occurred for similar reasons, and among persons with pre-existing immunity (as shown by the Schick test or endemic diphtheria exposure). (Galazka AM et al. *Vaccine* 1994;14:845)

Extensive limb swelling (ELS) after DTaP doses 4 and 5 occurred in 2-3% after DTaP (and Td), but less often after DTwP and other vaccines, and with no clinical sequelae. The cause remains unknown (under study by CISA) , but could relate to tetanus/diphtheria toxoids, pertussis antigens, alum; IgE mediated responses; and Arthus. The latter is rare after vaccination but can produce immune complex deposition and inflammation due to the vaccine antigen's interaction with existing IgG antibody.

Based on this information, the Workgroup asked two questions: 1) What is the shortest safe interval from Td to Tdap to allow boosting protection against pertussis? After review of two studies, they concluded that an interval between prior Td and a dose of Tdap could safely be given at an interval as short as two years.

- Prince Edward Island (PEI –Halperin et al, presented at the February ACIP meeting) found local reactions not increased at 2-3 year intervals after DTwP and Td vaccination, compared to study participants who were received Td containing vaccine ≥10 years earlier. Local reactions (increased redness and swelling) increased at 4-7 year intervals after mixed DTP/DTaP compared to that same group, but were well tolerated. There was no increase in severe local adverse events or Arthus. (However, it was also noted that no study participant received meningococcal conjugate)

- Yukon territory (Candow et al) followed students aged 14-17 who received Tdap catch-up vaccination 3-4 years receiving after five DTwP plus a Td booster. Another group received Tdap >5 years after 5 doses of Td whole cell vaccine. Again, no increase in severe local reactions were seen 3-4 years post-Td compared to those who were at >5 years after the fifth dose. There was more injection site pain with short intervals according to self-report and again, no meningococcal vaccine had been received.

Second, they investigated what schedules of Tdap including Td and MCV4 provide optimal safety. Inferences were taken from the prelicensure trials, which were conducted with Td rather than Tdap.

- sanofi pasteur *MTA-12, Study 3*: double-blind immunogenicity and safety study of MCV4 with Td, with solicited reactions 0-7 days after vaccination. Moderate and severe systemic reactions were defined as those which interfered with or disabled movement, respectively. *Results:* Moderate injection site pain was relatively common for Td (20%-22%) and MCV4 (11%-14%) sites, when administered either concurrently or sequentially. Severe pain was uncommon. Overall systemic adverse events were similar among adolescents receiving concomitant Td and MCV4 (58.6%), and Td and placebo (54.1%)
- *MTA-19, Study 4:* Since there are no data on Td or Tdap administered after MCV4, this study examined the safety of diphtheria and tetanus-containing vaccines among adolescents (15-17 years) who already received MCV4. sanofi pasteur examined the safety of two MCV4 doses among three groups, who received MCV4 first, or polysaccharide first, or who were naive, and who all then received a dose of MCV4. (Routine Td vaccination was assumed, but there was no history of that). *Results:* The rates of local and systemic reactions at 0-7 days were similar for the first dose of MCV4 and its second dose 3 years later: local injection site and systemic adverse events were moderate and there were no severe adverse events. These data are under FDA review.

Gaps in knowledge remain concerning the intervals between diphtheria and tetanus toxoid containing vaccines, for: Tdap and MCV4, all sequences; Td administered at intervals longer than 1 month *before* MCV4 ; Td administered after MCV4; and 5 DTaP received before administration of Tdap. However, the Workgroup concluded safety for use of Tdap under the following situations:

- Use of Tdap 2-5 years after Td among adolescents, as indicated by the two Canadian studies (given that no subjects received meningococcal vaccine).
- Use of Tdap (Td) with MCV4 inferred from one pre-licensure trial comparing concomitant Td and MCV4, or Td *before* MCV4 28 days later. However, there are no data on intervals >1 month between Td and MCV4
- Use of Tdap/Td *after* MCV4 was inferred from one small clinical trial of MCV4 3 years after a first dose of MCV4. However, Td vaccine history was not documented and data are limited on Tdap use among adolescents who received 5 DTaP vaccinations in childhood. They will reach adolescence in ~2008-08.

Discussion included:

- The PEI Tdap study used the same vaccine lot as that used in the U.S. studies and vaccination programs

- Before introducing nationwide meningococcal C conjugate, the U.K. that vaccine given a month before, concurrent with, or 1 month after a low-dose diphtheria vaccination, and found no serious adverse event. Since 2000, all adolescents presenting for Td or Td-IPV will have had meningococcal conjugate C vaccine. Dr. Salisbury knew of no increased reports of reactogenicity among school age children already exposed to meningococcal C conjugate. However, the peak concentrations to diphtheria found in children given the meningococcal C conjugate in the U.K. were all <10 IU/ml. The magnitude of response to the U.S. meningococcal vaccine was a different scale, frustrating any interpretation of whether the U.K. data could be reassuring. In the end, the U.K. and U.S. vaccines were too different to compare.
- There were no data known on the possibility of immunological tolerance with repeated diphtheria immunization, but that could occur. The MTA12 trial that gave Td first and meningococcal vaccine second showed lowered responses to the latter when they were given close in time versus simultaneously. The latter group had a 4-fold higher rise in titer than those receiving it sequentially and had levels similar to those who got the vaccines alone. There is some question about augmentation from simultaneous administration. Rather than the 4-fold rise, the proportion of those at a certain threshold may be more significant. For that criterion, there was no immunogenic difference between sequential or simultaneous Td administration (although safety is a different issue).

Safety Monitoring

Presenter: Dr. John Iskander, Immunization Safety Office.

> Overview: Postlicensure safety surveillance for new diphtheria toxoid containing vaccines; background on routine U.S. vaccine safety surveillance (VAERS, VSD, CISA); preliminary MCV4 (Menactra) safety data; enhanced passive surveillance for DT-containing vaccines; recommendations for adverse event reporting and research needs.

Postlicensure safety surveillance to identify new and/or rare adverse events that may suggest further study is done by the CDC-FDA Vaccine Adverse Event Reporting System (VAERS) and Clinical Immunization Safety Assessment Network (CISA), and by CDC's Vaccine Safety Datalink (VSD). VAERS' national passive surveillance is supplemented by the VSD's active surveillance through a national network of managed care organizations. CISA provides hypothesis clarification through focused research at the patient- and case-series level.

Most of the few adverse events reported on MCV4 and Tdap since April 2005 involve adolescent patients who often received coadministered vaccines. However, the rare serious adverse events reported showed no pattern of clinical events. Systemic and local events were similar to those seen in prelicensure studies and a number of adverse events were due to preventable vaccination errors. The reports include syncope and two shoulder-to-elbow ELS cases linked to MCV4. The latter has also been seen with DTaP boosters, Td and hepatitis B, and one case in the Tdap prelicensure studies. The pathophysiology is being studied but remains unknown. VAERS will track the effect of the new vaccines' diphtheria toxoid content through enhanced surveillance for local and systemic events. Use of the NVAC secure Web-based reporting of adverse events by clinicians is encouraged.

New protocols for evaluation/management of injection site reactions are needed. Such tools as

the VSD's rapid-cycle analysis can identify adverse event incidence related to Tdap and MCV4 and suggest studies of risk factors for preventable adverse events.

Discussion included:

- Neither of the ELS reports was serious or resulted in hospitalization. Other reports included exacerbation of pre-existing migraines, coincidental aseptic meningitis, dermatitis, and one vaccine administration error.
- The CISA network centers' academic centers are in Boston, New York, Baltimore, Nashville, and Oakland.

Manufacturer Comments

sanofi pasteur comments were offered by Dr. Michael Decker. Post-licensure studies for Tdap are planned or underway.

1. *MTA 21*: Menactra-Adacel™ study: enrollment is complete; the vaccine will be given simultaneously or one vaccine initially and the other one month later.
2. *Safety.* Post-licensure safety surveillance study will be conducted in multiple U.S. regions (all west of the Mississippi) at VSD sites, mostly among adolescents but also across the age spectrum.
3. To address the question of vaccinating children who had already received five Td injections, a study in Germany of the cohort who received Tripedia for dose 4 and 5 will be completed this year. It examines the reaction to a sixth dose with Adacel.™ Canadian cohorts immunized with Pentacel (the Canadian Adacel) will receive dose 6 next year. The U.S. population in general will be ready in 2008 for a sixth consecutive dose of acellular vaccine product.
4. Pending postmarketing studies include one of Adacel used as dose 5 rather than Tdap, to evaluate any potential improvement in the safety profile.
5. To address the concern about administering Menactra after previous large vaccinations with diphtheria toxoid, a study will explore the outcomes of administering Menactra consecutively.
6. Boosting studies are underway. A toddler vaccine clinical development program is in full operation and FDA has been petitioned for a 2-10 year-old indication for Menactra. An infant program is beginning and large-scale safety studies are underway.

GSK. Dr. Glen Friedman reported GSK's three post licensure studies for Boostrix:™

- A co-administration study with Menactra has the same design as that described for sanofi pasteur's.
- Safety surveillance will be done with 10,000 adolescents vaccinated with Boostrix
- A report was recently filed with FDA on a study of 320 German adolescents who received a sixth consecutive dose of acellular pertussis vaccine. Two-thirds received five prior doses of Infanrix and all the others, four doses. Many received Boostrix as their fifth dose at age 4-6 years. Data will be presented at HICPAC's fall meeting. ELS was documented in three of the 319 adolescents, all self-limiting cases that generally resolved in 5 days. No clinical care was required and there was no association found with either CRM or postantibody concentrations to any of the Boostrix antigens.
- The Boostrix supply for the U.S. population is expected to be adequate.

Public Comment
Ms. Chauntell Veit, of Harahan, Louisiana, speaking for parents of children with infectious diseases and from her own experience, stressed the importance of recommending this vaccination for adults as well as adolescents. She inadvertently infected her infant son Jeffrey with pertussis, which she thought to be only a cold. He was hospitalized in isolation for 9 days before being released for a 3-month recovery. She urged much more education on pertussis, which most adults are unaware that they can contract and transmit. She and her child fully recovered, but only after "three hellacious months," and others are not quite as fortunate.

Proposed Recommendations For Use of Tdap and Td Vaccines In Adolescents
Presenter: Dr. Karen Broder, NIP

Overview: Rationale/proposed recommendation of Tdap and Td vaccine use in adolescents aged 11-18 years.

Routine administration. Tdap vaccine is licensed for adolescent/adult use in the U.S. and is marketed as Boostrix®(by GSK Biologicals) and Adacel™ (by sanofi pasteur). They are both a tetanus toxoid, reduced diphtheria toxoid and acellular pertussis adsorbed vaccine (Tdap).

Four tetanus and diphtheria toxoid vaccines are licensed for use among adolescents/adults (>7 years old) in the U.S.: sanofi pasteur's Decavac™ and Tenivac™, the latter licensed to age 59 years, and the Td adsorbed by sanofi pasteur and the Massachusetts Public Health Biologics Laboratory. Td vaccination is universally recommended at age 11-12 years and for catch-up from age 13-18 years.

The proposed adolescent Tdap and Td recommendations for tetanus, diphtheria and pertussis vaccination preferred a single dose of Tdap over Td in most situations to provide protection against pertussis. It addressed routine Tdap vaccination, contraindications and precautions, and special situations for use.

Routine administration. The Workgroup considered and answered three questions:

1. Should Tdap replace Td on the adolescent immunization schedule? Td should be replaced by Tdap for use among adolescents aged 11-12 years and for those aged 13-18 years who miss the Tdap or Td dose. This was based on the data presented on safety/efficacy, 62% incidence among adolescents (Massachusetts data), ease of introduction to the routine schedule as a replacement, and data on its likely cost effectiveness.
2. How should Tdap be used among adolescents who already received Td? A routine 5-year interval between Td and Tdap should be recommended, as supported by clinical trial data and program considerations. The recommendation should be permissive, as this is an extra vaccination to the currently recommended one dose of Td for adolescents. That might indirectly facilitate spacing of MCV4 and Tdap and minimize the risk of local adverse events. This also is hoped to be a temporary situation as 11-12 year-olds routinely received Tdap.
3. Are there scheduling preferences for Tdap and MCV4 vaccines, both of which contain diphtheria toxoid? Yes, based on the current standard of care and program considerations, simultaneous vaccination is preferred, but non-simultaneous is acceptable. Although there are no data on either simultaneous or nonsimultaneous

administration of Tdap and MCV4, FDA approved simultaneous administration as safe and immunogenic for all vaccine antigens. Some experts suggest deferring Tdap for 3 years if MCV4 is administered more than a day earlier to avoid possible increased rates of local reactions. The 3-year interval between two MCV4 doses was shown in a small study of 76 subjects by sanofi pasteur (unpublished data). Non-simultaneous vaccination is a programmatic challenge and risks reduced coverage for Tdap and MCV4, but it allows provider flexibility and conveys the pertinent safety information.

Discussion included:

- In the complete absence of evidence of any safety problems, only reactogenicity should be a concern for question #2.
- It was acknowledged that permissive recommendations are less effective in altering current practice than universal ones, and that all trial data suggest that safety is no concern. In fact, the recommendation is essentially universal for adolescents who never received Td, in order to prevent pertussis. But a universal recommendation with a 5-year minimum interval would require vaccinating older adolescents (i.e., aged 16-18), a group hard to get back in to the physician's office.
- To avoid that problem and alleviate the confusion stemming from an artificial delineation of adolescent to adult at age 18 years, Dr. Middleman suggested recommending universal vaccination at age 11-12 and again at 18 (when they are still VFC-covered) to increase coverage and compliance rates and to eliminate the confusion of considering the 5- and 3-year intervals. Age 18 should be stressed rather than college entry to ensure that all 18 year-olds are addressed.
- A permissive recommendation could produce a lot of variation in practice and encourage physicians to shorten the intervals (e.g., for parents requesting Tdap for a 13 year-old who received Td at 11 and Menactra this year).
- Dr. Turner reported ACHP's recommendation of simultaneous MCV-Tdap vaccination this summer for incoming students who will live in dorms. This ~600,000 cohort is generally 18 years old and constitutes an estimated 20-25% of the pertussis reservoir. If ACIP's recommendation does not match ACHP's, those students will not be able to receive Tdap for 4 years.
- The recommendation's text on special situations will address some of these concerns, but there are also licensure considerations. That is, Tdap is licensed for single-use; it has no licensed indication for a repeat dose of Tdap. One product is licensed for use in age 10-18 and the other for 11-64.
- One option suggested, since definitive data is expected soon for some of these considerations, was to vote on provisional statement.

Contraindications and precautions for Tdap and Td Use. *Contraindications* include, as with pediatric DTaP, a serious reaction and history of encephalopathy within seven days of administration of pertussis vaccine. *Precautions to defer Tdap and Td use* are Guillain-Barré syndrome ≤6 weeks after a previous dose of a tetanus toxoid vaccine, progressive neurological disorders; uncontrolled epilepsy, or progressive encephalopathy until the condition stabilizes (not a precaution only for Td); latex allergy (not all vaccines contain latex); moderate or severe illness with- or without fever; and history of Arthus hypersensitivity reaction after receipt of tetanus and diphtheria toxoids. Pediatric DTaP precautions, less clinically applicable to adolescents, were dropped for Tdap and Td, as were ELS, stable neurological disorder and pregnancy (addressed in Special Situations), breastfeeding, immunosuppression, intercurrent

minor illness, and antibiotic use.

Special situations for Tdap and Td use. General principles include*:* a general preference for a single dose of Tdap over Td; permissive administration at intervals <5 years after Td; and a preference for simultaneous administration of Tdap (or Td) and MCV4, as the benefit of protecting against tetanus or pertussis may outweigh the potential risk of associated adverse reactions. Special situations outlined on a table were:

- Pertussis outbreaks or increased exposure: Control measures for outbreaks, including postexposure prophylaxis, were not addressed on this day, but the proposed recommendation was to consider Tdap catch-up vaccination, including at intervals <5 years for those who received Td.
- Tetanus prophylaxis and wound management: Tdap is preferred over Td if no prior Tdap and Tdap available.
- History of pertussis: Administer Tdap when otherwise generally indicated, since immunity wanes, diagnosis is difficult to confirm, and no data suggest that Tdap is unsafe.
- Adolescents with an incomplete DTP/DTaP vaccination history: If no DTP or Td vaccination, administer a three-dose Td series, with the first Td dose (only one) preferred to be Tdap. For adolescents with a completed tetanus and diphtheria series, one dose of Tdap was recommended.
- Children aged 7-10 years with incomplete DTP/DTaP vaccination history, for whom there are no U.S.-licensed pertussis vaccines: Use Td for children. Tdap is not recommended for those aged <11 years, but serological testing could be considered. Children found to have protective tetanus/diphtheria antibody levels could wait for their routine adolescent vaccination time, or complete their series using the Td instead of Tdap vaccine.
- Pregnancy: For this recommendation, the Workgroup discussed pregnancy as related to pregnant adolescents needing tetanus and perhaps pertussis immunity. The standard of care is to prevent maternal neonatal tetanus by giving Td to any woman not vaccinated against tetanus for >10 years, preferably in her second or third trimester. Being inactivated, Tdap and Td are not contraindicated during pregnancy and both are acceptable alternatives for tetanus protection.

Discussion included:

- The impact of adolescents in a household with an infant is probably less than that of adults, but whether that would alter the interval between Td and a pertussis containing vaccine has not been concluded. That involves questions of cocooning. That will be considered on the adult side, but could also affect the adolescent recommendation (i.e., an infant without the first two doses could necessitate immunization of the whole household). Dr. Susan Lett asked for further consideration of scheduling, as the longer interval would prevent vaccination of several hundred thousand Massachusetts children ineligible for Tdap, even though their need is very strong (90% of seventh graders had received Td). She advised careful analysis of all the factors involved.
- The primary purpose of the recommendation was to protect the adolescent against pertussis; reducing the overall reservoir of infection was secondary.
- Dr. Gall commented that the recommendation's 10-year interval essentially discriminates against pregnant adolescents. Since pregnant women are less reactive

to vaccines, they should have the same 5-year interval for pertussis vaccination as non-pregnant women, to protect both them and their infants in their first two months of life. Dr. Baker added a suggestion to shorten the interval to 5 years for patients with a tetanus-prone wound.

- Boostrix® was expected to be licensed as a Category B drug, but one study required by the FDA inadvertently was not performed. Despite data indicating the B classification, the CFR required a C classification since all the criteria were not met. Those regulations are now being rewritten.
- Dr. John Iskander stated that VSD and VAERS are working to fill the data gaps affecting clarity about intervals after prior vaccination with diphtheria toxoid-containing vaccines. In the meantime, a conservative approach in the absence of data is being followed. However, other than analyses underway, more safety data could come from potential situations as use of Tdap with reduced intervals in outbreak situations.
- Dr. Broder clarified that work is proceeding on a separate and specific adolescent ACIP statement, which will be published before the next meeting.

Proposed Tdap Recommendation

Simultaneous administration. "Vaccine providers are encouraged to administer Tdap and MCV4 during the same visit if both vaccines are indicated."

Discussion included that Tdap is indicated when MCV4 is administered (e.g., for an arriving college freshman living in a dorm). If both vaccines are on hand, both should be administered at the same time. The same is true for Td, but these recommendations focus on pertussis.

Nonsimultaneous administration: "According to ACIP, inactivated vaccines can be administered at any time before or after a different inactivated or live vaccine, unless a contraindication exists… Based on limited data [2 doses of MCV4 spaced 2 years apart] some experts suggest a conservative practice of deferring Tdap (which has less diphtheria toxoid content than MCV4) for 3 years if MCV4 has already been administered ≥1 day earlier."
Discussion included:

- Since the 3-year interval is based on the only data available, rather than expert advice, text was suggested to say "Existing data show that vaccination at 3 years does not have any adverse effects." However, the data were from a small study of 70 children, and were interpreted differently by Workgroup members. The "experts" text was to convey those opinions, but later the full document will comment that "if MCV4 is indicated, it would be recommended."
- It was felt that leaving it at "either is okay" would be difficult guidance to follow. Other suggestions were:
  - To reassure any fear of administering them non-simultaneously, state that "unless a contraindication exists, some physicians may want to administer vaccine based on pertussis risk in their geographic location."
  - In view of sparse epidemiologic evidence, text of "…potentially increased incidence of side effects if administered in <2 year interval" could be made almost parenthetical.
  - Even the use of the word "contraindication" is significant as opposed to "precaution."

    - If the language is retained about deferring Tdap for 3 years when MCV4 is given first, the recommendation should also address the reverse, when Tdap is given first.
- Much of this text was designed to be consistent with the ACIP's General Recommendations. Another refinement offered was to specify "unless a contraindication exists," referencing "some information that close spacing of doses may lead to increased side effects," and that physicians will have to weigh the advantages and disadvantages. "A small study suggests no serious adverse events if ≤3 years have elapsed," the latter replacing "experts."
- Dr. Plotkin demurred that, in the absence of any hard data to suggest any problem, a theoretical issue regarding intervals poses no contraindication That should be stated. He also advised removing the term "conservative" to avoid any risk of inhibiting the use of acellular pertussis vaccine in adolescents and defeating the objective of controlling its incidence. That goal is not clear in the recommendation or the general tenor of the suggested modifications.
- Dr. Nancy Bennett of NACCHO expressed concern about the intervals and the possible dampening effect on uptake even during regional outbreaks, which are already occurring. Dr. Broder reassured her that the general principles stated in the document would address that.
- Since this recommendation was based on safety issues, the data on a 4-fold rise in titers after MCV4 was not the main immunological concern. There were some differences in the immunogenicity of Menactra with various sequences of Td, but the titer rises of 1-28 and 1-4 were all acceptable. FDA will be looking at this relative to coadministering Tdap and meningococcal vaccine.

Dr. Broder summarized the committee's general feeling that simultaneous MCV4 and Tdap vaccination was supported, as was the approach of summarizing the data for the physician, including the concept of the significance of the 3-year data that can be considered. Dr. Levin concurred with her understanding.

Menactra discussion.

- Dr. Friedland asked where the strong data on the study of Menactra and Td administered one month apart would be inserted. The statement will say: "No contraindication exists. As discussed above, no data are available on the safety and immunogenicity of vaccination with Tdap and MCV4, which contains diphtheria toxoid as a carrier protein, on different days. However, limited data are available on nonsimultaneous vaccination with Td and MCV4. See page X." It also discusses the MTA-12 study's immunogenicity and safety results: "Although there are no safety data on administering MCV4 followed by Tdap on a later date, immunological considerations suggest the sequence might be associated with increased rates of local adverse reactions, e.g., substantial swelling and pain at the injection site related to diphtheria toxoid based on limited data from a small study discussed above."
- Dr. Decker feared the reader might misunderstand "limited" data. No trial data on Td and MCV4 have indicated any safety problem. But while MTA12 was a small study, there were thousands of children in the clinical trials. Those did not record their previous Td history, but that could be presumed. The safety results were good and reasonable inferences can be drawn from the experience of Td followed by MCV, to MCV followed by Td.

- Dr. Barbara Slade reported an additional theoretical factor related to the Menactra-to-Td or Tdap dose, in that the resulting anti-diphtheria titer was higher than any previous studies. However, they found that despite a high pre-vaccine titer, the rapid decline in the first 1-2 years after the booster dose brought the titer down to levels of no concern.

Interval and Permissive or Universal Routine Tdap Vaccination Recommendation. The recommendation would be consistent with the current adult recommendation, physician practice and the (smaller) clinical trial data:

> *"Adolescents aged 11–18 years who received Td may receive a single dose of Tdap to provide protection against pertussis if they completed the recommended childhood DTP/DTaP vaccination series. A 5-year minimum interval between Td and Tdap is encouraged."*

A *permissive* recommendation was supported by the following comments:

- It does not put physicians in medical legal bind and, since more data will be available in the near future, it would provide some needed flexibility.
- To match the age-specific disease curve in adolescence and late adolescence (similar to the discussion about Menactra and MCV), high school entry vaccination could be recommended.
- The term "encouraged" could be used to allow flexibility in either direction (i.e., a longer interval for diphtheria, or less time in an outbreak setting). The latter should be explicitly stated, since it is not intuitive.
- *The 5-year intervals are "hard-wired" into many practitioners, and changing the T-to-T intervals from 5 years will be an educational challenge.*
- Dr. Sarah Long, of the AAP, cited the lack of data on Tdap and Menactra. She advocated a conservative approach to avoid the risk of unexpected reactions from Menactra, the "48 microgram guerrilla of diphtheria antigen," particularly since children vaccinated with acellular pertussis vaccines will provide data in a couple of years.

The Universal recommendation was supported by the likely refusal of third party payers to cover a vaccine permissively advised.

Interval:

- Having a consistent 3-year interval would avoid confusion.
- The issues of diphtheria toxoid and the 3-year interval were studied in the MCV4 studies, and the Halperin study of Canadian children who received Tdap as little as 2 years after vaccination with tetanus and diphtheria-containing vaccine found no safety issues. Adverse events were mostly after multiple short-interval doses. For the purposes of this recommendation, the assumption has to be that this is a one-time Tdap vaccination.
- Dr. Decker explained that the reason all the clinical trials used a 5-year interval was based on the ACIP recommendation and CBER's requirement. That was why the shorter interval had to be studied in Canada. The Prince Edward Island data on 7000 children should be used, since he did not expect much additional data on this issue except that from passive surveillance. No studies are planned until sufficient time has passed to begin examining Adacel's ability to maintain pertussis immunity

throughout life, but an immunity lasting ~10 years (as with T and D) is expected. The question of Tdap following Menactra should not be linked to this discussion, which is, given a prior tetanus and diphtheria immunization, what the safe minimum interval is before the next tetanus and diphtheria immunization.

- Dr. Friedland stated that GSK's trial of Td was driven by the strict 10-year interval requirement by the MBPHL Td product used as their Td comparison. Nonetheless, 60-70 enrolled adolescents slipped by who had had Td within the last 10 years, from "quite short to quite long" intervals. None had serious reactions.
- There was support expressed for a 14-15 year-old recommendation for Tdap as well as 11-12 year-olds, to simplify the complex immunization schedule for overwhelmed physicians and to incorporate both the 2- and 3-year intervals. Although an NIP survey indicated that many practitioners, especially family physicians, tend to give Td at age 14 or 15, potentially risking a very short interval, the simplification might better reduce the burden of disease.

Dr. Abramson reported the Workgroup's discussion of these issues and their conclusion that increasingly the complexity would not eliminate adolescent pertussis in the two years before more data was in hand. For that reason, they proposed the permissive recommendation, which he again supported.

Dr. Broder summarized, to general agreement, that the recommendation would state: *Adolescents aged 11 to 18 years who received Td should receive a single dose of Tdap to provide protection against pertussis if they completed the recommended childhood schedule"* The "should" strengthened the "may" somewhat; language on the interval would follow. She also agreed to return on the following morning with alternate language to address a 3-year or 5-year interval in the recommendation.

HEPATITIS

Hepatitis B Vaccine Recommendation

Presenter: Dr. Tracy Lieu, Workgroup Chair.

Overview: Activity of the Workgroup re-formed last October to consider the hepatitis A and B recommendations; outline of presentations.

Even given the related infant mortality and the knowledge that adolescents infect infants, development of a recommendation on these vaccines was challenged by several factors: the vaccination's risks and benefits; waning vaccine immunity requiring periodic boosters; an unknown vaccine price; and the difficulty of achieving good vaccine coverage among adults as well as adolescents.

The draft recommendation language developed by the Workgroup in February received a lot of public comment. In two subsequent meetings, they polished the text. CDC also held a May consultation on how to better implement adult vaccination in general. The child and adult recommendations have been separated. This meeting's vote would address the children's recommendations, which were updated in the following areas: standing orders for administration of hepatitis B vaccine at birth; other delivery hospitals' policies/procedures to prevent perinatal HBV transmission; and recommended upgrade/expansion of screening for HBsAg among

immigrant children. The Workgroup reached good consensus on these issues, other than some discussion about the birth dose.

The proposed birth dose recommendation was: *"For all medically stable infants weighing at least 2,000 grams at birth and born to HBsAg-negative mothers, the first dose of vaccine should be given before hospital discharge (birth dose) . . . On a case-by-case basis and only in rare circumstances, the first dose can be delayed until after hospital discharge" . . . A physician's order to withhold the birth dose and a copy of the laboratory report indicating that the mother was HBsAg negative during this pregnancy should be documented in the infant's medical record."* The strength of the last statement would require great confidence for a physician to ignore it. It is a compromise with advocates of a no-exceptions policy, but keeps the ACIP recommendation more aligned with that of the AAP.

No change was made to the adult recommendations updates. The CDC centers involved in their implementation will discuss them and the plan's rationale will be presented in October.

Comprehensive Immunization Strategy To Eliminate HBV Transmission In the U.S.

Immunization of Infants, Children and Adolescents
Presenter: Dr. Eric Mast, NIP

> Overview: Review of hepatitis B incidence in the U.S.; priorities and progress in strategy to eliminate its transmission in children; current implementation priorities; new recommendations to address the latter.

Hepatitis B incidence in those aged <20 years was charted by race/ethnicity and showed a 93% drop in incidence among children across all racial and ethnic groups. Similarly dramatic declines were charted from two studies of overall and chronic infection in Hawaii and Georgia. The immunization strategy clearly has been successful and new recommendations were developed to consolidate those successes and address remaining gaps. The gaps to be addressed are better identification of HBsAg-positive mothers to identify their infants for case-management (which produces higher rates of administration of HBIG at birth, and completion of the vaccine series); management of infants of mothers with unknown HBsAg status (infants are tested for HBsAg at time of delivery and vaccinated); and tracking of infants born to identified HBsAg-positive mothers (to ensure they receive appropriate post-exposure prophylaxis).

Three implementation priorities drive the strategy by emphasizing:

1. Strengthening of the perinatal prevention program through standing orders in delivery hospitals to ensure identification of HBsAg-positive mothers and delivery of immunoprophylaxis to their infants; case management programs to ensure antigen testing of all pregnant women and reporting and tracking those found to be HBsAg-positive; case management for their infants and those of HBsAg-positive mothers; completion of post vaccination testing; and program monitoring and evaluation.

The birth dose recommendation was for standing orders: "1) *For all medically stable infants weighing ≥2,000 grams at birth and born to HBsAg negative mothers the first dose of vaccine should be given before hospital discharge. 2) Policies and procedures should ensure initiation of postexposure immunization of infants born to HBsAg positive mothers and*

mothers not screened for HBsAg prenatally and document the maternal HBsAg test results on the infant's medical record ." 3) Exceptions to this should be rare, and if the birth dose is delayed, the medical records should document the physician's related order and a copy of the laboratory report confirming the mother's antigen negativity during this pregnancy."

2. Maintaining and improving hepatitis B vaccine coverage among children (aged 19-35 months) and adolescents. Coverage for children is about equal to other childhood vaccines, but that for adolescents needs improvement from the ~80% overall coverage (2002) for those 13-15 years old.

The adolescent recommendation advised that: *"Hepatitis B vaccine should be offered to all unvaccinated adolescents in all settings that provide healthcare services to this age group. States are encouraged to implement immunization registries for adolescents."*

To implement that, providers were encouraged to conduct an immunization record review for all children aged 11-12 years and all children and adolescents (including international adoptees) born in HBV-endemic countries, or who have at least one parent who was born in these countries. States are encouraged to adopt regulations/laws requiring hepatitis B vaccination before middle school entry, and when feasible, to consider vaccination requirements for older high school students and students before college entry.

3. Improving HBsAg screening among U.S. residents born in HBV endemic countries and their children. A map showed the global distribution of chronic hepatitis HBV infection, with high rates in most of Africa and Asia, northern Canada, and Alaska (≥8% prevalence), intermediate (2-7%) in most of the former Soviet Union and eastern Europe; and low (<2%) in the rest of the world.

The recommendation for those foreign-born was: *"All foreign-born children from Asia, the Pacific Islands, Africa, and other countries with HBsAg prevalence ≥2% should be screened for HBsAg. All persons found to be HBsAg positive should a) have susceptible household members, sex partners identified and vaccinated; b) receive appropriate medical follow-up, including counseling, evaluation for chronic liver disease, and antiviral treatment (if indicated) and c) be reported to health departments according to state reporting requirements.*

To implement that, HBsAg screening and appropriate follow-up was recommended during the medical examinations required for persons from HBV-endemic countries applying for permanent U.S. residence. Those persons should be considered eligible for immigration and adjustment of visa status, and should be earmarked for follow-up medical evaluation and management in U.S. resettlement communities. Providers were encouraged to identify children born in HBV-endemic countries and to provide HBsAg testing and follow-up in all settings providing health care for this age group. Consideration of retests for persons tested for HBsAg in other countries also was advised.

The birth dose discussion included a thorough dialogue on whether the birth dose should leave any element of flexibility for the practicing physician, or be a firm recommendation with no opt-out clause. The points favoring the opt-out included:

- The public health threat is not sufficient to remove the possibility of individual choice. ACIP should not over reach, potentially adding to immunization hesitancy and resistance. The Workgroup's compromise indicates that exceptions should be rare and provides guidelines, requires a copy of the lab report, and addresses the concerns about encouraging exceptions. The stringency of the recommendations should be comparable to the threat.
- A recent California survey indicates that hospitals with uniform procedures and preprinted orders successfully administer the birth dose, even in the highest risk areas.
- ACIP recommendations have been positive, supported practitioners to do the right thing. Establishing a mandate requiring documentation would set a negative new precedent.
- A neonate may not be diagnosed with thrombocytopenia and bleed from the injection.
- Parents may reject the birth dose.

Those favoring a firm recommendation were:

- Dr. Offit noted that children born to antigen positive mothers are clearly at very high risk (>90%) of developing hepatitis B virus infection and there are documented cases of children tested incorrectly or not vaccinated, who died or now are chronic carriers of hepatitis B. The mandate provides a good catchment mechanism and lowering the bar would not be in the best interest for the health of young children.
- Dr. Wexler reported the Immunization Action Coalition's receipt of >500 reports of errors related to birth dose in 2001-02, from every state. A mandate would be the best public health recommendation to stop these errors. The birth dose is the best medical practice to protect all children, and physicians always have an option to opt out for their patients, deferring 7 days or 2 weeks if they judge the baby or mother not to be at risk. She also advised deletion of the last column of Table 4, which infers that no birth dose is acceptable.
- There was some fear expressed that physicians might gravitate to the exception.
- The more prescriptive the recommendation, the less respect for the professional decision of the physician, nurse or nurse practitioner. The birth dose should be recommended, but without prescribing what the providers must do if they do not give it.
- The value of a mandate is in its setting a high bar of things to do other than just checking a point of the standing orders, and the birth dose is the standard of care.
- Dr. Plotkin noted CDC's and AAP's concern about an accumulation of susceptibles, which made the birth dose mandate (as well as catch-up vaccination) logical to prevent that cohort from passing into adolescence and an age of severe disease. He also suggested emphasizing the ability of the first dose to prevent varicella.
- Recommended testing of pregnant women was outlined by Dr. Gall: HIV, rubella, and syphilis at the first visit; retest and vaccination at 36 weeks if the person engaged in high risk behavior. Twenty-three of the latter are listed, the major one of which is exposure to another STD (e.g., Chlamydia or gonorrhea) during pregnancy. While those who present for delivery with no prenatal care or who had no regular provider are of most concern, hospital blood testing should be complete by 2 days, while the baby is still in the hospital.
- Dr. Allos supported language to strengthen the birth dose.
- Other suggestions for the recommendation were to state that the hospital should: receive a copy of the original lab report from the prenatal care provider; note that

states have pregnancy testing requirements as well as school entrance requirements; change "migration" to "immigration" and clarify "adjustment of visa status" (A medical exam is required upon request for entry is requested or for adjustment of visa status); and change "physician" to "provider," since nurses, nurse practitioners and midwives also issue these orders.

- Identification of antigen-positive children before they enter the country prompts interventions to vaccinate their household and sex contacts, to ensure that they are under medical care, and to give them treatments that are now improving for those with chronic infection.

Public comment: none.

Dr. Finger **moved to strike the opt out language, to fully recommend giving the birth dose in hospitals.** Ms. Stinchfield seconded the motion. Dr. Chapman recommended, for greater clarity, voting on whether to retain the current language on (in favor) or to change it (opposed).

Vote to delete rare exceptions to birth dose administration.

Conflicts: Merck, GSK

In favor: Finger, Salamone, Stinchfield
Opposed: Treanor, Morita, Marcuse, Lieu, Gilsdorf, Campbell, Birkhead, Allos, Abramson
Abstained: Poland, Levin (conflicts)

The motion failed.

Dr. Treanor then moved to accept the entire recommendation with the edits provided and Dr. Allos seconded the motion.

Vote to accept the childhood HBV recommendation, retaining the opt out clause

In favor: Treanor, Stinchfield, Salamone, Morita, Marcuse, Lieu, Gilsdorf, Finger, Campbell, Birkhead, Allos, Abramson
Opposed: None
Abstained: Poland, Levin (conflict)

The motion passed.

Before adjourning for lunch, Dr. Pickering clarified that the successful vote was to recommend to CDC that this be approved and published in the *MMWR.* That publication is the last step, after CDC and DHHS approve the action. The members then adjourned for lunch. Upon reconvening, Dr. Pickering introduced three honored guests from Japan: Dr. Yokota, Chairman and Professor of the Department Of Pediatrics at Yokohama City University School of Medicine; Dr. Okabe, Director of the Infectious Disease Surveillance Center and the National Institute of Infectious Diseases; and Dr. Taya, Chief of the Division Of Immunization Program Infectious Disease Surveillance Center and the National Institute of Infectious Diseases. Those present welcomed them with applause.

Recommendations for Use of Hepatitis A

Epidemiology of Hepatitis A Vaccination
Presenter: Dr. Beth Bell, NCID

Overview: History/rationale of the ACIP recommendation; temporal trends in hepatitis A epidemiology

Recommendations for routine vaccination of children have been issued incrementally: in 1996, for children living in "high rate" communities and in 1999, for children living in states or communities with consistently elevated rates during the defined "baseline period." Universal vaccination of all children nationwide is the next and last step.

Incidence is now at 1.9/100,000 population, a historical low. Age-specific incidence charted geographically showed a precipitous decline in states where vaccination was recommended, particularly in the age groups targeted for routine vaccination. Incidence also declined in states without vaccination, reflecting the disease's periodicity. Data from 2001-04 charted hepatitis A incidence rates according to age group and region, superimposing the vaccination states upon that if non-vaccination states. While adult rates and overall rates are declining, the overall rates are not declining among the 2-9 year-olds in the non-vaccination areas. In fact, they have increased slightly, with the highest 2004 age-specific rate among children aged 2-9 years. Vaccinating states showed no change in their children's age-specific incidence rates. Charted 2003 NIS data showed an overall coverage of ~50% (range=6-73%) in 11 of the states recommending vaccination, ~25% (range=1-32%) among those suggesting it, and essentially none in the balance of the states.

In considering the final incremental step to nationwide childhood vaccination, the Workgroup considered several factors: 1) the fact that the formerly high-rate states that began vaccination now have lower hepatitis rates than the formerly lower rate states, making more difficult their explanation of the rationale for universal vaccination; 2) making hepatitis A vaccination universal increases the probability of achieving higher coverage and lowering rates over a longer period of time; 3) possible labeling changes would drop the lower age of hepatitis A vaccine and could further facilitate implementation; and 4) the economics of a universal recommendation (to be presented at this meeting; already presented to the Workgroup in detail).

The economic analysis was done from a societal perspective to evaluate the impact of expanding routine childhood hepatitis A immunization beyond the areas specified in ACIP's 1999 recommendations, and to compare such a program with the economics of other routine vaccination programs for young children. The approach was based on a single-age cohort vaccinated at age 1 or 2 years, in the perspective of a overall national program and by ACIP region. Vaccination coverage was assumed to be more or less similar to that of other, relatively newly recommended, early childhood vaccines.

Economics of Hepatitis A Vaccination in the U.S.
Presenter: Dr. Gregory Armstrong, NCID, Division of Viral Hepatitis

Overview: CDC-funded analysis by Research Triangle Institute (RTI) of the immunization effects (direct and herd immunity) on regional incidence (as defined by ACIP as low-, intermediate- and high-incidence regions).

Direct effects are defined as those which prevent disease among vaccinated persons. Herd-immunity effects are those which lower disease incidence among unvaccinated persons as a result of the immunization program, both within and outside of a cohort. The "full model" analysis considered the direct effects and herd immunity both within and outside the cohort, and estimated the vaccination impact during the first 10 years of immunization. The cohort-only model analysis estimated the long-term impact of immunization and considered only direct effects within the cohort (including herd-immunity effects), because outside-of-cohort effects diminish over time.

The measures used were Cost per Life Year (LY), which accounts for mortality (years of life lost from premature death), and cost per quality-adjusted life year (QALY), which accounts for mortality and morbidity (i.e., decreased quality of life during illness).

Analytic Scenarios, Cohort-Only Model
Presenter: Dr. David Rein, RTI International

A discrete-state Markov transition model was developed in which patients can be susceptible, infected, recovered, or dead from either hepatitis A or another cause. Their movement through these different health states was followed, based on surveillance data or the literature. Cost was assigned to the different states, to patients or cohorts, based on the disease states that they encountered.

The analysis assumed a birth cohort of 4 million children born in 2005. Two different vaccination options were used to assess their lifetime cost: vaccination at ages1 or at age 2 (only the latter is currently licensed). The cost of vaccinations in year one of life can be shared with other routine vaccination, something not true in year two. The model assumed that all children receive routine hepatitis A vaccination and that they benefit from herd immunity even before vaccination. The incremental effects of the latter are small since immunization levels are so high.

The model parameters were outlined: cost of vaccine and its administration; baseline incidence; annual incidence rate of decline of 1.4% annually; probability and cost of symptoms and disease complications; productivity losses associated both with morbidity, mortality, and for the child's caretakers.

The analysis of within-cohort herd immunity used current adult vaccination levels and assumed that hepatitis vaccination would end with nationwide childhood immunization; public health costs (i.e., response to outbreaks), those for hypothetical adverse events, and others. The model was run twice; once without childhood vaccination and then with it. The disease outcomes, cost, life-years lived, and QALY lived were compared and economic ratios were calculated for cost per QALY and life-years gained (i.e., the change in each).

Results. Without vaccination, the analysis estimated 200,000 infections and outpatient visits, a number of hospitalizations, liver transplants, and deaths, and their associated costs in terms of

the healthcare system (direct medical costs) and societal cost per life-year (i.e., all costs). This was adjusted for societal cost per QALY.

- Estimated costs with- and without national vaccination were charted. The difference showed that with an increased cost of immunization, the related cost of public health decreased slightly, and medical costs and productivity losses decreased even more. Nationwide immunization reduces the number of overall infections dramatically and increased life-years and QALYs. But it also increased costs: $49,000 healthcare cost per QALY, and societal costs of $293,000 per life-year and $37,000 per QALY. Nonetheless, those costs are highly cost saving in the high- and intermediate-incidence areas, warranting full immunization there. For the low-incidence regions, immunization is relatively more costly "but not outrageously so."
- Analysis of immunization at age one or two years indicated that doing so at age 1 lowered the immunization cost and provided moderately increased health benefits that improved the cost-effectiveness ratios versus vaccination at age two. Variables involved included vaccine cost (in this analysis, $30/dose) for public and private buyers and cost of administration. A threshold (lowest) price was calculated for co-administered vaccine and the public sector price. The closer to the threshold price, the better the cost-effectiveness ratios were, both nationwide and for the low-incidence areas.
- Point estimate sensitivity to the model parameters' uncertainty was checked through a probabilistic sensitivity analysis. Randomly varying all the model parameters across their confidence intervals 1000 times, the cost per QALY ratio remained the same. For vaccination at age two, 71% of the simulations were <$50,000/QALY for the nationwide scenario, and 99% were <$100,000/QALY.

Out of Cohort/Full Model Analysis
Presenter: Dr. Gregory Armstrong, NCID

Since most hepatitis A virus infections occur in young children, a very strong herd-immunity effect could be expected from immunizing them. The economic effects on out-of-cohort immunity due to hepatitis A vaccination were evaluated. Three studies were the basis of this analysis:

- Butte County, California, achieved a 66% vaccination coverage between 1996-2000, which produced a 94% decline in incidence among children. That decline was paralleled among adults, most of whom were not vaccinated.
- Israel achieved a 99% coverage from 1999-2002 among children aged 2-4 years, which produced a 90% incidence decline. Again, that decline included other age groups which generally were not immunized.
- Anecdotal state reports to CDC between 1996-2001 noted plummeting incidence despite relatively low immunization coverage rates. A more formal analysis of national data, even adjusting for temporal trends and changes in adult immunization coverage, also determined that a 1% increase in vaccination coverage in children correlated to a 3.9% decrease in incidence among unvaccinated children and a 1% decrease among adults. With 1% coverage, the absence of herd immunity would produce 1% less in children and no decrease in adults.

Analysis. The total economic burden of hepatitis A in the U.S. was estimated using a modification of the 2005 RTI model, adjusted downward to account for assumed future

incidence declines without immunization. The proportion of disease burden prevented by outside-of-cohort herd-immunity effects was then estimated (based on the literature).

Results. For children, prevented cases ranged from 0-100%, depending on coverage levels. The adult cases assumed that, based on surveillance data, 25% percent of adult infections originated in children, so that only 25% at most could be prevented by herd immunity. That may be a very conservative assumption. Also conservative was the finding that, in terms of cost, the estimated $151 million cost of the vaccination program's benefits would be cost saving in the first 3-4 years, but not subsequently. That was because the model assumed that even without immunization, hepatitis A incidence would slowly decline.

The within-cohort herd-immunity effects were small. The estimated outside-of-cohort herd-immunity effects declined greatly over time with increasing numbers of children but, despite that, they persisted for a very long time. Data on the first ten years of immunization was arbitrarily selected to calculate the cost per QALY for immunizing all one year-olds in the U.S. and then for all those age two.

- The cost-utility ratio in the cohort-only model was ~$28,000/QALY gained, but with the out-of-cohort herd-immunity effects added, the CE rises to only $1,000 per QALY gained. The cost-utility ratio for 2 year-olds dropped from $41,000/QALY to $9000/QALY and, in the high- and intermediate-incidence states, it was cost saving in the full model. For the low-incidence states, the cost per QALY decreased to either $53,000 or $73,000 per QALY.
- The changes for cost per life-year were even more dramatic. The $327,000 cost to vaccinate all 2-year olds plummeted to $13,000 in the full model, thanks to prevention of adult infections very early in the model and their related productivity losses. Adults also are much more likely to die from hepatitis A, resulting in many more years of life saved early on in the model. The full model also showed a big difference in the low-incidence states, decreasing the CE ratio to either $232,000 or $320,000 per life-year saved. This model is most sensitive to vaccine cost assumptions and is somewhat insensitive to the coefficients used to estimate this herd immunity.
- Analysis of the cost-utility ratio of routine childhood hepatitis A immunization in the U.S. demonstrated cost effectiveness for immunizing either at age 1 or 2 years, both in the cohort-only and in the full model. It is cost saving in the high- and intermediate-incidence regions regardless of the assumptions. Analysis of the low-incidence regions produced a significant difference between the cohort-only model and the full model.

Conclusion. Overall, routine childhood hepatitis A immunization in the U.S. is cost effective, with an economic impact similar to that of recently approved vaccines. However, policy decisions about this vaccine should also consider other factors, such as the feasibility and sustainability of different immunization strategies and possible future incidence trends.

Discussion included:

- The analysis confirms that national incidence is low. Hepatitis A incidence has always fluctuated in a natural cycle of 5-15 year cycles. It peaked in the late 1980s, decreased in the early 90s, and peaked again in 1996.

- The initial analytical goal was to calculate the cost/benefit of an incremental change from the current policy, but the difference in policies across the nation frustrated that. It was found to be cost effective to increase the numbers of those immunized, but it was not practical from a policy standpoint to recommend titrating immunization coverage to a certain level.
- Other challenges to a universal policy include the belief by some that the decreases seen relate more to periodicity than the intervention. Another is that rates will decline with any vaccine introduction and then begin to climb again to reach another steady state.

VARICELLA

Recommendations for Use of Varicella Vaccine in Children <13 Years
Introduction: Dr. Jane Seward, NIP

Overview: With regard to updating varicella vaccine policy statements (1996 and 1999), issues related to a two-dose policy; catch-up; middle-, high-school and college vaccination requirements; HIV-infected children, those aged >13 years and those without evidence of immunity; prenatal assessment and postpartum vaccination. An FDA decision on MMRV vaccine licensure is expected in September.

MMRV Workgroup Report
Presenter: Dr. Judith Campbell, Chair

Overview: Background of vaccine development, ACIP and AAP recommendations and Workgroup activity.

Following the varicella vaccine's licensure, the AAP recommended it in 1995 and ACIP did so in 1996. Updates to the latter in 1999 included its use for child care and school entry, outbreak control, postexposure prophylaxis, and among those with HIV. In 2003, the MMRV Workgroup was formed to review and summarize, for potential ACIP revisions, the relevant data and policy statements on the prevention of measles, mumps, rubella, and varicella. They also presented data on the development of MMR and VZV vaccines. The workgroup decided to focus first on varicella to review and update related statements and recommendations, particularly pertaining to MMRV use among children aged ≤13 years. A review of the literature to update the varicella zoster statement would follow.

The HP2010 goal for varicella is to achieve >90% vaccine coverage for children aged 19-35 months and adolescents, and to reduce by 90% the 1998 rates of varicella disease. The long-term varicella vaccination program goal of varicella elimination (the absence of sustained endemic transmission) was stated in October 2004.

Workgroup activity included examination and discussion of:

1. The characteristics/transmission of breakthrough infections, their effect on public healthcare systems, transmission of varicella in highly vaccinated populations, and data on postlicensure vaccine effectiveness and correlates of protection.
2. The two-dose VZV vaccine regimen's safety, immunogenicity, and efficacy; possible fiscal barriers to implement such a schedule and the CE of a one- versus two-dose

strategy.

3. Issues related to programmatic implementation of a two-dose recommendation, including dose timing, education required, and a catch-up strategy. Given those, the Workgroup was in consensus that a two-dose regimen should be implemented.
4. Partners' views on the two dose varicella vaccination protocol: AAP, AIM, ASTHO, CSTE, AAFP, ACOG, and HICPAC. They agreed.
5. Continued safety/immunogenicity research and the pending licensure application of MMRV.
6. An alternative to VZIG, soon to be unavailable, for postexposure prophylaxis.
7. Update of the existing ACIP statements on varicella prevention as regards postvaccine era epidemiology; revised definition of evidence of immunity; re-emphasis of the importance of school-entry requirements; and addressing the issue of postexposure case management for healthcare workers.

The Workgroup supported the recommended revisions to be presented for a vote: routine two-dose vaccination strategy; catch-up vaccination for children who received a single dose of varicella vaccine; vaccination of susceptible persons aged ≥13 years; requirements for middle school, high school, or college entry; screening and immunization of postpartum women; and expanding the recommendation for HIV-infected but minimally symptomatic children with HIV.

Review of 2004 U.S. Varicella Epidemiology
Presenter: Dr. Dalya Guris, NIP

Overview: Vaccination program goal; disease burden in the pre- and post-vaccine eras; rationale for and data on a second dose strategy; potential impact of two-dose regimen.

Overall, varicella has caused a significant societal health burden. In the pre-vaccine era, an estimated 4 million cases of varicella caused 10,500-15,000 hospitalizations annually and 100-150 deaths (>1 child and adult varicella mortality weekly). The main risk factors for severe disease were extremes of age and immunodeficiency. Congenital varicella syndrome occurred in 1-2% of pregnancies within the first 20 weeks of pregnancy.

Reduction of incidence in the post-vaccine era was summarized with several examples:

- As of 2003, vaccine coverage ranged from 77%-89% and was 85% among children aged 19-35 months. Varicella incidence data consistently reported by four states was compared for the period 1993-95 versus 2004. With coverage rates ranging from 77%-89%, case reductions declined in a range of 52%-87%.
- CDC's Varicella Active Surveillance Project (VASP) sites in Antelope Valley, CA and West Philadelphia showed a decline of 83% and 93%, respectively, over the period 1995-2004, from >4000 cases to <1000. Although incidence declined in all age groups, the drop was the greatest in the age groups primarily targeted by the vaccination program, children 1-4 and 5-9 years old. Over the same period, charted VASP data also showed a decline in varicella-related hospitalization rates from 3/100,000 population to 0.6/100,000.
- Varicella related mortality also declined an average of 87% among persons aged <50 years from 2001-02.

Outbreaks. However, improvement in vaccine-induced immunity remains a need. Data from outbreak investigations in child care centers or schools indicated a 1-dose varicella VE of 71%-100%, most at 80%-85%, and a 93%-100% VE against severe varicella. Nonetheless, the VE in three outbreak investigations was <70% (range of 44-59%). While those lower rates constituted the minority of VE data, the reasons for this discrepancy remain unclear.

VE failure risk factors. Several risk factors for vaccine failure have been investigated: age at and time since vaccination, asthma, use of steroids, eczema, and cold chain failures. Age and time since vaccination seemed likely in some studies, but the data were neither consistent nor verified in a large prospective study, and data presented to ACIP last February (N=7000 vaccinated children followed for 8 years) showed no relationship to those factors for vaccine failure.

Disease severity/breakthrough disease. In general, varicella in vaccinated persons is less severe than that among those unvaccinated. VASP data of 2003-04 indicated that 30% of vaccinated children had 50-500 lesions, versus 66% of those unvaccinated. Hospitalizations and deaths are rare among vaccinated varicella cases. Only two death are known of vaccinated children, both in Pennsylvania and both with severe underlying conditions.

Varicella is infectious among vaccinated persons. A household contact study of VASP data found that vaccinees with ≥50 lesions were as infectious as unvaccinated cases with the same number of lesions. However, while vaccinees with <50 lesions were only a third as infectious as unvaccinated cases with ≥50 lesions, they were also more mobile and therefore may have a higher number of contacts that result in infections.

Outbreaks. Reported varicella outbreaks among highly vaccinated (coverage 96%-100%) school children indicate an overall attack rate of 11-17% among vaccinated children, going as high as 41%. The vaccinated cases were infectious and their one dose was not sufficient to provide herd immunity capable of preventing school outbreaks. Varicella outbreaks also are not isolated. Of a recent survey of 57 immunization grantees, 85% had been contacted about varicella cases or outbreaks in 2004. Of those, 62% had <10 outbreaks and 18% had ≥10. Only 15% of grantees thought that they had heard of nearly all of the outbreaks occurring in their area; 87% responded to the outbreaks. In 2004, the median age in most of the outbreaks was 5-9 years, and most of the outbreaks had <10 cases identified.

The estimated cost of outbreaks was developed from data collected from seven 7 grantees (public health and other involved institutions). Excluding the costs of time lost by cases and parents, the average outbreak response cost was $3000, rising to $6000 for active (i.e., VE assessment) outbreak response. One reported hospital outbreak investigation cost $7700.

Vaccination program implementation experience.

- Massachusetts had one of the highest vaccination coverage rates in the nation in 2003, at ~89% among children aged 19-35 months. School entry laws required varicella vaccination for grades K-12 by 2005 (except sixth grade). Post-vaccine varicella incidence declined by 80%, but cases and outbreaks (including school outbreaks) continue. Schools and state/local health department staff are increasingly burdened by investigations and response to inquiries on breakthrough cases. The largest proportion of cases occurred in the 5-9 year-old age group (of those, 87% were

vaccinated in 2004), but the number of cases among those aged 10-14 years increased in the last three years. Overall, 73% of cases were vaccinated.

- Texas' varicella incidence dropped dramatically in 1999, as vaccination coverage rose. By the 2004-2005 school year, Texas students K-4 and 7-10 were covered by varicella vaccination. Despite that, the number of cases plateaued in the last several years, and there were 53% more cases reported in 2004 than in 2003. Most of the reported cases were among children aged 5-9 years, but like Massachusetts, cases reported among 10-14 year-olds also increased over the last 3 years. Data on 41% of the cases reported in 2004 indicated that 75% of the cases aged 1-4 years and 82% of the cases aged 5-9 years were vaccinated.
- Connecticut had the highest vaccination coverage in the nation in 2003, at ~93% among children aged 19-35 months. Since varicella surveillance began in 2001, the annual case counts have varied only slightly, as vaccination coverage rose from 84% to 93%. Yet again, most of the cases were reported among 5-9 year-olds, and case totals rose among 10-14 year-olds over the last 4 years. In 2004, 58% of the cases in 10-14 year age group were vaccinated. About 25% of the ~1500 private and public schools in Connecticut reported at least one case in the last four years, with 5-7% of those with $\geq$10 cases.

Active surveillance data from West Philadelphia and Antelope Valley reflected differences in disease reduction rates. Antelope Valley maintained an annual variation in cases, peaking in 2004 mainly among school-aged children, while the number of cases declined steadily in West Philadelphia. The latter adopted school entry laws earlier and achieved wider vaccination coverage among school children. They also instituted strict exclusion policies for cases and susceptible contacts when a case is reported in a school environment. From 1995 to 2004, the age distribution of varicella incidence changed from a peak age of 3-6 years to 9-11 years.

Accumulation of susceptibles. Exposure risk declines along with overall incidence, but with an 80% VE, even a 100%-covered population will have 20% susceptible. The total number of susceptibles is rising, both those vaccinated with one dose and those unvaccinated. Those persons are at risk for disease and outbreaks later in life when disease can be severe. A graph charted the rapid accumulation of susceptibles in a 1-dose vaccination program, a 4 million birth cohort, with 95% vaccination coverage and an 80% VE. That accumulation is likely to produce larger varicella outbreaks in the future.

Comparison: varicella and measles. While measles vaccination has dramatically lowered disease incidence, accumulation of susceptibles resulted in periodic epidemics. Between the vaccine's licensure in 1964, epidemics in the 1970s and in 1990 involved 55,000-75,000 cases. The continuation of school outbreaks despite effective school entry requirements made it apparent that single-dose measles vaccination was insufficient to prevent transmission in all settings. While earlier implementation of varicella vaccination school entry requirements raised coverage rapidly, its VE (less than that of measles vaccine) still leads to accumulation of susceptibles. As those children move toward adolescence and adulthood and the risk of more severe disease, concern is rising.

Second dose studies. The Ngai study (PIDJ, 1996) examined one- versus two doses of varicella vaccine in a cohort of 2000 healthy children, aged12 months to 12 years. They were divided into groups of one dose and a second group vaccinated with two doses 3 months apart. The two-dose

recipients had significantly lower systemic reactions and injection site rash, but a slightly higher rate of injection site reactions, excluding rash. Immunogenicity (titers ≥5 gpELISA units) were achieved 6 weeks post-vaccination, suggesting a correlate of protection. Six weeks after dose 2, 99.5% of children had antibody titers ≥5 and slightly more of the two-dose group maintained higher gpELISA-measured titers for the first 3 years after vaccination, compared to the 1-dose group. Thereafter, a smaller difference remained. (Kuter, PIDJ, 2004)

Watson (CID, 1995) studied a smaller group of children, using lymphocyte proliferation assays to measure VZV-specific CMI response. The children in the two-dose group had a higher mean stimulation index (at 34.7) after the second dose compared to the 1-dose group (23.1). Another group of 419 vaccinated children aged 12 months to 17 years received a second dose 4-6 years after the initial vaccination. At 52 weeks, the mean CMI for the 1-dose group was 23.1 versus 34.7 for the two-dose group. Large antibody level increases (from pre-booster 25.7 gpELISA GMT to 143.6) at day 5-16 post vaccination suggested an anamnestic response in most (77%) of the children. Among 74 children tested for CMI, a significant increase in lymphocyte proliferation response was seen at both 6 weeks and 3 months, (from 40.3 to 58.6 and 61.4, respectively) compared to the pre-second dose levels.

While the rate of breakthrough disease after one dose increased throughout the 10-year follow-up period, it plateaued at year 6 among the two-dose group and rose no further. And, after 10 years, there was a 3.3-fold difference in cumulative breakthrough rates: 2.2% for the two-dose group versus 7.3% for the 1-dose group. At the end of the follow-up period, the two-dose VE was 98.3%, significantly higher than that for one dose (94.4%). Similarly, when children with household exposures were included, the 1-dose VE was 90.2% versus 96.4% for the two-dose group.

Potential impact of two-dose regimen. Dr. Guris estimated the disease immunity for a two- versus 1-dose vaccination program:

- One dose, 95% coverage, 80% VE: 76 children immunized; 24 children susceptible.
- Two doses, 95% coverage and 93% VE: 88 children immunized, 12 susceptible. (The 93% VE of the second dose was estimated by calculating a 66% reduction in attack rate compared to 80% VE for one dose.)
- With herd immunity (calculated with the highest published reproductive rate published for varicella, 12), one 1-dose vaccination protects 83% of children and two doses protects 96%. The number of unprotected, susceptible children drops from 17 to 4. The second dose drops residual disease rates by 79%.

Discussion included:

- Of the 150 varicella-attributed deaths in the prevaccine era, ~45% were children, 55% were among adults from 1990 to 1994. Prevaccine pediatric deaths in the 1970s accounted for ~80% of the deaths.
- Varicella vaccine coverage is only ~20% in Japan, but they have documented breakthrough cases among vaccinees, and report VE in the same range as presented here.
- The current 1-dose vaccination program produces an ~80% reduction in cases. About ~80% of the residual cases should be reduced by dose two, based on a conservative 93% VE. A dynamic analysis model is now being used to account for the dynamic contact in the population.

- Based on the virus' reproductive rate, the herd immunity threshold is 92% coverage; 96% might maintain immunity.
- Dr. Watson reported no breakthrough cases among children in her district who had received two doses. College outbreak reports are beginning for this year; Philadelphia area colleges have had about two outbreaks/year. Most of the cases were unvaccinated, but the generation that has had one dose is now arriving on campus. Dr. Seward reported one death of a college student who was from Nigeria.
- Dr. Florian Trudeau reported that the infectiousness of breakthrough cases was reduced three-fold. There are no data to indicate the proportion of cases that were primary vaccine failures as opposed to secondary vaccine failures, but the reported number of lesions categorized them as mild cases.

Survey of Physicians' Opinions of Varicella Disease Burden and a Second Dose Vaccination.
Presenter: Dr. Mona Marin, NIP

Overview: Preliminary results of an ongoing CDC- University of Michigan study of physicians' opinions on varicella disease burden and second dose varicella vaccination.

Even with high 1-dose vaccination coverage and the >80% decrease in varicella incidence from the pre-vaccine era, cases of breakthrough varicella cases and outbreaks are common. The stable number of reported varicella in the last 3-4 years indicates that some overall plateau with annual variation has been met.

To gauge the likely compliance with a second dose vaccination, a study was done of 550 randomly selected general pediatricians (289 responses) and 550 family physicians (233 responses) between April and June 2005. The study population was profiled. A mailed two-page questionnaire was provided with information on the impact of the 1-dose vaccination policy and data on the efficacy of the second dose. Two follow-up mailings were sent 4 weeks apart; responses to a third mailing are still being received.

Physicians of both specialties considered the varicella vaccination program successful in reducing the number of cases, case severity, and time lost from school/work. A greater proportion of pediatricians than family physicians considered the program very successful, but more of the latter considered the program somewhat successful. Almost all pediatricians and 60% of family physicians treated breakthrough varicella in the last 5 years; ~75% agreed that breakthrough cases are infectious (~22% of the remainder had no opinion). Seventy percent of physicians of both specialties found the breakthrough burden to be acceptable and 42% of both believed that 42% of parents are upset when breakthrough cases occur..

Almost half of the pediatricians agreed that a second dose is needed to address breakthrough disease, while a third were neutral about that; the balance disagreed. Among family physicians, 25% agreed, 50% were and 25% disagreed. But an ACIP recommendation of a second dose would prompt almost 50% more of physicians of both specialties to administer it. About 66% of pediatricians would recommend a second dose, as would ~33% of family physicians. Three quarters of both specialties would recommend dose 2 if a combination MMR-V vaccine was available at a reasonable cost. About 78% said they would administer it with the second dose of MMR. Regarding parents, 71% of pediatricians and 59% of family physicians expected

compliance and almost 90% of both groups expected greater compliance if a combination MMR-V vaccine were used.

Discussion included a suggestion to ask about acceptance if the AAP or AAFP had recommended the vaccination. Dr. Marin appreciated that; it may be done for a planned herpes zoster survey.

Economic Evaluation of the Universal Varicella Vaccination Program in the U.S.
Presenter: Dr. Fangjun Zhou, NIP

> Overview: Update on economic evaluation of a U.S. universal varicella vaccination program

This study re-evaluated the economic impact of the universal 1-dose and a projected 2-dose varicella vaccination program in the U.S., from the payers' and societal perspectives. The societal perspective included direct and indirect costs. The analysis included varicella-related invasive group A streptococcal diseases, herpes zoster, and varicella outbreak costs.

The methods where quickly reviewed and were the same as were presented to the ACIP in October 2004. The model was based on the 2004 birth cohort of ~4 million children. A decision tree and treatment algorithm were used to calculate benefit-cost ratios (BCR: the (program benefit [costs averted by the program], divided by program costs) and cost-effectiveness ratios (CER: cost per outcome, such as cost per year of life saved). Data used were on demographics, vaccination, including vaccine cost, incidence of varicella and proportion breakthrough, direct medical and non-medical costs for varicella diseases, work loss costs for varicella diseases, and hospital infection-control costs. New parameters in this analysis were the costs of varicella-related invasive group A streptococcus infections, incidence of herpes zoster among vaccinees, and outbreak management.

For pre-vaccination incidence rates, 1990-1994 NHIS data were used, and for post-vaccination, the 2003 & 2004 VASP data, adjusted for underreporting. The proportion of post vaccination varicella incidence and the proportions of total cases among vaccinees was 49% in 2003-04.

Assumptions: Milder varicella among in vaccinated persons; a reduction of 67% in herpes zoster incidence with a 1-dose VE of 80%. For the second dose, coverage was assumed to be 95%, as with MMR2, VE of 93%, and resulting reduction of residual disease, 79%. Other assumptions were: no outbreak response in the pre-vaccine era; that for the 1-dose program was 977 outbreaks and a response rate of ~66%; average cost per outbreak of ~$6,000 (for public health response only). For a two-dose program, outbreaks were reduced by 79%.

Results. Total program costs included direct and indirect costs.

- 1-dose program: direct costs, $293 million; societal costs, $330 million
- Two-dose program: direct costs, $549 million; societal costs, $585 million.
- Incremental second dose program: direct and societal costs, $256 million.

Results then were presented in four, progressively comprehensive scenarios::

A. The parameters previously presented to ACIP meeting, the base case. Both 1- and two-dose programs were cost-saving from the societal perspective. For Scenario A,

the direct BCR for one dose was ~1.0 and the societal BCR was ~4.0. For a two-dose program, the direct BCR was 0.55 and the societal BCR was ~2.4. From the payers' perspective, the 1-dose program was close to break-even. The direct BCR for the incremental second dose was ~0.1; the societal BCR was 0.4. The second dose program prevented 6 additional deaths and save 458 additional years of life. From the societal perspective, it cost about $1,239,400 to save one year of life.

B. Scenario A, plus the additional cost for varicella-related invasive group A streps. There were no substantial changes for the BCRs of 1-dose and two-dose programs but the second dose program would prevent 8 additional deaths and save 549 additional years of life. For the societal perspective, it costs $993,337 to save one year of life.

C. Scenario B, plus costs for herpes zoster in vaccinees. The BCRs for 1-dose and two-dose programs rose significantly. The 1-dose program became cost saving from the payers' perspective (BCR of ~1.2) and the societal BCR for 1-dose rose to ~4.4. The direct BCR for the two-dose program was 0.76; the societal BCR for two doses was 2.72. The incremental second dose cost was $708,725 to save one year of life.

D. Scenario C, plus outbreak management costs, produced no substantial BCR and CER changes, but not all costs for outbreak management were included.

Conclusions. All the 1-dose scenarios that included herpes zoster in vaccinees were cost-beneficial (cost saving) from both the payers' and societal perspectives. Compared to no varicella vaccination, the two-dose program would be cost-beneficial (cost saving) from the societal perspective, saving $2.72 for every dollar spent. But compared to the 1-dose program, the two-dose program may not be cost effective.

Study limitations were the model's non-inclusion of a hypothetical increased herpes zoster in persons with a history of varicella due to reduced exposure to varicella; pain and suffering to family and friends of the ill patient; possible underestimation of outbreak management costs and varicella-related mortality (bacterial complications resulting in death may not list varicella on the death certificate); and potentially higher future post-vaccination incidence due to further accumulation of susceptible persons and future outbreaks.

Other vaccines BCR and CERs. A BCR >1 indicates a profitable investment; the intervention should be implemented upon funding. *Limitations:* Different studies could use different methods (e.g., assumptions, year of cost, discount rate, etc.), which could skew the mortality or morbidity results. Decisions should not be made only based on these ratios.

- DTaP, two-dose MMR and Hib are cost saving, with societal BCRs of 27.0, 26.0 and 5.4, respectively.
- Incremental MMR dose 2 and meningococcal vaccine (catch-up and routine) had societal BCRs of 0.49 and 0.27 and cost $161,647 and $138,000, respectively, per year of life saved.
- The earlier vaccines (e.g. DTaP, MMR) have high cost-benefit ratios although the incremental second dose of MMR was not cost saving. For the more recent vaccines, societal BCRs are lower (e.g., Hib) or not cost saving (meningococcal). The costs per life year saved from the societal perspective ranged from a savings to $1 million.
- The change in polio vaccination policy, from an OPV- to an IPV schedule, prevented 9.5 cases of VAPP per year, at a cost of ~$3.0 million per VAPP case.

Discussion included:

- Dr. Lieu thought the ~$700,000-$1 million cost per LYS to be quite a bit higher than other recently recommended vaccines. Dr. Seward commented that this analysis only considered mortality, not morbidity; the vaccine would have been more cost beneficial if that was also factored in.
- The incremental cost of VZ versus that of MMR alone was inquired, since costs should be lower with co-administration. Mr. Rick Haupt, of the Merck Vaccine Division stated that the price of MMRV would not be determined until the product is approved by the FDA
- The societal benefit calculation includes the parent/care taker's lost work time. The probably underestimation and exclusion of herd-immunity effects (which cannot be predicted with a second dose) would raise the CBR. On the other hand, the zoster estimate is based on a theory of aversion with leukemia and the anecdotal data to date are based on the vaccine's use among normal children. It is possible that over time, zoster could become more frequent and not be reduced as dramatically as varicella has been.
- The conservative 93% VE was used because the first-dose 94% VE seen in the trial wais not what NIP saw in the field.
- The herd-immunity effect was also included in the CE analysis conclusion of an 80% reduction of residual disease.
- A sensitivity analysis of vaccine cost could be done to determine the threshold that would reduce the cost per life-year saved to $50,000-$100,000.
- NIP is preparing for the same push toward indigenous elimination of sustained endemic transmission as was done for measles, when the epidemiology indicates a point of reasonable control. With a future vaccine to prevent zoster, the two vaccines together may make elimination of the herpes virus possible.
- Dr. LaRusso commented that the greater benefit of a two-dose schedule has been underestimated. Well beyond a reduction of breakthrough cases, he expected the real long term benefit to come in the reduction of zoster cases as these children age into that risk group. He urged less of a focus on cost effectiveness and more on future benefit from a current investment.

Summary of AAP Recommendation on a Two-Dose Varicella Vaccination Schedule
Presenter: Dr. Cody Meissner, AAP , COID

Overview: Discussions by the AAP's Committee on Infectious Disease (COID) of the two-dose schedule, for approval by the AAP.

Rationale. The COID was in favor of universal administration of a second dose of a varicella-containing vaccine to increase the number of vaccinees with a gpELISA of ≥5 (the serologic marker of cellular and humoral immunity) and to reduce the risk of of breakthrough disease after exposure. The second dose also will immunize the small percent of vaccinees with a primary vaccine failure with the first dose.

Timing The time of the second dose should be consistent with the 2003 Red Book measles recommendation: "The first dose should be administered at 12-15 months of age (this may change to 18 months) . . . The second dose is recommended routinely at school entry (i.e., 4-6 years of age) but can be given at any earlier age…" (e.g., a measles component in an international travel vaccine or an outbreak). There will be a minimum four-week interval

between two measles doses and a minimum interval of three months between any varicella-containing vaccine.

Data show an increasing number of breakthrough cases in highly vaccinated populations, even in states with high coverage (e.g., the Antelope Valley data), and no further rate reductions in recent years' data. Varicella may have plateaued in communities with high immunization rates. The varicella zoster virus may be able to sustain transmission among the 10%-30% vaccinees still susceptible to breakthrough disease. To prevent further outbreaks and further reduce the varicella disease burden, a two-dose schedule may be needed. Such a percentage of breakthrough disease can lead to misunderstanding by physicians or parents regarding vaccine efficacy and weaken the argument for and confidence in an immunization program overall. While breakthrough disease is mild, it is frequently the cause of school outbreaks, and it places an increased burden on public health.

Vaccinees who have breakthrough disease may be at lesser risk of zoster than vaccinees who do not have breakthrough disease. The zoster risk is lower after a single vaccine dose, and is also lower than that after wild type varicella infection, and it reduces such complications as post-hepatic neuralgia. Those developing breakthrough disease after vaccination presumably become infected/latently infected by both the attenuated strain and the wild-type varicella zoster virus. Theoretically, a vaccinee with breakthrough disease may be at increased risk of zoster than a vaccinee without breakthrough disease**.**

Waning immunity. There is concern that the immunity provided by a 1-dose approach may be insufficient to last into adulthood, when the effects of the disease are more severe. One sign of this may be when breakthrough disease becomes more common among college students or adults, as occurred with measles outbreaks before the second dose was recommended

Second dose. As Dr. Guris presented, one study demonstrated a three-fold lower risk of breakthrough disease in children who receive a second dose than those receiving one dose. evaluated children. A second study assessed the immunogenicity of varicella vaccine administered 4-6 years after initial dose and showed a brisk anemnestic response to both cellular and humeral immunity in the 2-dose group 4-6 years later.

The COID concluded that a second dose is indicated, and made that recommendation to the AAP. They also hoped that MMRV will be licensed and then considered in this recommendation.

Discussion included:

- Dr. Plotkin commented that an accumulation of susceptibles at risk as they enter adulthood suggests the need for catch-up vaccination. He suggested emphasis on the success of the 1-dose regimen to date, and that the incidence plateau is not an increase in varicella. Dr. Meissner expressed AAP's agreement that catch-up is important, and AAP is addressing such related issues as timing. The costs of stocking multiple new vaccines have been raised as barriers by pediatricians, beginning with Prevnar. The COID expected the price increase of the combination- versus single-dose varicella and MMR to be modest. However, their recommendation will address the issue of the vaccine's reimbursement by third party payers as much as possible. In effect, the cost has probably been the reason that the field is waiting for the combination

vaccine; there is always a transitional period between recommendation and implementation.

- The analogy to the measles dose experience was rejected on several counts. While the MMR2 is given to capture the 5% of primary vaccination failures, a second varicella dose is principally to raise the number of vaccinees with a gpELISA marker >5, since the vaccine has only a 1-2% primary failure rate after one dose. In addition, unlike measles, there is no international varicella eradication program underway, surveillance is inadequate, and waning VE implies that 3-5 doses may be necessary over a lifetime. There may be another solution to waning immunity than multiple doses, such as developing a more potent dose, as with the shingles vaccine.
- Dr. Poland saw no compelling reason to issue a recommendation at this point, since MMRV may be available within months. He suggested, if a statement was to be issued for an interim period, that ACIP perhaps say "parents and physicians may wish to consider…" as done with meningococcal, Lyme disease, and other vaccines without the supportive data the ACIP has come to expect. He questioned on what basis there should be confidence that two doses would solve the problem of waning immunity.
  - *Response.* Dr. Mark Silber, of Merck, responded that across studies, studies, 80%-90% of children have a level of 5 after single dose, making that the starting point. Even at titers <5, some response will produce much milder disease. But a level of 5 gpELISA is not absolute; people with titers of ≥20 could still have breakthrough disease. Regarding a more potent vaccine, or giving Zostervax to children, there are no safety data to support that in a naïve population, unlike older adults who have primary boosting and endogenous or exogenous disease over years. In addition, the immune response plateaus at ~10,000 pfu, meaning little further immune response after dose 1 is likely, but the gpELISA levels and remains stable after the initial fall. Most of the breakthroughs after one or two doses occur within the first few years. After one dose, that falls to ≤1% per year, but continues. But the ten-year study found no cases at all with the two-dose regimen after the fifth or sixth year, suggesting that the primary failure point may have been passed.
- Dr. Dan Hopkins, of the Wisconsin Immunization Program, urged consideration of the state, city and county health department levels. They are "barely getting by" now and, for example, have two provision tiers for Menactra: those VFC funded and all others. Particularly states without universal purchase programs will have a hardship with this added recommendation. On the other hand, it was noted that further prevention of school outbreaks due to breakthrough disease would help relieve these agencies' response burdens. Dr. Howard Beck also estimated California's ability to save millions if the MMRV requires only refrigeration, but Dr. Wallace responded that the MMRV proposed for U.S. licensure still would require freezing.
- Input from the Canadian and U.K. experiences was requested. Dr. Naus reported routine varicella programs as operational in the past two years, so they are still focused on the 1-dose schedule at this point. Dr. Salisbury reported the U.K.'s more cautious approach, to avoid potentially increased zoster rates, shifting case rates into older age groups, and considerations of cost/benefit. They have had sophisticated economic and mathematical modeling done on the latter (tools he recommended), that clarified for him the complexity of the related questions. However, he could not share the results as these had not yet been published.

- The unlikelihood of WHO or PAHO to institute varicella elimination programs, and the likelihood of continued importations, reinforced the importance of maintaining a high population immunity in the U.S.

Dr. Seward summarized that the MMRV would just be a combination vaccine that can be used to implement a second dose of either measles or varicella, but this policy recommendation would be made on the basis of the current varicella vaccination program's status, independent of the availability right now of MMRV.

Dr. Cochi focused on the main question, of whether or not to go to the next program level, in terms of consolidating and further enhancing the control of varicella in the U.S.. Good varicella control is in place, but the program's impact is plateauing at 80-90% reduction in varicella cases, hospitalizations, and deaths, with some uncertainty at this time as to whether the Healthy People 2010 goal of 90% reduction in varicella cases will be reached. State and local immunization programs are spending increased time and human and financial resources chasing school and daycare-based outbreaks of mild cases of varicella. That would continue for the foreseeable future without implementation of a two-dose program, and over the next several years vaccinated children and adolescents will become no longer easily reachable to give them a second dose after they graduate from high school. The second dose's increased CMI and plateau at the low 2%-3% breakthrough rate indicated to him that a 2-dose schedule provides both quantitatively and qualitatively substantially improved protection against varicella compared with one dose of vaccine. The accumulating data and experience are in many ways not unlike that associated with the implementation of 1-dose schedules of measles, mumps, and rubella vaccines during the 1970s and 1980s, which ultimately led to introduction of a second dose (MMR vaccine) as those intervention programs matured and continued outbreaks of these diseases persisted in school and other institutional settings. From a cost standpoint, he acknowledged that increasing stresses are being felt at every level. But, he felt, action should still be taken for vaccines that still offer some cost benefit, and a 2-dose varicella vaccine program is cost saving from the societal perspective (i.e., including indirect costs). He urged that cost not be the driving force in this decision.

Vote on Varicella Vaccination Policy

Use of varicella vaccine in children aged <13 years. Issues were:

- New strategies are needed to improve varicella disease control and to move towards varicella elimination.
- The effectiveness of one dose of varicella vaccine is not adequate to prevent school outbreaks.
- Vaccinated cases, although mild, are contagious and may infect others, including persons at high risk for severe disease who cannot be vaccinated themselves.
- As disease incidence decreases, opportunities for exposure to VZV diminish for susceptible persons (vaccinated or unvaccinated); therefore, susceptible persons will accumulate and be at risk for varicella disease or large outbreaks later in life when disease can be more severe.
- Improved protection is provided by the second dose.
- Compared with no vaccination program, a 2-dose policy is cost saving from a societal perspective.

Vote to approve the second dose strategy
Children aged 12 months to two years should receive 2.5 mL doses of varicella vaccine, dose 1 at age 12-15 months (is to harmonize with MMR vaccination), and dose 2 at age ≤4-6, provided there is a three-month interval between the first and second dose.

Dr. Campbell **moved to approve the second dose strategy** as presented. However, **no second to the motion** defeated it and also eliminated the need to vote on catch-up immunization.

In discussion, it emerged that the reason for nonsupport of the motion was the unknown cost of MMRV, the uncertainty that it would be licensed as soon as expected, that ACIP cannot recommend on an unlicensed product, and that a permissive recommendation is not useful if the user is unable to pay for it (due to no VFC purchase and non-reimbursement by third party payers).

Recommendation of a second varicella dose for outbreak control. The precise wording for this aspect of the policy was not available, but Dr. Seward summarized that this would be in the context of a varicella outbreak, in which a second dose of varicella vaccine would be used for outbreak control in children aged 12 months to 12 years, providing three months have elapsed between the first and second dose.

Dr. Treanor moved to support the use of a second dose of varicella vaccine in an outbreak setting. Dr. Campbell seconded the motion. *Discussion* included note of one critical aspect to this, that being that the stock of VZIG is running out. In July, FDA was to discuss a substitute for VZIG

Vote to support a second varicella vaccine dose in outbreak settings

In favor: Treanor, Stinchfield, Salamone, Marcuse, Morita, Lieu, Gilsdorf, Finger, Campbell, Birkhead, Allos
Opposed: None
Abstained: Levin and Poland (conflicted); Abramson (uncertain of how effective this approach would be.)

The motion passed.

Middle-, High School and College Requirements. Issues were:

- Varicella outbreaks occur in school and college settings.
- Current ACIP recommendations (1999) specify requirements for child care facilities and elementary school.
- Because of the changing epidemiology of varicella, outbreaks among middle-, high school and college age students are likely to occur in the future unless students are protected.
- Adolescents and young adults without a history of varicella are now less likely to be exposed to varicella and are at risk of cohorting into adulthood still susceptible to varicella.
- Persons without evidence of immunity should be protected through vaccination.

Recommendation: *"ACIP reiterates its previous recommendation that official health agencies should take necessary steps, including developing and enforcing school immunization requirements, to ensure that students at all grade levels (including college) and those in child care centers are protected against varicella and vaccine-preventable diseases (ACIP, General Recommendations, 2002). School immunization requirements should be implemented when the vaccine has had time to be well incorporated into practice and supply is adequate."*

The change wrought by this recommendation from the current 1999 recommendation was to go beyond childcare and elementary school requirements to include middle school, high school, and college aged children and adolescents in the recommendation. This would address the concern about cohorting susceptible children.

Discussion included:

- This implies an endorsement of school entry requirements for all vaccine preventable disease, including such as rabies. Specificity to varicella was needed.
- History of chicken pox among children born before 1998 would be accepted as evidence of seroimmunity.
- Clarification of what the "necessary steps" are. This text was lifted from the General Recommendations, which also need to be revised.

Dr. Marcuse moved to amend the recommendation to say ". . . should develop and enforce school immunization requirements for varicella." He later clarified that this also applied to child care and all grade levels. Dr. Campbell seconded the motion.

Discussion included:

- The ACHA recommends that students be vaccinated against varicella, so practice guidelines are in place. This would reinforce states to move toward legislative requirements to ensure the implementation of the practice guidelines.
- Most of the college requirements in place apply to MMR or perhaps to diphtheria or tetanus; they do not include all universally recommended vaccines.

Vote on school immunization and child care requirements

In favor: Treanor, Stinchfield, Salamone, Morita, Marcuse, Lieu, Campbell, Gilsdorf, Finger, Birkhead, Allos, Abramson.
Opposed: None
Abstained: Levin, Poland (conflicted)

The motion passed.

Vaccination of persons ≥ 13 years without evidence of immunity.
Related issues were:

- Varicella infection is more severe and complications are more frequent among adolescents, posing twice the risk for hospitalization versus that of children aged 5-9 years and 2- to 7-times the risk for death versus that of children aged 1-4 years.

- Varicella infection is more severe and complications are more frequent among adults, who have 19 times the hospitalization risk of children aged 5-9 years and 27 times the risk of death versus that of children aged 1-4 years.
- Prevention of infection through vaccination is important in these age groups

Current recommendations from the 1996 and 1999 statements advised vaccination of healthcare workers, family contacts of immunocompromised persons, and persons at high risk for exposure or transmission. The latter included day-care center employees, teachers, people living in institutions, correctional facilities, nonpregnant women of childbearing age, adolescents and adults living in households with children, and international travelers.

Added to this recommendation is that *". . . Vaccination of other susceptible adolescents and adults is desirable and may be offered during routine health care visits. All healthy adults should be assessed for varicella immunity. Those without evidence of immunity should receive two doses of varicella vaccine (the current age-appropriate recommendation) 4-8 weeks apart."*

Discussion included:

- Evidence of immunity can be provided by: U.S.-born before 1965; for persons born between 1966 and 1997, a valid history of varicella based on healthcare provider diagnosis or self- or parental reporting of typical varicella disease; for persons born after 1998, written documentation of age-appropriate vaccination; evidence of two doses of vaccination or serological evidence of immunity; valid history of herpes zoster, or lab evidence of immunity. Some guidance is provided for atypical cases.
- State that the two doses should be "at least" 4-8 weeks apart.
- Dr. Neuzil was hesitant about this recommendation, fearing confusion without the provision of further guidance, particularly with impending zoster vaccine and a higher dose of varicella vaccine. Dr. Seward responded that the adults in this recommendation essentially all fit into the high risk groups. As with influenza vaccine, the Workgroup felt it better to not recommend according to risk, but to make it available to all susceptible adolescents and adults; that is, all those without evidence of immunity, again to reach the cohort that may mature into the age of risk for severe varicella disease. The licensure indicates no upper age limit, but virtually no one over 30 is susceptible to varicella. The prevaccine immunity susceptibility was 4.5% among people in their twenties, 1% of those in their thirties, and <0.5% in those aged ≥40. This still involves relatively small numbers but that could change with the epidemiology. Dr. Neuzil advised wording to make it clear that this applies mainly to those aged ≤40, to avoid any confusion with a potential zoster vaccine.
- Dr. Schaffner advised waiting on this recommendation, as he felt the motion to be too unstructured and unlikely to gain internists' attention the way the publicity for the shingles vaccine has. Dr. Seward responded that clarifying the wording on susceptibility and pertinence mainly to adults aged ≤40 could be done. But she saw no need to delay this recommendation, since ten years of multiple recommendations for use among adults has had no debate. This statement was simply to reach the very few who have not been covered by the recommendations to date.
- Dr. Wexler favored a simplified recommendation for adults because the harmonized schedule language now includes almost all the 5% who are susceptible. She suggested that it just be age-based to better ensure that attention to it.

Dr. Marcuse moved to recommend that all healthy persons born since 1965 should be assessed for varicella immunity and vaccinated if needed. Dr. Campbell seconded the motion. **Friendly amendments offered by Dr. Abramson and Dr. Birkhead** were to simply specify all those born since 1965 and to advise their vaccination "if they have no contraindication." Dr. Marcuse accepted the amendments.

Vote for immunization of all those born since 1965.

In favor: Treanor, Miss Stinchfield, Mr. Salamone, Morita, Marcuse, Lieu, Gilsdorf, Finger, Campbell, Birkhead, Allos, Abramson
Opposed: None
Abstained: Levin, Poland (conflicted)

The motion passed.

Recommendation for Prenatal Assessment and Postpartum Vaccination. Issues were:

- Varicella infection is more severe and complications are more frequent among adolescents and adults
- Pregnancy may further increase risk of severe varicella
- VZV is teratogenic – the risk of congenital varicella syndrome is 1% for women infected in the first 20 weeks of pregnancy, 2% risk at 13-20 weeks, 0.4% risk at 0-12 weeks.
- Congenital varicella syndrome may be manifested by low birth weight, cutaneous scarring, limb hypoplasia, microcephaly, cortical atrophy, chorioretinitis, cataracts and other anomalies
- There is no evidence that varicella vaccine virus is excreted in breast milk.

Recommendation: "*Prenatal assessment of women for evidence of varicella immunity is recommended. Upon completion or termination of their pregnancies, women who do not have evidence of varicella immunity should receive the first dose of varicella vaccine before discharge from the hospital, birthing center, or abortion clinic. The second dose should be administered 4-8 weeks later, after delivery at the post-partum or other health visit. The use of standing orders is recommended for health care settings where completion or termination of pregnancy occurs to ensure the administration of varicella vaccine."*

Discussion included:

- Again, say the second dose should be administered at least 4-8 weeks unless contraindicated…"
- Education of pharmacists will be needed, particularly as regards breastfeeding, to reassure them that the vaccine is safe for postpartum administration.

Dr. Treanor moved to approve the recommendation text as amended. The motion was seconded by Ms. Stinchfield.

Vote on vaccination of pregnant women

In favor: Treanor, Stinchfield,. Salamone, Morita, Marcuse, Lieu, Gilsdorf, Finger, Campbell, Birkhead, Allos, Abramson

Opposed: None
Abstained: Levin, Poland (conflicted)

The motion passed.

Administration of live varicella vaccine to HIV-infected children

> Overview: Studies reviewed for data regarding extension of the present recommendation beyond the present recommendation to vaccinate children qualifying under CDC's immunologic Class 1 and Clinical Class A and N criteria, children with current or past significant depression of CD4+ T-cells.

Data were presented on symptomatic children as defined under CDC Class B or Immunologic Class 2 (N-2, A-2, B-2), who have CD4 percentages ≥15% and a minimum CD count that is based depending on their age.

Study design, ACTG 265 involved a cohort of 37 varicella-naïve (antibody-negative) children, 17 who graduated from AIDS to Class I on HAART, 43 CDC Class A1 or N1, and 37 CDC Class N2, A2, B2. The control group had natural varicella ~1 year before entry to study; A1/N1; no vaccination. Two doses of Varivax were given in a three month interval; follow-up was done through weekly calls and a clinic visit for grade ≥3 serious events, maintenance of a report card for six weeks, as well as chemistries and hematology.

Antibody levels to VZV were measured by CMI at baseline and 8 weeks after each does, then at year 1, 2, and 3, as shown by LPA and RCF assays. These were used to ensure that the levels of viral load and memory cells against VZV remained stable. Those who had neither antibody nor CMI received a third dose.

Results. Local reactions occurred in 10-21% of the children, similar to uninfected children's rates, and systemic reactions were identical to uninfected children. Of the systemic reactions, ~20% were grade 3. Most were due to concurrent and unrelated factors: fever, otitis media, viral syndrome reaction, all minor events. There were far fewer such reactions with subsequent dose(s) due to their partial immunity, but the viral syndrome and otitis remained similar

Safety. Some significant events occurred: a child with otitis media had a seizure with a high fever, but late after vaccination; four children's "pneumonia" was not related (three negative x-rays, the fourth recovered quickly without antivirals); one child with a minor vesicular rash as also is seen in healthy children. There were no changes in viral load or CD4 count. As seen with healthy children, 60%-70% of the participants had a FAMA antibody response. Of those negative at one year who received a third dose, <50% seroconverted, but at years 2 and 3, these children had the same level of antibody responses as HIV-infected children who had natural varicella.

Immune response. CMI was measured by the LPA assay for all the children and those with a negative baseline. At 8-, 20-, and 52-weeks, a ~65% immune response was seen, for all the children and those with a negative baseline. The same result was seen when the analysis was limited to the negative baseline. Overall, 75% had a positive LPA CMI at year 1, and the same was true of the RCF assay: 70-80% positive CMI response to VZV at week 20 or 52, with no high

baseline. False positives were rare. More than 65% had a response after two doses, as did 80% by one year. Of the 16 reported exposures, no child developed varicella, although one child may have had herpes zoster.

Use of varicella vaccine in HIV infected children. Issues were:

- HIV-positive children are at risk for increased morbidity and mortality from varicella and herpes zoster.
- Two doses of varicella vaccine administered 3 months apart are safe and immunogenic in HIV-positive children with age-specific CD4+ T-lymphocyte 15%-24%.

Recommendation: *"HIV+ Children with age-specific CD4+ T-lymphocyte 15%-24% should receive two 0.5-mL doses of varicella vaccine 3 months apart. The updated ACIP recommendations will reflect CD4+ T-lymphocyte ≥ 15%.*

Dr. Treanor moved to approve this recommendation, making the text to parallel that for the use of MMR among HIV-infected children. Dr. Finger seconded the motion. *Discussion* included note that this was essentially an off-label recommendation. However, Dr. Levin cited the vaccine's ability to spur a detectable response in children with >15% CD4 cells, including those who reconstituted from <15% CD4 cells. The MMR vaccine posed more of a risk than this vaccine, for which there also is a therapy.

Vote on vaccination of HIV+ children

In favor: Treanor, Stinchfield, Salamone, Morita, Marcuse, Lieu, Gilsdorf, Finger, Campbell, Birkhead, Allos, Abramson
Opposed: None
Abstained: Levin, Poland (conflicted)

The motion passed.

Other areas updated in the document addressed***:***

- Evidence of immunity.
- The health care worker section was updated with HICPAC. Some changes address how health care workers are dealt with after vaccination: not doing anamnestic testing, but monitoring daily to day 21 after exposure. If they develop any symptoms, they are placed on sick leave immediately.

The committee agreed to think overnight about whether to proceed with updating the ACIP recommendations, which now were not in harmony with AAP recommendation on two doses (if the AAP approves the COID advice), or to wait to vote on a two-dose policy once MMRV is licensed. Aspects offered for their consideration overnight included:

- A permissive recommendation was still possible, as was used both for influenza and meningococcal vaccine as a stepping stone to a recommendation.
- Dr. Watson expected public skepticism in the absence of an ACIP recommendation, as occurred when the hepatitis B vaccine was implemented in schools. That, coupled with the conflict to the AAP schedule, will make public health's job very difficult.

- Dr. Neuzil noted that the Workgroup would have to discuss guidance for adults with HIV, as done for the infected children, as there currently is none.
- Dr. Lewin related his decision to get a second dose for his 11 year-old. The pediatrician tested her serology first and found that she did not need it. He expected insurance companies to require a test to show no immunity, which will probably discourage people from getting vaccinated.

General Recommendation Workgroup Report
Presenter: Dr. Andrew Kroger, NIP

Overview: Status and process of revising the ACIP General Recommendations every five years; update on storage and handling of immunobiologics.

Sections of the General Recommendations that are expected to require some minor edits were those that addressed:

- Timing and spacing of immunobiologics.
- Contraindications and precautions.
- Vaccination records.
- Reporting adverse events after vaccination.
- Vaccination programs (including school entry vaccination).
- Vaccine information sources.

Status. To date, revisions are complete on the vaccine administration section and partial revisions are beginning on the sections addressing special situations, altered immunocompetence and hematopoietic stem cell transplants. Now separate, those last two sections may be merged.

Storage and Handling of Immunobiologics were addressed on this day. The goal is to have the document ready for submission to the *MMWR* after October 2005 for publication in 2006. The changes included (referenced pages in parenthesis):

- Preferred equipment for maintenance of cold chain (P1): Combination refrigerator-freezer unit sold for home use is acceptable for vaccine storage if the refrigerator and freezer departments each have a separate external door. The presence of food or drinks in the refrigerator leads to frequent opening and closing of doors …… Therefore, food and beverages should not be stored in vaccine storage units. (P2, L3)
- Procedures for out-of-range temperatures added (P3): Temperatures for both the refrigerator and the freezer should be documented twice a day and recorded. The backup person should review the log on a weekly basis.(P2, L12). An out-of-range temperature reading should prompt immediate action….Next, determine if the vaccine is still useable by contacting the manufacturer or state/local health department. (P3, L5). The proper response to out-of-range temperature storage is briefly outlined and includes: Have a plan; label the vaccine "do not use;" check for quick-fixes (e.g., is the door left open?); contact the manufacturer/state local health department to determine if the vaccine can be used. If it can, move it (unless there is a quick fix possible) or if not, discard it.
- Language on use of expiration dates strengthened (P3) providers …should note whether there is an expiration window for vaccine stored at room temperature or at an intermediate temperature. (P3, L19) After opening the vial, the remaining doses in

a multiple-dose vial can be administered until the expiration date printed on the vial or vaccine packaging (P4, L1)

- Procedures for mishandled or inappropriately stored vaccines was strengthened (P4). If a vaccine has been administered and subsequently found to be mishandled or stored inappropriately, the state health department should be contacted. In general, the dose should not be counted as valid and should be repeated, unless serologic testing is performed and indicates an adequate response to the vaccine (P4, L26)

Next steps: Revisions will begin to the Altered Immunocompetence section of Special Situations. Two realities drive the major revisions to this section: 1) there are many new drugs that compromise immunity to variable degrees and 2) some of these drugs, e.g. Tumor Necrosis Factor antagonists, are in common use, and used for rheumatoid arthritis, Crohn's disease, and psoriasis. There's an article in August of 2004 about TB as an adverse event related to these drugs. Consultation has been requested from individuals specialized in allergy/immunology medicine/research

Discussion included:

- *What information sources are available to guide the state/local departments who will be asked what to do?* Whether or not there is information at state/local level does not preclude recommending that they know about it, but the information may lie with the manufacturer or elsewhere.
- Dr. Halsey reported facing exactly this cold chain problem twice in the last six weeks. Few have the knowledge needed to give advice; some relevant tables really need to be developed. He urged the manufacturers and CDC to do so. He felt that the current wording was too rigid and could lead to over-immunization of some children. For example, DTaP would not need to be readministered even if it was stored for <24 hours at <13º F. However, ACIP has already recommended two doses for the elderly, so a qualifier is needed for that and to address the expiration date for yellow fever vaccine, which cannot be stored after reconstitution. Dr. Wallace responded that developing such tables to address decision-making for vaccines stored outside the proper temperatures has been frustrated by the manufacturers' unwillingness to release the related proprietary information. However, one certainly is that vaccine stored too cold is a much bigger problem than that stored too warm.
- Dr. Birkhead advised the state/local health departments be kept in the loop on these discussions, as they advise practitioners and conduct the quality assurance visits, so as to have some consistency of advice around the country.
- Dr. Grabenstein, as the author of ImmunoFacts, reported also finding manufacturers' uniform reluctance to discuss anything outside of the package insert. CDC needs to commission the studies of such common events things as what to do if a refrigerator is left off all weekend, to avoid wasting of millions of dollars of vaccine.
- Dr. Becker agreed that referring questions to the states is appropriate, but they do not have the proper information either. Any way that CDC can either promote that research, or get the manufacturers to address it, will be appreciated. Many health departments have documented practices that dutifully recorded fluctuating improper temperatures for weeks or even years. In view of the difference between repeating one dose or a whole series, those data are urgently needed.
- Dr. Baylor commented that all the data the manufacturers have for various scenarios cannot fit on the package insert, but they do include the data on stability. He

suggested that CDC call on the manufacturers to discuss these issues. Dr. Levin agreed.

With no further comment, the meeting adjourned at 7:05 p.m. and reconvened at 8:00 a.m. on the following morning.

JUNE 30, 2005

On the following morning, Dr. Levin presented a certificate of appreciation to Mr. John Salamone for his service on the ACIP board. Mr. Salamone recalled first attending the ACIP with other parents of children who had developed VAPP after immunization with the oral polio vaccine. He appreciated the committee's response to their plea for an ACIP recommendation for use of only the injectable polio vaccine in the U.S. Now, he expressed his great appreciation of the unexpected opportunity to actively work with the committee and its liaisons, whose pursuit of a safe and excellent immunization program is an immense service to the nation.

UNFINISHED BUSINESS

Completion of Tdap Discussion/Vote
Presenter: Dr. Karen Broder, NIP

Dr. Broder presented the proposed recommendations on the use of Tdap, based on the previous day's discussions.

1. Routine Tdap vaccination of adolescents (11-18 years):

"Adolescents aged 11 to 12 years should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood DTP, DTaP vaccination series and have not received Td. Routinely administering Tdap to young adolescents will reduce the morbidity associated with pertussis in adolescents.

"Adolescents aged 13 to 18 years who have not received Tdap should also receive a single dose of Tdap instead of Td if they have completed the recommended childhood DTP, DTaP vaccination series and have not received Td."

There was no discussion on this recommendation.

2. Universal or permissive recommendation for adolescents who received Td but are not protected against pertussis.

"Adolescents aged 11 to 18 years who received Td may receive a single dose of Tdap to provide protection against pertussis if they have completed the recommended childhood DTP-DTaP vaccination series. A five-year interval between Td and Tdap is encouraged. In settings of increased risk from pertussis, shorter intervals can be used."

Readers are directed to the Special Situations section for text on increased risk from pertussis, in which outbreaks will be addressed, with language allowing the provider to use Tdap at shorter intervals.

"Vaccine providers can consider administering Tdap after Td at shorter intervals than

five years, particularly when the benefits from providing protection against pertussis are likely to be increased. Situations include those where an adolescent is at increased risk of exposure to pertussis, e.g., during a pertussis outbreak, or when protection for an adolescent is desired because close contacts of the adolescent may be at increased risk for severe pertussis, e.g., an adolescent who has close contacts with infants. The safety of intervals as short as two years between Td and Tdap is supported by a Canadian study of nearly 6,000 children and adolescents." A detailed description of the study will be provided.

Discussion included:

- Dr. Marcuse felt the use of "may receive" to be too loose to provide guidance and preferred "should provide." Dr. Abramson explained why the more permissive language was desirable at this stage. It would not require practitioners to recall patients, something that many cannot do; and since realistically, universal vaccination would not occur for a few years, it was felt preferable to wait on the data to come. On the other hand, Dr. Cochi raised the goal of maximizing the public heath impact on pertussis among adolescents, and suggested the text "are encouraged to receive," with the circumstances and limitations of potential side effects then listed.
- The intervals received extensive attention. Dr. Orenstein advised greater clarity on why the 5-year interval was chosen and on assessing the risk of Arthrus and local reactions versus that of pertussis.
- Coverage by third party payers is likely upon an ACIP recommendation. A permissive recommendation to ensure the 5-year interval and minimum risk of reaction will be reassuring to them.
- *Outbreaks.* Altering the recommendation from a permissive to an advised status in an outbreak situation was discussed. While Australian data presented to ACIP in the past did not support the effectiveness of the vaccine to intervene in an outbreak, it may have been the delay in vaccination that defeated the vaccine.
- Alternatively, it was suggested to simply state up front that an interval as short as two years could be used, to allow maximum flexibility to the provider.
- Dr. Treanor suggested splitting this discussion two ways: 1) For routine adolescent vaccination, is the risk of pertussis in late adolescence so high as to require a recommendation for a catch up campaign?; and 2) What is the interval recommended between diphtheria- and tetanus-containing vaccines?
- A 5-year interval could age potential vaccinees out of the biological, pubertal range of adolescence and lose vaccination opportunities, including VFC coverage. Without strong data to validate that risk, Dr. Middleman urged reconsideration of that.
- The Canadian study data did not include meningococcal conjugate vaccine. Since adolescents will be exposed to another diphtheria vaccine, a 5-year interval is reasonable unless they are in risk settings (e.g., with an infant in the household or another increased risk outside of an outbreak).
- Currently, the recommendation encouraged the 5-year interval but cited Canadian data in support of 2-years. No language prohibits a shorter interval than 2 years if the provider determines that the benefit outweighs the risk.

Alternative text suggested included the following: "Very large studies show the 5 year interval to be safe, but there are theoretical concerns that a 20-year interval may involve reactions such as

Arthrus." Say "encouraged to receive," and be technically correct about the definition of 11-12 year-olds as children, not adolescents (perhaps use "pre-adolescents"

Conclusion. There was general agreement to change the text to say: *"Adolescents aged 11 to 18 years who received Td are encouraged to receive a single dose of Tdap to provide protection"* and to separate the guidance points as Dr. Treanor suggested. It should also explain that the 5-year interval was designed to limit the theoretical risk of local reactions, perhaps by routing them to another section (in favor of brevity). (The term "minimum" was removed to avoid any implication of safety data to support that.)

3. Simultaneous Administration. *"Vaccine providers are encouraged to administer Tdap and MCV4 during the same visit if both vaccines are indicated."* (There was no discussion on this point, an agreed basic principle.)

> *"Simultaneous administration of Tdap or Td and MCV4, which all contain diphtheria toxoid, during the same visit is preferred when both vaccines are indicated. If simultaneous vaccination is not feasible, ACIP recommends that inactivated vaccines can be administered at any time before or after different inactivated or live vaccine unless contraindications exist. MCV4 and Tdap or Td can be administered using any sequence.*
>
> > *There is a theoretical risk of increased rates of severe local reactions when two diphtheria-containing vaccines are administered within a short interval not on the same day. Td followed one month later by MCV4 in 512 subjects was studied, and the rates of local reactions were comparable to simultaneous vaccination. MCV4 followed by Td has not been studied. Tdap and MCV4 schedules have not been studied."*

The reader will then be routed to detail on the postlicensure studies. The 3-year interval discussed on the previous day was dropped. As discussed by the Workgroup, the administration of MCV4 first was advised, as it has the high diphtheria content, followed by Td or Tdap, although some theoretical concerns lingered. The 3-year sequence was replaced by a directive for the clinician to attempt simultaneous administration; if that is not possible, they can use any schedule to achieve coverage. The safety data limitations are discussed, as are the theoretical concerns, and the likelihood of more guidance in future. The ACIP had agreed to cite expert opinion, the 3-year interval could be cited, with information for the practitioner's use to decide if the benefit would exceed the risk. However, the Workgroup feared that this approach might create confusion, and favored instead guidance that simultaneous administration is best but, if not possible, the practitioner should just do the best they could, being aware of the concerns and await further information.

Additional comments included:

- Dr. Levin advised adding some short text to explain why in some cases, simultaneous vaccination would not be feasible (e.g., not indicated or one vaccine is not available).
- Dr. Baker advised keeping things as simple as possible to help the practitioners understand what will get the largest number of eligible people vaccinated. In this language, "are encouraged" clearly does not equate to "recommended" and risks defeating the purpose of giving both vaccines if one or the other is recommended. She suggested, instead, the following: " . . . should be administered during the same visit if both vaccines are indicated. When administering either Tdap or MCV4, the

other vaccine should be administered simultaneously." That would provide for insurer reimbursement for both vaccines, make the guidance much simpler, and advance the goal of replacing Td with Tdap to prevent pertussis. While there may be special situations when that is not feasible, she urged as much clarity as possible to the overall rule so that the readers get the point.

- Dr. Salisbury commented that Tdap's likely replacement of Td will make the advice on Td followed a month later by MCV4 quickly obsolete. Advice is needed, rather, on MCV4 and Tdap, which will both be in use but are only referred to as "not studied." That leaves practitioners on their own, even though the previous paragraph allows the vaccines to be administered in any sequence.
- Dr. John Iskander reported VAERS data indicating that practice patterns are adopting MCV4 according to the childhood schedule, including among children who were vaccinated with Td on schedule.

Conclusion. Dr. Abramson stated, to no dissent, that the proposed recommendation text is on the first page. Its purpose is to acknowledge that for the first few years, this vaccine will probably will not be given simultaneously, in part because of the mixed payment system of the states. Given that, some guidance is given about nonsimultaneous administration for transparency, to advise what is known or not ─ but later in the document. The recommendation text is short and clear.

Contraindications were applied to persons with a history of encephalopathy following DTaP or DTP, progressive neurologic disorders, uncontrolled epilepsy, and progressive encephalopathy until the condition is stabilized. Rather than the absolute contraindication for pediatric DTaP, the Workgroup suggested that here it be a precaution and reason to defer for Tdap. Other precautions for pediatric Tdap will be clearly depicted as *not* contraindications or precautions for Tdap, as outlined on the previous day.

Special situations had been reviewed on the previous day. Text was added to discuss the risk of pertussis beyond outbreak situations where the vaccine might be useful and to provide examples of that.

Pregnancy. This section was reworked overnight to recognize, as the first principle, the complexity of pregnancy as regards pertussis vaccination.

> *"The ACIP has previously recommended Td routinely for pregnant women who received the last tetanus-toxoid-containing vaccine greater than ten years earlier to provide protection against maternal neonatal tetanus. No evidence exists of risk from vaccinating pregnant women with inactivated bacterial toxoids or inactivated viral vaccines.*
>
> *"Vaccine providers should consider vaccinating a pregnant adolescent with Tdap if it is otherwise indicated. Tdap is preferred over Td to protect the adolescent against pertussis. Td is an acceptable alternative.*
>
> *"A pregnant adolescent who has not received a tetanus-toxoid vaccine within the past ten years should receive a tetanus-toxoid vaccination (this wording could be changed to Tdap or Td) to prevent the maternal and neonatal tetanus."*

Discussion included:

- The recommendation advised consideration of vaccinating a pregnant adolescent when it is indicated, rather than "should vaccinate," to match existing ACIP statements and policy guidance.
- "Tetanus toxoid containing vaccine" should add "in the form of Tdap" as preferred, while Td is still acceptable.
- Dr. Baker strongly reiterated her point of the previous day that pregnant woman and their babies are so vulnerable to tetanus that its risk is greater in adolescence than that of an interval <10 years. She advised text to state that pregnant women "should be vaccinated with Tdap" and that a 5-year interval is acceptable. FDA classified Tdap as a Category C drug, but so is influenza vaccine, and that the latter's recommendation should be paralleled. Both mother and baby receive plenty of tetanus diphtheria protection; the point is to provide the pertussis protection.
- The current ACIP recommendations prefer vaccination in the second or third trimester: "Administering Tdap ("or Td" could be inserted) during the second or third trimester is preferred when feasible to minimize the perception of an association of vaccination with adverse pregnancy outcomes which are more common during the first trimester vaccination." This was dropped from the influenza recommendation, but there might be have some immunologic benefit for pertussis to defer vaccination to the second or third trimester. Dr. Gall agreed. The text on standard of care was retained that clinicians should vaccinate pregnant women with preference to the second and third trimester, with Tdap as the preference in pregnancy.
- While the ten-year interval will remain in the background section, as relevant to tetanus, five years will be the interval of focus in the rest of the document.

Conclusion. Dr. Broder summarized, to agreement, that the pregnant adolescent will be covered as are pregnant women.

Dr. Poland moved to accept the recommendations as changed (with a "should" for simultaneous administration [referencing special situations], retaining the paragraphs on catch-up vaccination in late adolescence and keeping the link to the text on the intervals. Dr. Abramson seconded the motion.

Vote on revised Tdap recommendation

Conflicts: GSK and sanofi pasteur

In favor: Treanor, Stinchfield, Salamone, Poland, Morita, Marcuse, Lieu, Gilsdorf, Finger, Campbell, Birkhead, Allos, Abramson
Opposed: None
Abstained: Levin (conflicted)

The motion passed.

VFC Resolution
Presenter: Dr. Gregory Wallace, NIP

Overview: Changes to the VFC Resolution 2/03-2 to incorporate the use of a new vaccine formulation: diphtheria and tetanus toxoids, and acellular pertussis indicated for adolescents and to update other provisions of the resolution.

Dr. Wallace summarized the changes to the VFC resolution:

- Changed the eligible groups to children and adolescents aged 6 weeks through 18 years.
- To the recommended routine schedule, added Tdap or Td booster at age 11 to 12 years, and preferred Tdap over Td as adolescents are susceptible to pertussis due to waning immunity.
- Recommended a Tdap or Td booster at any age from 11 to 18 years of age if the child has completed the recommended childhood TdP-Tdap vaccination series but has not received a Td dose. In some special situations, Td may be indicated over Tdap.
- Added text about Boostrix and Adacel formulations and age indications.
- Added pertussis to the footnote.
- Revised the table of Dosage Intervals for Vaccination for Diphtheria, Tetanus, and Pertussis Containing Vaccines to correct errors with the combination Tdap-HIB vaccine to reflect Tdap administration at ages 10 or 11 years; deleted catch-up from the title because the intervals could apply to even a routine schedule; added a Td catch-up schedule to clarify that people over age 7 years only need three or four doses of Td if they had not previously been vaccinated; corrected the Tdap Haemophilus vaccine footnote to show that it is only indicated for the fourth dose; indicated Tdap as recommended/preferred at age ≥11 years as a booster dose, indicated Tdap as a single booster dose if the primary series has been completed; encouraged a five-year interval if administered after Td.
- *Td.* Changed the Td recommendation such that its use as a booster among those aged ≥11 years may be indicated in some special situations; stated that Td may be used as early as age seven if needed for catch-up, including the primary series, if indicated; the interval from the third or fourth dose may vary for catch-up schedules, depending on the timing of previous doses; inserted the reference for the latter.
- *Contraindications and precautions*: Edited language on the infant doses of Tdap for consistency; added general language about latex allergy such that formulations containing latex should not be administered to adolescents with a history of severe anaphylactic latex allergy, but Tdap may be administered for less severe allergies.
- No changes to the text on DT except for the added latex text.
- Tdap contraindications and precautions were aligned with the recommendations reviewed: standard language on immediate anaphylactic reaction, encephalopathy not attributable to a known, identifiable cause. *Precautions* are Arthus reactions, progressive neurological disorders and latex. Specific information is provided (e.g., one Boostrix formulation contains latex, the other one does not, nor does Adacel). Inserted standard language on Guillain-Barré, and cited acute, moderate, or severe illness as a precaution, as in all the VFC resolutions.
- For the Td vaccine, moderate or severe illnesses with- or without fever was moved from the contraindication to that of a precaution. The balance paralleled the Tdap section except to add Guillain-Barré for completeness and the general latex allergy statement.

Discussion included:

- A VFC-eligible child who has had TD and is now encouraged to receive Tdap for pertussis protection would be covered by VFC under this resolution.
- Dr. Friedland, of GSK, clarified that it is not the formulation, but the presentation of the vaccine that relates to a latex allergy. The wording will be changed to add "presentation."
- The bottom line of the table will add an asterisk to the Td catch-up schedule to reference the footnote.

Ms. Stinchfield moved to approve this resolution as edited for the VFC program. The motion was seconded by Dr. Birkhead.

Vote on VFC Tdap resolution

Conflicts: GSK and sanofi pasteur

In favor: Treanor, Stinchfield, Salamone, Poland, Morita, Marcuse, Lieu, Gilsdorf, Finger, Campbell, Birkhead, Allos
Opposed: None
Absent: Abramson
Abstained: Levin (conflicted)

The motion passed.

VARICELLA

Recommendations For the Use Of Varicella Vaccine In Children Aged <13 Years
Presenter: Dr. Judith Campbell

Overview: Options for a permissive recommendation

On the previous day, the committee had agreed to recommend extension of the varicella recommendations to a two-dose schedule for outbreak control and to include middle- and high school and colleges for school-entry requirements and to expand the adult recommendation to basically all susceptible adults. It was also agreed to recommend screening of pregnant women after delivery, offering vaccination to those susceptible, and to children with HIV but minimally symptomatic. Several options of recommendations for a two-dose schedule, at the option of the healthcare provider, were offered.

Options of a Permissive Recommendation
Presenter: Dr. Jane Seward, NIP

1. Children aged 12 months to 12 years.
   "Two doses of varicella vaccine should be considered for a routine two-dose vaccination program, with the first dose given at 12 to 15 months and the second dose at four to six years, or earlier provided a three-month interval has elapsed."

Discussion included:

- If the data on efficacy, CMI, etc. provide conclusive evidence that this approach is better, perhaps the recommendation should be universal rather than permissive.
- While varicella incidence is clearly a public health problem that is likely to increase and the second dose will help to resolve it, the epidemiology is not clear that the second dose is better given in adolescence or childhood. Adolescent vaccination misses an opportunity to prevent outbreaks, but if immunity from vaccination at age 4-6 years wanes, the problem may just be moved to later in life when disease is more severe. The availability of modeling to shed light on this was inquired. *Response:* Dr. Seward agreed that the epidemiology cannot answer that. She compared this question to the 1980s' discussions of MMR2, which the AAP supported at age 11-12 and the ACIP wished it age 4-6. The only certainty is that the second dose provides >99% of children with a gpELISA >5. She stressed the importance of providing the best protection before school age, the major age of transmission.
- The varicella vaccine's waning immunity differs from questions of MMR vaccine failure. The central question to answer was, given vaccination at age 4-6 years, what immunity will be present at age 20. Dr. Silber reported, beyond the data showing dose two's very large boost, on other long term data indicating that gpELISA levels were almost identical from one or two doses, from years 2 or 3 onward. But what does differ is the disease incidence. The fact that no cases were reported after 5-6 years in the two-dose group suggests a qualitative difference in immune response after two doses administered close together. While the initial antibody titers drop in both groups, they stabilize for the one dose group at ~10 and at ≥120 after two doses. For whatever reason, that benefit lasts out to 10 years, the extent followed to date.
- Dr. Cochi wished to not reprise the measles experience, when the susceptible groups aged into high school and college. He saw no advantage to delay a decision on a second dose, whether administered as single antigen or a combination vaccine, to consolidate the public health gains ─ as done with MMR.
- The data on rising numbers of outbreaks, and COID's agreement that the varicella burden warranted another dose, was raised again.
- Dr. Birkhead supported a permissive proposal, observing that a two dose outbreak control schedule should be paralleled by the routine schedule, as done with measles. The downside of that was that public health would then have to respond to every school outbreak by vaccinating the entire school, a significant work increase.
- Dr. Abramson was certain of only two outcomes from two doses: a decrease in breakthrough disease and the accompanying hospitalization. At question was the impact compared to the substantial cost of implementation. The second dose is not cost-saving because one dose substantially reduces varicella; however, that may be likely to change in the future.
- Dr. Susan Lett expressed concern that the two dose schedule's lack of clarity concerning VFC and third party reimbursement will be difficult for physicians to deal with, and raised the difficulty that health departments will have chasing outbreaks with vaccination. She favored Dr. Salisbury's suggestion of more modeling to assess the potential impacts before committing to the schedule.
- Dr. Orenstein disagreed, noting that the MMR2 was basically 5% effective, with MMR's 95% VE. The same challenges were present for MMR2 in terms of cost, effectiveness, etc., until the college outbreaks of 1999. His impression of the issue was whether a public health response to outbreaks is needed, something the states

seemed to want. The only way to provide that is with a second dose, after which the next logical step is prevention of the outbreaks with a routine second dose.

- Dr. Rick Haupt, of Merck, reported their recent surveys' findings that many physicians were delaying the vaccination to an older age to counter the risk factor of early age of vaccination. The family physicians also expected, and wanted, a two-dose schedule.

Dr. Campbell moved to allow consideration of a two dose varicella vaccination schedule, at the discrimination of the practitioner. The motion was seconded by Dr. Birkhead. The only discussion was Dr. Treanor's opinion in support of a universal policy.

Vote on a permissive varicella vaccination recommendation

In favor: Stinchfield, Salamone, Campbell, Birkhead, Marcuse
Opposed: Treanor, Morita, Lieu, Gilsdorf, Finger, Allos, Abramson.
Abstained: Levin, Poland (conflicted)

The vote failed and there was no response to Dr. Levin's question of whether anyone wished to move for a universal recommendation.

2005-06 Revised Adult Immunization Schedule
Presenter: Dr. John Strikas, NIP

The October 2005 to September 2006 adult immunization schedule had received tentative approval from the AAFP and ACOG. The revised schedule will be sent to them with the changed varicella recommendations.

Changes to the 2005-4-05 schedule were:

- On the age-based adult schedule, the yellow and green bars were merged to yellow, the yellow now being the universal recommendations for all persons in the category who lack documentation of appropriate vaccination or have no evidence of prior disease. The purple bars reflect vaccine schedules recommended in the presence of some risk factor. Varicella will be moved up to below MMR, per the previous day's vote, and modified to be for all adults born after 1965, as MMR is for all adults born after 1957. The order of the vaccines was changed to match the childhood/adolescent harmonized schedule. Universally recommended vaccines for adults were at the top of the chart, and those for adults with risk conditions were at the bottom. A broken line divides the two categories.
- The vaccine schedule for medical/other indications was also simplified to three colors. The yellow and purple bars reflected the categories as above, and two red bars reflected contraindications. Again, varicella will be moved up to below MMR. Varicella is charted in red as contraindicated for adults with immunodeficiency conditions such as HIV, based on the 1996 and 1999 ACIP recommendations, as is MMR. The decision to allow its use among HIV-infected children prompted discussion about the adult schedule.
- Meningococcal vaccine was added because it is now routinely recommended for certain age categories and people with asplenia. A footnote cites the recently

published recommendations. Additional text was added to indicate the number of doses and the intervals recommended for the different vaccines.

- *Footnotes.* New text was added to each schedule to direct readers to the footnotes. The previous schedule's footnotes were merged and numbered and some asterisked items were incorporated in the column headings. All but two *MMWR* citations and some links to the CDC were deleted. A general statement advised reading of the other ACIP statements, as done in the childhood and adolescent schedule. Some electronic links were retained for hepatitis A and hepatitis B. The tetanus-diphtheria toxoid footnote was modified to say that, while not everyone should receive a primary series, all adults with uncertain history should do so. A footnote was added citing Hib study data to support that its administration to patients with specific conditions is not contraindicated. The influenza footnote added the new recommendation for vaccination of persons with compromised respiratory function. The varicella footnote will be modified with the text agreed upon the previous day about adults to be assessed for vaccination status and vaccinating those born since 1965, as well as that on prenatal screening and postpartum vaccination .
- *Contact information* is provided for the CDC hotline with immunization data and the U.S. Court of Federal Claims.

Discussion included:

- The pertussis vaccine for adults, Adacel, could not be listed since it does not yet have an ACIP recommendation.
- Dr. Neuzil urged the Workgroup to re-examine the issue of the vaccine's use in HIV-infected adults.
- Dr. Levin suggested that NIP explore an expansion of its distribution list of these recommendations beyond the current partners, to include other professionals who care for immunocompromised patients (e.g.,. oncology and hematology clinics, and others targeting those immunocompromised), perhaps through their professional associations. Dr. Birkhead added state and local health departments to that dissemination list.
- Dr. Decker suggested including language to note that any recommendations made during the period covered by this schedule are automatically included.
- The ACP will not publish the schedule in their *Annals of the ACP* until it is evidence-based with some grading system, although they disseminate it informally at their

Dr. Poland moved to accept the adult immunization schedule. Dr. Allos seconded the motion.

Vote on the 2005 adult immunization schedule

The vote passed unanimously with no abstentions.

Tdap: Epidemiology of Adult Pertussis
Presenter: Dr. Katrina Kretsinger, NIP

Overview: Adult pertussis morbidity; challenges to recognize the disease; adults as a reservoir for infant pertussis; pertussis among college students.

Adult pertussis symptoms range greatly from the classic symptoms of paroxysmal cough with whoops to milder disease with a persistent cough; it can even be subclinical.

Morbidity among adults. Lee et al (*CID* 2004;39:1572-1580) conducted a retrospective study of the rates of adult pertussis symptomology among 936 affected Massachusetts adults from 1998 to 2000. These may be the severe end of spectrum due to nonrecognition of the disease. However, rates of complications and symptoms were greater than those reported among adolescents except for post-tussive vomiting. They included paroxysms (86%) and coughing a median of 48 days after onset (83%); another 3% were hospitalized for a median of 2.5 days. Lee also prospectively studied 205 adults diagnosed in 15 months from 2001 to 2003. Of those, 84% had trouble sleeping, 33% had weight loss, 28% had urinary incontinence. Aside from other complications such as pneumonia (5%) and rib fracture (4%), 62% percent were still coughing a median of 93 days after onset. Fortunately, data of the National Notifiable Diseases Surveillance System (NNDSS) indicate that pertussis-associated deaths among adults are rare (five reported sine 1990) and are accompanied by comorbid conditions. However, due to the lack of recognition of pertussis, undiagnosed pertussis-associated deaths could occur. Studies by Mink et al (*CID* 1992;14-464-71) and Nennig et al (*JAMA* 1996;275;1672-74) described undiagnosed cough cases of 6 days (31 students) and 2 weeks (153 students) duration. *MMWR* (2003;53:131-132) describes the same even for a severe case that resulted in death.

Challenges to pertussis diagnosis among adults include the difficulty to distinguish it from other respiratory symptoms and cough illness, lack of physician awareness, and insensitive laboratory diagnostics that rely on early culture specimen collection. PCR and serology methods are not standardized.

Six U.S. studies estimating pertussis-attributable morbidity were outlined. Comparison between them is difficult due to differing methods, populations, inclusion criteria and methods, etc. Ward's 2001 APERT trial estimated a range of 1%-7%; the other five ranged from 12%-21% for adult cohorts to 26% for college students. Case rates have risen over the past decade, but that could be attributed to either a true disease increase or simply greater awareness and detection.

Provisional 2004 data showed ≥30% of cases in adults aged ≥19 years. Incidence of those aged 19-29 years, 3.5/100,000, dropped to 1.5 for those aged ≥50 years. Infants had the highest reported incidence at >100/100,000. Data were charted of five studies done from 1996-2001 of pertussis incidence in adults and adolescents, showing a range from 69-507/100,000, but the 2003 national average reported incidence for those aged ≥19 years was 1.4/100,000.

Adults role in pertussis transmission to infants. The highest pertussis incidence is among infants, especially among those too young in age (0-4 months) to have received the first two doses of pertussis vaccine. Pertussis mortality by age was charted and was highest among those <2 months of age than all other age groups combined.

Among outbreak and longitudinal studies of adults as a source of infant pertussis is that recently published by Bisgard et al (*Pediatr Infect Dis* J, 2004). Enhanced surveillance in four states identified case-infants aged ≤4 months and persons with acute cough illness who had contact with a case-infant 7-20 days before the infant's cough onset. The primary contact among multiple coughers was identified as the source. Of 494 case infants aged ≤4 months, the source relationship of 57% was unknown, but of the remaining 212 cases with an identified source

relationship, >50% were a parent or grandparent; and, of those whose age was known, >50% were ≥20 years old. Clearly, successful adult immunization strategies will have a beneficial effect on infant incidence.

College students. There were 13.7 million undergraduates in the U.S. in 2003. The largest proportion of them were aged 18-19 years in fall of 2000, but 74% were aged ≤29 years. The age distribution of reported pertussis cases (provisional NNDSS data) in Massachusetts and nationally was charted by age groups. Even excluding the Massachusetts data, enhanced surveillance of school outbreaks indicated a lower proportion of reported cases among college-aged adults aged 19-29 years than among adolescents. From 2000-2003, 46% of the 2,222 pertussis cases reported among those aged 19-29 also reported the transmission setting; of which only 6% was on college campuses.

Data from two sero surveys of college students indicated that, compared to controls' sera, 26% of students with a ≥6-day cough had serologic evidence of recent cough, an incidence of 69/100,000 (Mink CM et al, *Clin Infect Dis* 1992;14:464-71). Another study (Jackson LA et al. *Clin Infect Dis* 2000; 31:3-6) investigated banked sera from college students for significant rises in FHA, pertactin (PRN), fimbriae-2 (FIM-2), and agglutinogens. Analysis showed 8% with evidence of recent infection with pertussis or Bordetella pertussis. Such data infer symptomatic pertussis infection to be common but under-recognized among college students.

Preliminary results were presented of the 11% (172 schools) responding so far to an ACHA survey of pertussis experience in the 2004-05 academic year. These schools represent 1.38 million undergraduates and 327,000 graduate students. Of the median enrollment of 5000, 90% are in four-year colleges and 58% are in public institutions. Responses were as follow:

- Approximate number of pertussis cases seen at the student health center, 2004 to 2005: at least one case at 31% (52) of 170 colleges. Most had 1-5 cases, but a few had substantial numbers of cases (all estimated case counts).
- Total number of identified cases: 424, or ~25 recognized cases per 100,000 student population, or 4100 student cases. One school reported >100 cases.
- Increased diagnosis of pertussis at student health centers over the past ten years: 19% (32 schools).
- Pertussis has a large impact upon the effected students' abilities to perform academically: 75% (124 schools) strongly agreed, agreed, or agreed somewhat. Only one institution had never cancelled a college event due to pertussis.
- In response to staff's occupational exposure to pertussis, student health service has had to: 1) administer chemoprophylaxis 6% (10 schools), furlough (3%, 10 schools) or send staff home (none).
- Trying to control pertussis by locating contacts and administering prophylaxis places a large strain on student health services: 45% (72 schools) strongly agreed, agreed, or agreed somewhat.
- Requirement of an up-to-date Td vaccination for matriculation: 42%.
- Likely source of primary pertussis transmission: 3% identified other students, faculty, or staff on-campus; 21% identified community sources outside of the college. This indicates that pertussis typically did not seem to be widely transmitted between members of the college community.

Whether college attendance is an independent risk factor for pertussis among young adults who happen to be college age remains unanswered. What is known is that pertussis is an under-recognized disease among adults, with substantial morbidity that includes prolonged cough, and that adults are a source of infant pertussis. The burden of pertussis among college students is not yet clearly defined.

Discussion included emphasis by Dr. James Cherry, of UCLA, that all of 14 studies of cough illness in adults since 1983 found pertussis and identified it as the cause of 13% of prolonged illness among all age groups, including those >65 years. He felt that targeting adolescents would not produce much of a herd effect; all groups need to be targeted, as seen by babies contracting it from their parents and grandparents.

Next Steps; Adult Use of Tdap
Presenter: Dr. Trudy Murphy, NIP

> Overview: Status of pertussis in the U.S.; elimination goal for circulating B. pertussis; options for next steps regarding adult use of Tdap; enhanced vaccines.

Dr. Murphy asked for feedback from the committee members on the information she was about to present, either at this meeting or e-mailed to Dr. Abramson and/or herself.

Status of U.S. pertussis. The >90% decline in morbidity and mortality since universal vaccination of children was begun in the 1940s was a major accomplishment. However, work is needed and ongoing to improve still-inadequate laboratory diagnostic methods. Prevention remains the most effective strategy for pertussis. There is no effective treatment; its severity can only be lessened if addressed early in the disease.

Immunity wanes among adolescents vaccinated in childhood and after natural disease, and that waning is associated with an increase in disease activity. Preliminary Australian data from targeted school-based catch-up campaigns are now showing some early declines in adolescent pertussis. Infants too young for vaccination can have severe complications and death. Another infant source of pertussis only occurs in ~45% of the cases; the source is often an adult, usually a parent or grandparent. Young adults have considerable morbidity. Among the many data gaps is the true incidence of adult pertussis. Serologic surveys provide some estimates, but national data bears improvement.

It is not clear whether a shift in pertussis to adults will occur with the use of adolescent Tdap, although modeling indicates that will not occur. Another question is Tdap's duration of immunity. Infant studies indicate a duration of 5-6 or perhaps 7 years, followed by substantial waning. Protection may last longer in adults who have a booster response.

CDC assembled an international pertussis panel in May, 2005. International experts, state health department officials and academicians were asked to advise on the pertussis vaccination program's goals. The primary goal was to reduce the disease burden in all age groups with priority given to those most affected and the long-term goal is to eliminate circulating pertussis.

Next steps for adult Tdap use. The programs' proposed initial objectives include individual protection for adults and vulnerable infants through adult vaccination. To accomplish this, two

options were offered:

1. Substituting a single dose of Tdap for TD for all adults. *Advantages:* Most likely to achieve the objective to reduce disease burden all age groups; programmatic simplicity; ability to reach unidentified adults with high-risk conditions, workers in institutional settings, caregivers of vulnerable infants, college students, etc. *Disadvantages:* Need for high population coverage, likelihood to not be cost effective (subject to incidence and vaccine cost, unless this is counterbalanced by the likely underestimation of actual incidence among adults), possibility that optimal protection may not be possible without a decennial booster; and, in the absence of a single acellular pertussis vaccine, TD will have to be part of the strategy ─ and there has been discussion of reducing adult TD exposures.
2. Substituting a single dose of Tdap for selected adult groups (e.g., older adults, those with high-risk medical conditions). Considerations included:
    a. Adacel is the only Tdap vaccine licensed to age 64; bridging data will be needed for those older.
    b. Data are very limited regarding high-risk medical conditions.
    c. Selected adults could be considered in "cocooning" strategies to protect vulnerable infants, but the selection criteria require discussion.
    d. Certain occupational workers want the vaccine, most prominently the healthcare community. Better data on that and other communities are needed. There also is no evidence on the effectiveness that such targeted strategies, although many think that would be helpful.
    e. Specific challenges include the a very uncertain ability to identify all adults with high-risk medical conditions requiring vaccination; the need for extensive educational efforts for adult providers; and unknown cost effectiveness for these strategies (although targeting could well raise vaccine coverage). This approach would take longer due to the extent of detail involved, is unlikely to reduce disease burden in all age groups, and may require more frequent dosing (raising the cost) to maintain immunity.

The long term goals of the international panel called for better pertussis vaccines and diagnostics. That may come through enhanced or improved bactericidal immune responses and improved specificity of immune responses for these vaccines.

Discussion included:

- The best data available on TD or tetanus coverage among adults is from the 1999 study. Of those participants, 66% of those aged 18-49 years, 64% of those 50-62, and 42% of those aged >62 years had received a tetanus-containing vaccine in the last 10 years. Those percentages correspond with serological studies' data.
- Dr. Gall suggested that "cocooning" text more clearly delineate the standard of practice for pregnant women.
- Dr. Clover stated that AAFP's support of the adolescent dose was contingent on the adult issue being addressed. If waning immunity causes pertussis in 11-19 year-olds, 20 year-olds certainly will not be protected, and they are the group with the babies who have the rising incidence. Future studies will be needed to explore the safety issues of repeated doses, particularly if Tdap replaces the ten-year DT booster, and if older adults are the group of particular focus.

Herpes Zoster

Overview of Herpes Zoster
Presenter: Dr. Rafael Harpaz, NCID

> Overview: Definition, clinical manifestations, risk factors, U.S. incidence, varicella exposure role to zoster risk, burden of disease. Further information will be presented at future ACIP meetings.

Herpes zoster (shingles) is a reactivation of the varicella zoster virus (VZV). After the initial infection causing chickenpox, VZV becomes a permanent latent infection in the dorsal root ganglia of the entire neuraxis. From years to decades later, it can reactivate in a rash of vesicular blisters distributed through the dermatome. The dermatome, a skin area supplied by sensory nerve fibers coming from one nerve root, lies in the cervical, thoracic, lumbar, and sacral regions.

Zoster symptoms include occasional headache, photophobia, and malaise. The rash usually involves only one dermatome. It can involve more, but few lesions appear outside the primary dermatome. It is almost always unilateral and occurs, in order of frequency, in the thoracic, lumbar, cervical and trigeminal, and sacral and other cranial dermatomes. The rash evolves to vesicles and then possibly to pustules, with new lesions arising from 5-7 days and cresting from 7-12 days. It usually fully resolves in 5-25 days. Fever and regional adenopathy can occur. *Sequelae* include potential secondary infections, scarring and pigmentation changes. Zoster is also ~20% as contagious as varicella.

Sometimes, there is no rash (zoster sine herpete). It starts as an abnormal skin sensation with itching or tingling in ~84% of all cases, followed by the rash stage and then the eruptive stage, with some degree of pain in ~89% percent of patients. Pain, the primary symptom of zoster, has been described as excruciating as childbirth and either continuous or paroxysmal. It sometimes involves changes in sensation to touch , such that small stimuli like bed sheets or a light breeze can cause pain. The pain can precede the rash itself by 1-5 days and sometimes lasts weeks or longer.

The final chronic phase (postherpetic neuralgia, or PHN) is a prolonged, sometimes incapacitating pain after the rash resolves. Differing definitions for the length of postherpetic neuralgia have frustrated study comparisons, but the pain may persist for months or even years. Sometimes it resolves only to recur later. Antivirals, with or without steroids, are used but are inconsistent in their ability to prevent postherpetic neuralgia. Treatment involves multiple neurologic modalities, including anticonvulsants, tricyclics, capsaicin, and nerve blocks. Their frustratingly similar partial effectiveness can cause secondary depression with social and physical disability, fatigue, anorexia ─ even suicide.

Less common zoster sequelae include ophthalmic, neurologic, and oral complications, which can be sight-threatening or life-threatening. These are more severe, aggressive and common among immunocompromised patients. The latter can also develop generalized rash with visceral involvement, including pneumonia, encephalitis, and hepatitis. Even immunocompetent patients can develop complications either coincident with the rash or months later. Mortality is rare among the immunocompetent; those immunocompromised comprise most of the related deaths.

Risk factors are led by age, followed by immunosuppression (less common, but much greater risk), bone marrow transplant or patients with immunologic malignancies, and HIV). Assessment of true incidence must consider those two factors.

- *Age*. Data from several studies indicate a risk of 0.4 to 1.6 cases per thousand person-years in those aged <20 years, 2-3/1000 person years among those aged 20-50, and 4.5-11 cases/1000 person years for those > 80 (Hope-Simpson,. *J R Coll Gen Pract* 1975;25:571-575). The risk is clearly markedly increased from age 50 upward.
- *Risk factors for inconsistent, unconfirmed or lower magnitude zoster* include female gender (increased risk, but with conflicting results); race (lower risk); countries with varicella at older ages (lower risk); local trauma, psychological stress, living near pesticide sites (increased risk); cigarette smoking (equivocal data); and association with certain genetic haplotypes.
- *Risk factors for pediatric zoster*. Infection in utero or at <18 months appears to greatly increase the risk. Any change in the varicella epidemiology can change the pediatric zoster immunology.
- *Exposure to varicella* and external boosting is a risk factor.

Incidence. Study comparisons are hampered by differences in ascertainment and age structure, prevalence of other risk factors, and health access. Nonetheless, six U.S. studies compared to calculate incidence produced estimated ranges of 1.3-3.7 per thousand person-years for all ages and 3.8-11.8 for those >65 years. The best estimate of U.S. incidence is 500,000 to a million cases annually and a lifetime zoster risk ranging from 15%-30%, rising to almost 50% for persons living to age 85. With our ageing population, the zoster burden will rise as well.

NHIS zoster incidence data from 1970 to 1994 were charted and showed a marked increase among the elderly (≥60 years) beginning around 1980, before the pediatric vaccine program's launch. Dr. Harpaz also cautioned that the complex epidemiology of zoster demands great care in attributing it to any particular cause.

PHN. Unlike zoster, immunosuppression is not necessarily associated with PHN. Age is the dominant PHN risk factor; it is rare in persons under 40. PHN, defined as 30 days' pain duration, has a risk among those aged >50 of almost 15-fold greater than those younger. The risk of pain lasting ≥60 days involves a 27-fold increase with another 12% for each incremental year of age. Depending on various factors such as PHN definitions, age, antiviral use, ascertainment, etc., the proportion of PHN in zoster patients ranges widely (8%-80%) among studies. But other PHN risk factors are less striking: a greater proportion of female zoster patients seem to have PHN, and there seems to be an increase with an ophthalmic distribution. Charted data (de Moragas JM, Kierland RR. *Arch Dermatol* 1957;75:193-6) for 1000 patients reporting PHN showed the dramatic increase with age of the PHN risk.

Varicella exposure. There is biologically plausible evidence that varicella exposure can prevent zoster, reducing the risk 86% in persons with ≥5 varicella exposures. The risk also is reduced in persons such as pediatricians who work or live with children (the surrogate for exposure) and among leukemic children exposed in a household setting. The zoster vaccine trial also suggested that external boosting is effective. Such factors support the theory that varicella exposure can prevent zoster, and if so, a varicella vaccination program could decrease zoster incidence.

However, related unresolved issues include:

1. Is external boosting necessary to prevent zoster? The understanding of the subclinical reactivation of the varicella virus in ganglia is incomplete, but it may cause boosting and increased anti-VZV immunity. It is not known if such internal boosting can compensate when external boosting declines.
2. How much varicella exposure is needed to be effective? The relevance of the effective ≥5 exposures to the general population is unknown, as is the duration of the effect and whether exposure would protect the elderly at risk as well as the young. Perhaps most important, and unknown, is whether a reduced exposure can increase zoster incidence or (equally plausible) shift it to younger populations. Regarding that, the low risk of PHN in the young could paradoxically reduce the burden of zoster even as it increases its incidence. That escalates the importance of monitoring PHN as well as zoster, a very challenging task.

Considerations of zoster burden of disease. The zoster disease burden includes direct medical costs to treat zoster, prevent PHN and control pain, as well as indirect costs associated with deaths, absenteeism, and reduced productivity. But perhaps the most important cost is in pain and suffering. That is not generally included in an economic analyses, but should be for zoster, especially as regards the older, largely retired population. Major factors in that analysis would include duration and intensity of pain, physical and social disability, reduced quality of life (shown to be comparable to that of congestive heart failure or diabetes, or following an MI), depression, and contagiousness.

Discussion included report of little data to indicate whether zoster reoccurrence is less likely among those who have had it compared to those who have not. One estimate is that 5% of people who got zoster once can get it again, and the immunosuppressed population, HIV in particular, is prone to repeated (although mild) bouts.

Zostavax™ Zoster Vaccine Clinical Trial Results

Presenter: Dr. Paula Annunziato, Director, Clinical Research, Merck Research Laboratories

Overview: Presentation of the Zostavax program, data on efficacy against zoster, PHN, zoster pain burden of illness.

Protocol 001 (dose ranging, immunogenicity and safety).

Protocol 002 (potency) looked at the immunogenicity and safety of Zostavax at two different vaccine potencies in subjects who had diabetes mellitus or chronic obstructive pulmonary disease, or neither condition. *Protocol 003* studied Zostavax immunogenicity and safety in subjects with either undetectable or low levels of VZV antibody.

Protocol 004 (or: pivotal efficacy study, shingles prevention study, *Veteran Affairs Cooperative Studies Program/Protocol 403)* also assessed immunogenicity and safety. This collaborative (VA, Merck, NIH) double-blind, placebo-controlled multicenter (22 sites) trial involved 38,000 subjects randomized one-to-one to receive either Zostavax or placebo. Randomization was stratified by two age categories: 60-69 years and ≥70. All subjects in this trial were followed for safety and efficacy. Key end points were zoster incidence, pain burden of illness, and PHN incidence.

Two substudies were conducted: 1) a detailed safety assessment at all sites of >6000 subjects who recorded adverse experiences through day 42 post-vaccination, and for hospitalization, to the study's end; and 2) a CMI substudy at two sites, with 1300 subjects who provided specimens for immunogenicity analysis at baseline, 6 weeks and 1-, 2- and 3-years post vaccination. Subjects who developed symptoms consistent with herpes zoster were evaluated by their study investigator, who determined the patient's need for a 6-month protocol-specified follow-up of a suspected HZ case. Five HZ experts clinically adjudicated all suspected cases, using defined procedures. PCR finalized case determination in >80% of cases and viral culture and clinical adjudication did so for the remaining 20%. Zoster surveillance in this study averaged 3.1 years within a range of up to 4.9 years. The primary analysis included 957 of these confirmed zoster cases, 315 in the Zostavax group and 642 in the placebo group. The calculated VE on HZ incidence was 51.3% (95% CI, range of 44.2 %-57.6%), well beyond the pre-blinding, FDA-agreed criterion of success (lower bound of 95% CI >25%).

Protocol 005 (booster dose) was a study of the immunogenicity and safety of a booster dose of Zostavax given some time after a previous dose of a varicella-containing vaccine. Protocol 007 was an immunogenicity and safety study of two doses of Zostavax given at a six-week interval. Protocol 009 was a safety study of the vaccine at its anticipated maximum release potency in subjects ≥50 years of age.

Protocol 049 (Varivax program, two doses in seronegative subjects aged >13 years.) The doses supplied in this study were in the Zostavax potency range, allowing data bridging.

Immunogenicity. VZV immunogenicity was measured by the gpELISA, which measures VZV antibody, as well as the VZV interferon Elispot and responder-cell frequency assays, which are direct assays of T-cell functions.

HZ burden of illness (BOI) was measured through a composite end point of zoster incidence and pain over six months. All subjects in the follow-up rated their HZ-associated pain from 0-10 at regular intervals. Each confirmed HZ case individual was scored according to pain response and time curve. Only pain scores of ≥3 were included in the BOI calculation to ensure that only clinically significant pain beyond day 30 after rash onset was considered. Subjects without confirmed HZ were assigned a score of zero. The VE against herpes zoster pain BOI was 61.1% (95% CI, range 51.1 %-69.1%). Again, these results also exceeded the prespecified criteria, a point estimate of ≥47% with a 95% CI lower bound >25%.

Also analyzed were cases of subjects with severe HZ, with a BOI score >600. That score would require a pain score of ten for at least 60 days or at least 200 days of combined pain and severity <10). Eleven such subjects were in the Zostavax group and 40 in the placebo group, a 72.6% reduction in the Zostavax group (95% CI range of 45.7%-87.3%).

PHN. The shingles prevention study defined PHN as the presence of pain or a score of ≥3 beyond 90 days after rash onset. Supportive analyses also were done with alternative definitions of pain, lasting 30 days, 60 days, 120 days, or 182 days after zoster rash onset. *Results:* A total of 107 PHN cases in the shingles prevention study met that PHN definition, 27 in the Zostavax group and 80 in the placebo group, for a VE against PHN of 66.5% (95% CI range of 47.5%-79.2%). Again, this exceeded the prespecified criteria for success of a point estimate ≥62%, with

the 95% CI > 25%. A supplementary analysis assessed pain severity by duration subjects with PHN, and showed a 57% reduction in zoster pain severity by duration among those who received Zostavax. VE for zoster PHN was followed over 48 months in the shingles prevention study and subject follow-up is ongoing at 12 of the 22 sites to obtain more data on VE duration.

Summary. Zostavax prevents herpes zoster, postherpetic neuralgia, and reduces the herpes zoster pain burden of illness. It has been shown to be generally well tolerated in adults ≥50 years old, based on the extensive Varivax safety database and Zostavax clinical trials involving >20,000 vaccinated subjects. While ~50% of Zostavax recipients reported more injection site reactions (erythema, pain, swelling) compared to placebo, they were generally reported as mild or moderate in severity. Safety data showed a similar overall incidence of systemic clinical adverse events and a slightly higher incidence of vaccine-related systemic clinical experience, but the latter was not driven by any individual specific adverse experience. Both varicella-like and zoster-like rashes were uncommon after Zostavax and in the shingles prevention study. Varicella-like rash incidence at the injection site was 0.1% in the shingles prevention study. Zostavax' application for licensure was submitted to the FDA.

Discussion included recognition of and applause for Dr. Michael Oxman, principle investigator for the Zostavax™ trial. Dr. Campbell reported that the ACIP statement being developed by the MMRV Workgroup will also look at issues related to zoster.

The committee then adjourned for lunch, after which Dr. Levin ceremoniously presented his successor, Dr. Jonathan Abramson, with the meeting bell.

Human Papilloma Virus

HPV Vaccine Workgroup Report
Presenter: Dr. Lauri Markowitz, NCHSTP

> Overview: Background on HPV vaccine trials, Workgroup activities in anticipation of HPV vaccine

Two candidate HPV vaccines are in Phase 3 clinical trials, a quadrivalent vaccine by Merck and a bivalent vaccine by GSK. These are both vaccine-like particle (VLP) vaccines that use the L-1 protein. They differ in that Merck's vaccine has VLPs to HPV-6, -11, -16, and -18, while the GSK vaccine contains Type 16 and 18. Types 16 and 18 account for ~70% of cervical cancers; Types 6 and 11 cause almost all genital warts. Both vaccines' trials involved a similar three-dose schedule. Merck used an alum adjuvant and GSK used alum and monophospholipid A.

Studies. Merck is planning clinical trials in both females and males, while GSK's focus in on females. Merck's pivotal efficacy trial will be among women aged 16-26 years and GSK's involves women aged 15-25. The efficacy trials' endpoints include CIN2/3 and cervical intraepithelial neoplasia, the basis for a license indication for prevention of cervical cancer. Bridging, immunogenicity, and safety studies in younger females (and males, in Merck's case) will be done. Post-licensure data will be developed from other studies in older women (and men, for Merck).

Data. Data originally presented in February were summarized. Phase II-B proof of concept

studies were published by both companies, Merck's monovalent HPV-16 vaccine and GSK's 16-18 vaccine. Both trials had some CIN related to the vaccine type, all in the placebo groups. The data showed a 100% VE for HPV-16, -18 and any CIN. A phase two efficacy study of the quadrivalent vaccine also showed 100% VE for HPV-6 and -11, 86% and 89% for HPV-16 and -18, respectively. The overall VE for those and for CIN or genital warts was 90% in a 95% CI range of 71%-97%.

Next steps. The workgroup will continue to follow both vaccines' development and clinical trials. They have developed recommendation options for Merck's vaccine, the licensure application for which is expected at the end of 2005. The Workgroup plans to present a draft ACIP statement in mid 2006. Specific plans include:

- October: Merck will probably present further data their Phase 3 efficacy and safety trial, and GSK on their clinical trial; HPV epidemiology, vaccine acceptability; introduction of possible general recommendation options.
- February 2006: 1) Cost-effectiveness analysis of HPV-16 and -18 vaccines' use among women. The latter will include cervical cancer screening, which complicates the models more than others; 2) modeling of a quadrivalent HPV vaccine's impact, the first model to assess this, which will be independently reviewed; 3) likely GSK and Merck data updates, and 4) further discussion of recommendation options.
- June 2006: The earliest possible time for an ACIP decision and vote on a recommendation.

HPV Biology and Natural History

Presenter: Dr. Elizabeth Unger, NCID

Overview: HPV biology and natural history

Human papillomaviruses (HPV) are in the papillomavirus virus family and are very species specific. The virus is an 8 kilobase, circular, double-stranded genome housed in a capsid shell composed mostly of the major capsid protein L-1 and less of the L-2. L-1 self-assembles into viral-like particles or (VLPS) that are nearly identical to the virus. The virus is completely dependent on the host cell's replication and transcriptional machinery.

HPV is not a single virus, but a family of >100 viruses referred to as viral types, which are distinguished by their L-1 region sequence. They were numbered according to their order of discovery, not biology.

HPV can be grouped based on the type of epithelium they infect. There are ~60 types in the cutaneous group that are associated with common hand and foot warts and skin lesions. There are ~40 types in the as mucosal or genital group (primarily in the anogenital region) which are further grouped into so called high- and low-risk types, based on the frequency of their detection in malignancies. However, the absolute risk of malignancy is low for all HPV infections.

Prevalence. Genital HPV is the most prevalent STD in the U.S., affecting an estimated ~80% of sexually active persons by age 50. Most of these infections are transient and asymptomatic. HPV prevalence in the U.S. is estimated from clinic-based study data, as it is not a reportable infection. HPV testing has been done on self-collected vaginal swabs from women participating

in the NHANES surveys from 2002 through 2004; those data will be available in 2006.

CDC sponsored a three-year HPV sentinel surveillance project among age-, race- and ethnically-diverse women seeking a Pap smear from 29 geographically diverse STD, family planning and primary care clinics in six cities. Preliminary sentinel surveillance data for >6000 women were charted. High-risk HPV prevalence reflected that in the HPV literature, with a peak prevalence in young women aged 14-19 years, followed closely by those aged 20-29. That decreases with older age, except for a slight prevalence increase in women aged >50 in some populations. The tendency of HPV to clear without disease in this young high prevalence group is the basis of age 30 as the cutoff for HPV testing and screening.

The viral life cycle was demonstrated with a cross-sectional diagram of a multilayered squamous epithelium. Papillomaviruses infect the undifferentiated basal layer of the epithelium, through micro abrasions or at the junction of two epithelial types such as the cervix transition zone. Cellular replication occurs, amplifying the viral genome in the differentiating cells that proliferate. CMI is associated with clearance of the virus. The viral genes responsible for prolonging the cellular replication, E-6 and E-7, also contribute to genomic instability, viral integration, and a stepped progression to malignancy.

The precancerous changes in the cervical epithelium are referred to as cervical intraepithelial neoplasia, or CIN, and are graded based on increasing severity as changes from one to three. CIN1 is not a true precancerous lesion, but can persist and progress.

Cervical pathology is defined through colposcopic biopsy of cervical lesions. The Pap test is the cytology screen used to the need for a diagnostic biopsy, suggested by characteristic changes in the cells shed from the surface. Atypical squamous cells of uncertain significance (ASCUS) are uncertain because the underlying lesion may range from reactive changes to CIN3. Low- or high-grade squamous intraepithelial lesions, LSIL or HSIL, are so called based on their tendency to reflect CIN1 or CIN2/3 histology, respectively.

A diagram illustrated the natural history of HPV infection and oncogenic progression from one to 20 years, from initial HPV infection through clearance or cancer. Persistent infections may eventually lead to neoplastic precursor lesions. Many CIN2 and some CIN3 lesions may clear, but they are likely to persist or progress. Without excision to prevent cancer, untreated CIN3 may develop into invasive cancer, although usually in a slow progression.

Age-specific HPV-prevalence data indicate that HPV acquisition typically occurs in the first several years of sexual debut and/or exposure to a new partner. About 70% of new infections clear within a year and 98% within two years, but high-risk types are more persistent than low-risk types. Consistently persistent high-risk HPV increases the risk of neoplastic progression and is associated with a 10- to 14-fold relative risk for HSIL.

Other important HPV-associated diseases include genital warts, nearly all cervical cancers; a high percentage of anal, vulvar, vaginal, and penile cancers; and ~25% of head and neck cancers, particularly tonsillar. Recurrent respiratory papillomatosis (warts or papillomas in the upper respiratory tract) is a rare but significant condition due to the recurrent surgeries necessary to maintain the airway. All of these lesions are associated with HPV-6 or -11.

HPV detection and diagnosis has few tools, without a simple in vitro culture system and with insensitive antibody methods. The required DNA-based assay for diagnosis challenges ascertainment of the infectious state of the virus. The adequacy of the cellular sample, the anatomic region sampled, and method of specimen collection impact the detection rate and complicate the definition of latent, occult, persistent, and recurrent infection. But advances in molecular-biologic techniques are generating new HPV detection assays with better sensitivity and type specificity. Again, that is a challenge to study comparisons.

HPV tests. HPV tests detect virus, not disease, and HPV itself is not treated; the associated neoplasia is. The negative predictive value of an HPV test is of the greatest clinical value by excluding the presence of a disease needing treatment.

- FDA has approved only one test for clinical diagnosis of HPV, the Digene hybrid capture (HC2) assay , whose high-risk probe mix includes 13 types. HCII is a robust clinical assay with good interlaboratory correlations to date, but its results are not type-specific, and some cross-hybridization can occur between high- and low-risk types.
- Clinically, PCR tests have the best analytic sensitivity to detect current infection; HPV type-specific PCR assays generally target the E6 and E7 regions. The good specificity of the consensus PCR assays (designed to amplify most genital HPV) which use a mixture of primers to determine the type.
- HPV serologic assays use ELISA-based detection of type-specific antibodies against the L-1 VLP particles. Peptide-based assays are much less efficient and sensitive. Antibodies can be detected in serum or cervical mucous and are IgA as well IgG.
- Natural infection results in very low titers and there are no gold standards with which to set a threshold for a positive reaction, nor is VLP production standardized. Antibodies indicate past or current infection, but <70% of HPV-positive subjects will eventually raise detectable antibodies. The uncertainties of HPV infection include whether HPV is eliminated from the host. A negative DNA result in cytology samples could indicate true HBV clearance, but also could be a false negative or indicate shedding below the limit of detection. Sampling errors could miss a residual lesion or not include the basal compartment of the epithelium. HPV often can be detected in histologically normal margins around gross lesions.

Overview of Cancer of the Cervix

Presenter: Dr. Herschel Lawson, NCCDPHP

Overview: Cervical cancer in the U.S.: surveillance, disease burden, screening, diagnosis, treatment and survival, costs

The natural history of cervical carcinogenesis was charted, from infection of a normal cervix to its clearance or to HPV infection. HPV persistence of 1-2 years produces some mild cytologic abnormalities and/or seroconversion which can regress or proceed to invasive cancer. The most common cancers among women worldwide were also charted, showing the dramatic difference in cervical cancer incidence effected by screening in the more developed countries. Overall cancer incidence in the U.S. is measured by CDC's National Program of Cancer Registries (NPCR) and the NCI's SEER registry. Together, these systems collect ~96% of information about cancer in the U.S. population. Cervical cancer deaths are reported by CDC's National Center for Health Statistics, as gleaned from vital records of the entire population.

NPCR 2001 data indicate ~10,500 new cases, a potential underestimate since California data were not included. In 2002, NCHS data indicated ~4000 deaths, and the American Cancer Society is estimating ≥10,000 new cervical cancer cases and ~3700 deaths this year. Invasive cervical cancer incidence in the U.S. is nested in data of other cancers (e.g., bladder, pancreas, leukemias, kidney, renal, pelvis), as it is eleventh in incidence for U.S. cancers. A line chart showed its steady decline in mortality from 1946-1984. Its decline began even before the Pap screening test became common in use in the mid-1950s. Charted SEER data from 1975-2002 also showed a slow decline in incidence and mortality that leveled off in the last several years.

However, health disparities persist, with black women's rates still higher for incidence and mortality, and higher for Hispanic women than for those who are non-Hispanic. Data charted by age group also demonstrated the highest incidence and progressive mortality among women in their aged 40-45 years, followed by those in their sixties. Asian women's rates parallel those of white women, with the exception of Vietnamese women, who have the highest incidence of all (43/100,000). And, coinciding with increased immigration to the U.S., cervical cancer mortality rates are rising for foreign-born women while decreasing for the U.S.-born.

Age-adjusted cervical cancer mortality data per 100,000 person-years were mapped by geography and economic area (socioeconomically similar counties within a state). The worst rates were in the rural Northeast, down the Appalachian mountains into the Southeast, along the Ohio and Mississippi river valleys, in southern Texas and eastern New Mexico.

Studies show that 50%-60% of incident cases are among unscreened women. *U.S. cervical cancer screening* uses the conventional Pap cytology or the liquid-based cytology (LBC) test. The latter, done since the late 1980s, provides a clearer image of a single layer of cells. The Pap is more specific (95-98%) but less sensitive (51%-99%) than the liquid-based cytology (LBC ─ 61%-95%, 78%-82%, respectively).

Prevalence of cervical cancer screening in the U.S. is measured by the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS). NHIS data from 2000 indicate that 82% of all U.S. women had a Pap test in the past three years. Group differences emerged by the proportion insured (85% screened) versus uninsured (62%), as well as by country of birth (83% U.S. born, 61% foreign-born), with Asian women the least screened.

The HC2 test detects HPV infection via long synthetic RNA probes similar to the DNA sequence of the 13 high-risk HPV types. The test is easy to perform in clinical practice and is used in triage (to determine the status of nonspecific ASC-US Pap test results) and primary screening (given in addition to the Pap test to women aged ≥30 years). If both tests are negative, the next cervical cancer screening is scheduled for ≥3 years later, since serious cervical changes are unlikely in that period.

Screening recommendations were issued by the U.S. Preventive Services Task Force, the ACS and ACOG. While all agreed that screening should begin at age 21 or within 3 years of sexual activity, they disagreed on the recommended interval (every three years; once a year; every two years for the LBC). ACOG and the American Society for Colposcopy and Cytopathology have recommended the HC2 test for cervical cancer screening. The USPSTF found insufficient evidence for its use in triage and did not address a primary screening use with the Pap. The ACS

did not address the ASC-US but left it as an option for primary screening with the Pap test.

There are no data collection systems to support an estimate of abnormal Pap tests (not cancers) in the U.S., but analyses of administrative data sets provide a range. Of the ~2 million ASCUS results, ~1 million are LSIL; 300,000 are high-grade SIL, and about 15,000 are cancer. Upon an abnormal Pap result, a pelvic exam and perhaps a repeat cytology is done, depending on the gravity of the suspected cytologic changes. Colposcopy and a directed biopsy are now recommended for LSIL, HSIL, ASC-H, and any glandular atypicality. Curettage of the endocervical canal is often done as well.

Treatment options for cervical cancer precursors: observation (for LSIL potentially associated with acute HPV infection that may resolve); local excision by loop electrode excision procedures (LEEP), CO^2 laser or cold-knife conization. In the most extreme situations, hysterectomy is considered but increasingly rare for cervical cancer precursors. Staging and survival range from Stage I, cancer confined to the cervix to Stage IV, cancer beyond the pelvic wall or bladder or rectal mucosa. Survival is very high (virtually 100%) among women detected with early-stage disease detected before it becomes invasive.

Costs. Of the annual direct medical costs associated with STDs, HPV accounts for ~$4 billion, of which 90% relates to abnormal cervical cytology and treatment of neoplasia. Only a very small proportion relates to the management of cervical cancer and anogenital warts.

Discussion included note that modeling produced the intervals recommended, which impact costs. Related assumptions included HPV prevalence, LSIL, HSIL, etc., in the age groups. Modeling revealed greater cost effectiveness to frequently screen younger women (≤20 years) among whom the prevalence is very high. The ACS decision to recommend a 2- rather than 1-year interval was based more on expert consensus that recognized the greater sensitivity of the LBC, despite its lesser specificity. The CDC's National Breast and Cervical Cancer Early Detection Program lengthened the intervals further for women having a number of normal tests prior, but no one has suggested going beyond 3-5 years.

Pandemic Influenza Preparedness: Vaccine and Antiviral Drug Decision Issues

NVAC Pandemic Influenza Workgroup Report
Presenter: Dr. Benjamin Schwartz, NVPO

> Overview: Summary of work by the NVAC Pandemic Influenza Workgroup, NVAC antiviral subgroup, and ACIP-NVAC vaccine subgroup.

The NVAC Pandemic Influenza Workgroup has been analyzing decision issues leading to NVAC recommendations on priority groups for pandemic vaccine when supplies are limited, priority groups and strategies for antiviral drug use, and the public sector role in pandemic vaccine purchase and distribution. It also will provide input to the ACIP recommendations on vaccine priority groups through its joint NVAC/ACIP vaccine subgroup/Antiviral subgroup. The workgroup as a whole will seek to increase communications with and engagement of stakeholder organizations. To meet the late August deadline for the final pandemic plan, a joint ACIP/NVAC meeting will be held in Washington, D.C. on July 19, 2004, for the committees to vote on the recommendations. Participation by telephone conference call is also possible. The

newly created DHHS Influenza Task Force will also use the recommendations in crafting its advice for the Secretary.

Vaccine purchase and distribution options are being developed, guided by Dr. Walter Orenstein. The options include: 1) the current annual, largely private-sector program, or 2) completing a complete early-pandemic federal purchase of all pandemic influenza vaccine, which would then transition toward the routine annual system. The relative advantages and disadvantages of the options have been circulated to the Workgroup and to industry for their comments.

The issues concurrently under discussion by the Antiviral Subgroup include identifying potential target vaccine recipients, defining antiviral drug-use strategies, developing options to guide stockpile purchases, and identifying other critical issues to address. The latter includes the use of antiviral drugs to contain an initial outbreak and to prevent a pandemic, or to slow the spread of disease once it occurs, as well as identifying critical research needs.

Target groups and drug-use strategies. The principles and assumptions supporting recommendations for target groups and strategies were outlined. The H5N1 isolates tested to date seem to be resistant to adamantine treatment, so neuraminidase inhibitors are the agents of choice. Since their supply is limited, strategies for their use must be efficient, flexible, equitable, and responsive to local needs. Complementary strategies for antivirals and vaccines are needed.

Target groups for antiviral drugs have not been finalized. Those being discussed are: hospitalized patients, and groups of outpatients at high risk for complications or death, such as immunosuppressed persons who could not be protected by vaccination; the groups ACIP recommends for early annual vaccination; key occupational groups that perform critical social infrastructure functions in society, such as healthcare workers, public-health responders, public safety workers; police and corrections officers, firefighters, and others. Modeling indicates that using these drugs as treatment rather than prophylaxis will prevent more deaths per amount of antiviral drugs. However, prophylaxis may be recommended for small, specific groups that are particularly critical to a pandemic response, such as EMS, ED and ICU staff.

Review of Meeting on Pandemic Vaccine Prioritization
Presenter: Dr. Carolyn Bridges, NIP

Overview: Report on joint ACIP/NVAC Influenza Workgroup discussions.

The vaccine and antivirals groups began discussions in April. In their four meetings since then, they assessed the impact of prior pandemics, defined healthcare worker groups and the impact of pandemics on them, defined critical infrastructure groups, and addressed ethical considerations. ACIP workgroup members participated in the June 22 conference call of the entire NVAC Pandemic Influenza Workgroup. The Workgroup's first draft was presented to the ACIP at this meeting for comments by July 11, in anticipation of the July 19 meeting. By August 1, recommendations will go to DHHS.

The June 22 agenda was to review the goals of pandemic planning, to review the impact of pandemic influenza by age and risk group and subprioritization options, to review the possible impact on the healthcare system and options for prioritizing healthcare workers, to define and possibly prioritize those persons in critical infrastructure sectors, and also to review ethical

considerations.

Results. The group listed two overriding priorities for pandemic planning: minimizing hospitalizations and deaths, and preserving critical infrastructure and minimizing social disruption. The goals were to: 1) vaccinate all persons in the U.S. wanting it, but in view of likely shortages, 2) vaccines should be prioritized to achieve the two stated priorities.

Key prioritization assumptions in the plan are:

- *Incidence:* 25%-30% of the population will become ill with influenza in a major pandemic wave lasting 6-8 weeks, and perhaps followed by one or more waves.
- *Hospitalization rates* ranging from .01%-8% and mortality rates of 0.001%-1%. Those at greatest risk of hospitalizations are children aged ≤1 year, people aged ≥65, and those with ≥1 chronic, ACIP-defined high-risk medical condition. Medical care services will be at least severely taxed and likely overwhelmed.
- *Absenteeism.* Uncomplicated pandemic influenza will keep someone out of work for five days. At a 25% overall attack rate at the pandemic peak, ≥10% of workers may be absent in an 8-week outbreak period.
- *Vaccine production/use*: ≥6 months will elapse between identification of a candidate vaccine strain to first production, the latter optimistically estimated at ~5 million doses of inactivated vaccine per week. Since those meetings, MedImmune estimated its production capacity for live influenza vaccine at ~ 1.5 million doses/week, but part of that production process is in the U.K.
- *Doses:* Two doses per person will be needed; the Department of Defense has prioritized 500,000-1.5 million people high for vaccine.
- *Antiviral medication supply* will be limited and require rational, explicit vaccine prioritization. The latter will undoubtedly have to be modified based on the pandemic's epidemiology.
- *Critical infrastructure* groups are those with a direct role in reducing hospitalizations and deaths, and subgroups of critical infrastructure sectors essential in maintaining those functions and preventing social disruption. There are few data to support an analysis of pandemic effects on the nonhealthcare and nonmilitary sectors, and old information may be inapplicable due to major changes in business practices. Much more work is needed on the critical infrastructure aspects.
- *Prioritization*. This work considered past pandemics' impacts by age and risk group as regards hospitalization and death. Data on interpandemic outcomes were used when there were none for pandemic-specific outcomes relevant to: likelihood of response to vaccination, anticipated influenza impact on the demand for healthcare and critical infrastructure services, the directness of the role of critical infrastructure sectors in preventing 1), hospitalizations and death and 2) social disruption.
- *Vaccine availability.* The estimated amount of vaccine available over time and the number of people who could be protected with the one- and two doses needed was analyzed, along with the population sizes for high-risk groups, healthcare workers, and critical infrastructure groups. For either healthcare workers or critical infrastructure groups, one month's supply of inactivated vaccine would be needed to fully vaccinate either group twice, or to fully vaccinate the high-risk population in that group for seven months (one dose) or 3.5 months (two doses).

Conclusions reached by the joint workgroup were:

1. To reduce the need for rationing, investment is needed to expand the U.S. vaccine manufacturing capacity to conduct research to extend the existing vaccine supply, (e.g., vaccine adjuvants or intradermal administration).
2. Develop and test seed lots of vaccine with pandemic potential.
3. Improve interpandemic vaccine delivery infrastructure.
4. Consider a stockpile of monovalent influenza vaccines with the greatest pandemic potential.
5. Consider the use of live attenuated influenza vaccine and early use of inactivated vaccine.
6. To minimize vaccine shortfalls, enhance antiviral medication stockpiling.
7. Revisit these recommendations regularly and during a pandemic to revise them as needed for the current epidemiology.
8. Reserve some vaccine for response to unforeseen emergencies.
9. Ensure public input to the development of any prioritization scheme. The draft prioritization list was as follows. More detail and rationale about the listed groups was provided in a ten-page meeting summary among the meeting materials.:
   Tier 1 (~ 46 million people)
   a. 1-A: Healthcare workers involved in direct patient contact and those in essential support services; vaccine and antiviral manufacturing personnel and their critical support staff.
   b. 1-B: Those at highest risk of influenza complication: those aged ≥65 years with ≥1 high-risk condition; those aged 6 months to 64 years with ≥2 high-risk conditions; those hospitalized in the last year with an ACIP high-risk condition or pneumonia and influenza.
   c. Group 1-C: Household contacts of children aged ≤6 months who cannot receive antivirals or vaccine; household contacts of those who are severely immunocompromised; pregnant women who will soon be household contacts of children aged ≤6 months.
   d. Group 1-D: Key government leaders; critical public-health pandemic responders.

   Tier 2: The balance of the high-risk group: all those healthy and aged ≥65 years; those aged ≤65 with ≥1 high-risk condition; children aged 6-23 months; most of the critical infrastructure groups and other public-health emergency responders (police, fire, utility workers, telecommunications, etc.)

   Tier 3: Other key government health decision-makers and mortuary services.

   Tier 4: Healthy people aged 2- to 64-years and not in other groups.

Groups for consideration of an antiviral strategy were:

1. Residents of nursing home and 24-hour skilled nursing care facilities (they are less likely to respond to vaccine, live in a semiclosed setting and have somewhat centralized healthcare).
2. Healthcare workers and critical support staff. In order, vaccination is recommended for staff, to limit ill staff and visitors; close monitoring of respiratory outbreaks; and aggressive use of antivirals among nursing home residents for outbreak control.
3. Severely immunocompromised persons not likely to respond to vaccination. In order,

vaccinate their healthcare workers and household contacts, close monitoring for respiratory illness, aggressive use of antivirals for treatment; consider prophylaxis with antivirals.

Comments received on this tiering to date have suggested no subtiering, which may be too complicated; collapsing Tiers 1-C and 1-D; subtiering Group 2; and moving key government leaders to Tier 1-A.

Canadian pandemic plan. The Canadians plan prioritized for Group 1, healthcare workers and public-health workers; Group 2, essential service providers; Group 3, persons with high risk conditions who are subprioritized into five different groups; Group 4, healthy adults; and Group 5, healthy children aged 2-18 years.

Discussion included:

- The entire tiering system may have to be reconsidered according to the epidemiology of the pandemic. However, since the overall attack rate was fairly consistent among the three past pandemics, the plan was based on that.
- Steps initiated by the government to augment vaccine and antiviral production capability include some contracts recently signed to ensure year-round availability of vaccine and a contract to promote diversification of methods (with cell culture vaccine) in the U.S. NIH also is doing a clinical trial with an experimental H5N1 vaccine, which includes dose stretching strategies like intradermal and adjuvant usage. Additional contracts will be let in the next few months.
- Also being discussed is adding a pandemic component to the trivalent vaccine used annually to avoid the need for two vaccines, but the current focus is more on stockpiling.
- Dr. Pickering stated that the ACIP members would be contacted in the next week to ascertain their availability to attend the July 19 meeting. Ms. Emma English, of the NVPO, stated their desire to maximize public participation. To do that, the meeting will be Webcast from a link on the NVPO Web page.

Draft ACIP/HICPAC Recommendation for Health Care Worker Influenza Vaccination
Presenter: Dr. Michelle Pearson, NIP

Overview: Summary of ACIP 2004 recommendations for healthcare worker influenza vaccination compared to similar HICPAC vote.

Agreement was reached at the February ACIP meeting to use the HICPAC evidence-ranking scheme for these health care worker recommendations. The scheme is as follows:

- *Category IA.* Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies.
- *Category IB.* Strongly recommended for implementation and supported by certain experimental, clinical, or epidemiologic studies and a strong theoretic rationale.
- *Category IC.* Required by state or federal regulation, or representing an established association standard.
- *Category II.* Suggested for implementation and supported by suggestive clinical or epidemiologic studies, or a theoretic rationale.
- *Unresolved issue.* No recommendation is offered due to lack of consensus or insufficient

or contradictory evidence regarding efficacy.

The ACIP and HICPAC recommendations were compared:

1. **ACIP:** Require all health care workers, including students, to participate in an influenza prevention program which includes education and provides annual vaccination. ***Category IB.*** **HICPAC:** Delete as redundant.
2. Vaccinate all eligible healthcare workers, including students, against influenza annually to protect their patients, themselves, their families, and their communities and to decrease healthcare worker absenteeism. ***Category 1A.*** **HICPAC:** Agreed.
3. Educate healthcare workers regarding the benefits of vaccination and the potential health consequences of influenza for themselves and their patients. Education should include information on influenza and epidemiology, diagnosis, and nonvaccine infection control strategies, in accordance with their level of responsibility in preventing health-care-associated influenza. ***Category II.*** **HICPAC:** Agreed.
4. Provide influenza vaccination to healthcare workers at the work site and at no cost as one component of the employee health program. Use strategies that have been shown to increase influenza vaccine acceptance. Strategies include mass vaccination clinics, mobile carts, flu deputies (i.e., peer vaccinators), vaccination access during all work shifts, role modeling and support by institutional leaders. ***Category IB*****. HICPAC:** Agreed.
5. Monitor healthcare workers' influenza immunization rates at regular intervals during influenza season. Provide feedback to entities such as patient care units and the institution's administration. If HCW declines, the HCW should sign a statement of declination. ***Category IB.*** **HICPAC:** Monitor healthcare workers' influenza immunization and declination rates at regular intervals during influenza season. Provide feedback of ward/unit- and specialty-specific rates to staff and administration. ***Category IB*** Declination should be viewed as part of a monitoring function and part of an overall quality-improvement program. Monitor both immunization and declination rates, provide feedback, and awarding unit-specific and specialty-specific rates to the staff and to administration.

   Issues related to declination were discussed by both HICPAC and ACIP relative to whether there should be a stand-alone recommendation on this, and if so, what that statement should be. ACIP wanted a signed statement from healthcare workers declining influenza vaccination for reasons other than medical contraindications and a copy kept of the declination. This was felt by some as likely to bolster acceptance. The declination would trigger vaccine-acceptance efforts targeted to them; and it would identify them in the event of an outbreak or institutional outbreak. In contrast, others urged a less punitive incentive for vaccine acceptance.
6. Use health care worker influenza rates as one measure of the institution's patient safety/quality program. ***Category II.***

Dr. Poland had departed, but had left language to be considered by the committee, "All healthcare workers with direct patient-care responsibility should be required to receive an influenza vaccine annually, unless an informed declination is signed."

Discussion included:

- The ACIP members' feeling remained that the declination requirement should not be diluted; if anything, it should be strengthened to ensure that health care workers are vaccinated to avoid influenza transmission. Ms. Stinchfield reported that 30% of her institution's health care workers were not recorded as vaccinated. While 10% received it at their own providers, 20% did not for other reasons, some relating to needle phobias.
- Dr. Finger agreed to the need for strong declination procedures, but endorsed the last HICPAC sentence (feedback provision) as stronger than ACIP's.
- The American College of Occupational Health Professionals and the SICU union were expected to oppose mandatory requirements.
- In view of the anticipated resistance from health care workers, Dr. Marcuse preferred an informed declination, and preceding the recommendation with consultation and education to aid compliance. One intermediate strategy that had been proposed was to institute a vaccination rate monitoring system across the healthcare spectrum to show low rates, for example, by geographic groups, facilities or occupational categories.
- Dr. John Iskander, of the Immunization Safety Office, cited emerging evidence among parents declining vaccination for their children that persuasive arguments work, and mandates are the least persuasive. He suggested an incremental approach, working with the implementers in the field to improve vaccination rates, rather than using mandates as the first step.
- One edit was needed, to insert "vaccination" between "influenza" and "rates" in the last recommendation.

Points were made in support of a formal declination, an approach that originated with the AAP. While that would remove the legal issues of forcing someone to take the vaccine, it still would require the declining health care workers to acknowledge that they are putting themselves, their patients and families at risk. Other suggestions offered were to: 1) research to see what has been effective to date; 2) work with stakeholders to understand why people decline and then craft the declination statement around those reasons; 3) make the declination part of patient information; and 4) list declination in Recommendation #4 as part of the effective strategies (as shown by that requirement for hepatitis B vaccine). A specific plan to issue this statement was also requested, since that did not occur last year despite good intentions.

Dr. Allos moved to require health care workers to sign a declination statement if they do not want to receive influenza vaccine. Dr. Finger seconded the motion.

Vote on requirement of a healthcare worker declination statement

In favor: Levin, Stinchfield, Morita, Lieu, Finger, Birkhead, Allos
Opposed: Marcuse, Gilsdorf
Abstained: None

The motion passed.

Next steps: Dr. Pearson reported that the Joint Workgroup would develop the background text in time for the upcoming influenza season.

Dr. Finger moved to ratify the recommendations as printed, deleting #1 and splitting #6 to provide for a separate signed declination statement, and to ratify #7 with the "vaccination" correction. Dr. Allos seconded the motion.

Vote 0n recommendation of influenza vaccination for health care workers

In favor: Levin, Stinchfield, Morita, Lieu, Marcuse, Gilsdorf, Finger, Birkhead, Allos
Opposed: None
Absent: Abramson

The motion passed.

Update: ACIP Rotavirus Workgroup
Presenter: Dr. Penny M. Heaton, Director, Vaccine/Biologics Clinical Research, Merck Research Laboratories

Overview: Characteristics of the investigational pentavalent human-bovine reassortant rotavirus vaccine (PRV); REST (Rotavirus Efficacy and Safety Trial) study design and efficacy results (clinical, prevention).

The oral investigational PRV vaccine for infants is suspended in a liquid buffer/stabilizer. It is administered in a three-dose regimen at 1- to 2-month intervals and its efficacy has been evaluated for 2-, 3-, 4-month and 2-, 4-, 6-month schedules. This is a pentavalent vaccine containing five human and two bovine reassortants in the human G serotypes G1, G2, G3, and G4 (which comprise >80% of the rotavirus disease in the worldwide and >90% in the U.S.), and bovine G6, as well as the human P1 serotypes, genotype 8, that most commonly associated with G-1, 3 and 4; and bovine P7(genotype 5). The process of how the vaccine was developed and how the reassortants were made was diagramed.

REST study design. The primary objective of the REST study was to evaluate the efficacy of PRV against rotavirus acute gastroenteritis (RV AGE) caused by serotypes G1, G2, G3, and G4 and, secondarily, to evaluate the efficacy of PRV against 1) *severe* RV AGE caused by caused by serotypes G1, G2, G3, and G4 and 2) health care resource utilization for rotavirus gastroenteritis, including hospitalizations, emergency visits, and office visits.

Safety. The large sample size of 69,274 subjects (randomized 1:1) was required to evaluate vaccine safety relative to the rare occurrence of intussusception, as well as efficacy against hospitalizations and ED visits for RV gastroenteritis resulting . The age at first dose was 6-12 weeks and three doses were administered every 4-10 weeks, depending on the country in which the subjects were enrolled. The final vaccine formulation was a potency of 6.7 to 12.4 ($10^{7)}$ infectious units per dose. In fall 2004, the study's DSMB verified that the study was complete because the primary safety hypothesis associated with intussusception had been met.

RV gastroenteritis was defined by forceful vomiting and/or ≥3 watery or looser-than-normal stools within a 24-hour period. RV antigen was detected by EIA in the stool and the serotypes were defined by PCR. Case severity was categorized according to a clinical scoring system validated in the Phase 2 program, based on fever intensity/duration, vomiting, diarrhea, and behavioral changes. Mild disease was ≤8; moderate disease was 8-16; and severe disease was

>16. After the first dose and over the following year, the children were contacted at weeks 1, 2, and 6 after each dose and then every six weeks to determine intussusception, hospitalization, and ED visits for rotavirus gastroenteritis. Any RV gastroenteritis healthcare contact was followed within 24 hours to 14 days by collection of a stool sample,

Efficacy was assessed in 5686 subjects (randomized 1:1) for clinical efficacy against rotavirus gastroenteritis and office visits for same, as well as the safety outcomes above. The efficacy study was enrolled from 2001 to 2004 and the cohort was embedded within the large safety cohort. Parents reported all potential acute gastroenteritis episodes after dose one and were asked about cases of rotavirus gastroenteritis during one rotavirus season (two seasons, for ~1000 children).

Results. VE was shown as follows:

- Against any disease, regardless of severity: 74% (95% CI lower bound, 66.8%).
- Against severe disease: 98%.
- Office visits for rotavirus gastroenteritis: 86.1% reduction in the in the vaccine group versus the placebo group (CE range of 74.2% to 92.6%).
- Overall reduction of RV gastroenteritis-related hospitalizations (95.8% (CI range 90.5%-98.2%) and ED visits (93.4%) (CI range 88.1 – 96.3%) (N=>34,000).
- Reduction by vaccine serotype of RV gastroenteritis-related hospitalizations: G1=94.9%; G2=87.6%; G3=93.4%; G4: 89.1%.
- Reduction of nonserotype-specific vaccine strain for hospitalizations (95.6%), ED (93.5%) and office visits (85.2%), for all cases of rotavirus gastroenteritis. Most cases were caused by G1, -2, -3, and -4.

Summary: The vaccine was efficacious (74%) against any severity of rotavirus gastroenteritis and highly efficacious (98%) against severe disease with just one breakthrough case. It was highly efficacious in reducing the rate of hospitalizations, emergency visits, and office visits for rotavirus gastroenteritis relative to placebo.

Discussion included that VE from the first dose for all gastroenteritis regardless of etiology was: 63% to reduce hospitalizations (CI lower bound of 55%), 39.8% for ED visits (CI range 31.5%-47.1%), and 21.8% for office visits (CI range 4.7%-35.8%).

Issues of Human-Bovine Vaccine
Presenter: Dr. Umesh Parashar, NCID

Overview: Issues discussed by the RV Vaccine Workgroup: type of recommendation, groups targeted, vaccine administration timing and concurrent administration, breastfeeding and immunodeficiency concerns.

Discussions by the Rotavirus Workgroup of key issues in developing recommendations for vaccine use included:

- Type of recommendation: universal, routine vaccination, permissive recommendation, or a recommendation targeted to high-risk groups.
- Timing of administration of different vaccine doses, particularly regarding vaccine safety among premature infants.
- Effect of concurrent administration at 6 and 14 weeks with the other routine

vaccinations (e.g., interference issues, breast-feeding impact on VE; appropriateness for immune deficient children; safety concerns for immunocompromised household members living with children vaccinated with this live vaccine and shedding it in stool.

- Vaccine administration to children with acute gastrointestinal disease or pre-existing conditions who may have a reduced vaccine take or to those recently receiving antibody-containing products.
- Redosing of children who spit, vomit, or regurgitate vaccine.
- Need to vaccinate those known to have had rotavirus gastroenteritis before vaccination is initiated.
- Intussusception and other adverse events.

The 2.7 million annual U.S. cases comprising the rotavirus disease burden were charted by mortality and morbidity. Relatively few related deaths occur in children, but 55,000-70,000 hospitalizations occur which constitute ~4% percent of all pediatric hospitalizations. More direct costs are incurred through emergency department and physician office visits, and indirectly through cost of care and caretaker time. Vaccination factors discussed in depth to date by the Workgroup included:

- The Newman et al study (*Pediatrics*, 1999; 103: 3) in Washington state explored the groups at risk for hospitalization, the most important severe health outcome of viral gastroenteritis. Risk factors included low birth weight, male gender, young maternal age, maternal smoking, and unmarried mother. They also developed an ROC curve to assess whether those listed variables predicted risk groups to target. A curve of.62 resulted, indicating that targeting identified groups of children at higher risk of hospitalization would not prevent a large proportion of hospitalization. In light of that, the Workgroup tended to favor a routine universal rotavirus vaccination recommendation. Discussion is ongoing and includes evaluation of the vaccine's cost effectiveness.
- *Age at immunization* Merck's REST trial administered the first vaccine dose between 6-12 weeks of age, and all three doses by age 8 months, with 3-week intervals between doses. Rotashield was licensed with the first dose recommended at 6 weeks but not licensed for use in children aged >6 months of age, due to the latter's higher rates of fever with lost maternal antibody and potentially higher reactogenicity. Those concerns remain and were supported by Swedish and Finnish studies, so 6 months remained as the upper limit for dose 1 and one year of age for any dose.
- *Dosing and intussusception*. Rennels et al (*PIDJ* Vol. 17, No. 10, Oct. 1998, 924-925) examined intussusception in New York State from 1991-95 and found a low incidence of naturally occurring intussusception in the first two months of life. The peaks begin from ~4 months. Since the first Rotashield dose was primarily associated with intussusception, giving it to a child at age 4-6 months may produce a natural intussusception that is temporarily associated with the vaccine, risking suspicion of a causal association difficult to ascertain.
- *Timing*. Establishing strict boundaries for dose 1 could frustrate the practical need to reach and immunize eligible children. Balance is needed.

The Workgroup expected by October to have draft language for many of these issues.

Discussion included:

- The risk factors for gastroenteritis hospitalization before Rotashield included socioeconomic status and access to medical care. Some of the variables presented (maternal age, maternal smoking, unmarried mother) are potentially related to low SES. There are surveillance data from three sites that involve SES, but the study analysis is still incomplete. That study probably could be presented in October. However, there are no known direct data on SES issues.

Dr. Schwartz suggested review of the REST study data to explore the type of care they received during outpatient visits for gastroenteritis, and any subsequent ED visit and hospitalization. Dr. Robin Ensler, of Merck, said the last could be done, but was uncertain the data would be detailed enough to describe the care given.

ACIP HIV Vaccine Workgroup Update
Presenter: Dr. Charles Vitek, NIP, for Dr. Gus Birkhead

Overview: Update on vaccine pipeline and implementation issues; requested ACIP endorsement of an annual workgroup update report.

Formed in the fall of 2002, the HIV Vaccine Workgroup has ten members from ACIP, NVAC, and federal agencies, as well as consultants from state health departments and other institutions. Its original charge was to review and report to the ACIP on the current status of HIV vaccine research, broad developments in the field, the challenges to effective vaccine development and implementation, and to provide a liaison to other HIV vaccine groups working on policy issues.

While progress is being made, a licensed vaccine is not imminent; the first two vaccine candidate efficacy trials failed to show efficacy. Dr. Birkhead recommended an annual Workgroup update to ACIP on research progress and preparation for vaccine availability, including attention to issues of implementation that are potentially important to recommendations, strategies to involve affected communities in the discussions about potential recommendations; information on the modeling of HIV vaccine impact which is underway; and approaches to create HIV vaccine readiness in potentially targeted high-risk communities.

Vaccines. Two HIV preventive vaccines are in joint testing with the NIH-sponsored HIV Vaccine Trials Network (VTN). They are in efficacy trials, one a large Phase 3 trial with a canarypox candidate in Thailand and the other a Phase II-B, small efficacy trial of Merck's adenovirus vector candidate. The NIH Website offers additional information on preventive HIV vaccine candidate clinical trials, as does the Website http://www.iavireport.org/specials/OngoingTrialsofPreventiveHIVVaccines.pdf.

Implementation issues include that:

- Prevention of HIV infection is not the only marker of vaccine effectiveness. Others include slowed clinical progression to AIDS (e.g., reduction of HIV viral load and preservation of CD4 count), reduction of infectivity in persons who do become HIV infected, and therapeutic use in HIV-infected persons to prevent disease progression, reduce infectivity, or possibly reduce mother to child transmission.
- There is significant concern that HIV vaccines could result in increased risk behavior among vaccinated populations with an exaggerated belief in their protection (disinhibition). For risk behavior to be closely monitored, both in vaccine trials and

eventually in implementation programs, both will have to be embedded within a comprehensive HIV prevention program with ongoing surveillance.

- HIV vaccines may result in HIV seropositivity among those immunized, which risks related possible stigma or social harm (e.g., denial of insurance, something already anecdotally reported in vaccine trials; the inability to donate blood; and restrictions on work). Ongoing work to counter HIV-related stigma is needed.
- HIV prevention and treatment policy development of the last two decades has been characterized by and benefited from a very high level of community involvement in policy decisions. Community involvement may be necessary to obtain acceptance of ACIP vaccine recommendations in some communities heavily affected by HIV, including ones that are historically suspicious of vaccine efforts or conspiracy theories regarding HIV. Targeted hepatitis B vaccination programs may have applicable lessons to share.
- The ACIP's HIV vaccination recommendations may differ significantly from those elsewhere in the world, due to the differing HIV burden and predominant risk factors. ACIP will need to be sensitive to the international context of recommendations.

Liaison and ex-officio reports

Dr. Levin had left the meeting, and Dr. Treanor assumed the Chair to the end of the meeting. He called for liaison and ex-officio reports and none were offered. On his request, Dr. Cochi reported that the cessation of polio vaccination in northern Nigeria for a year resulted in the virus' wide exportation throughout west, central, and east Africa, across the Red Sea into Saudi Arabia and Yemen, and on to Indonesia. On the positive side, the south Asian countries of India, Pakistan, and Afghanistan have had great success, reducing their cases to 18, 10, and 3, respectively. NIP is cautiously optimistic that southern Asia may have eliminated endemic polio by year's end, and the Indonesian and Yemen outbreaks are being aggressively addressed with multiple campaigns. In sub-Saharan Africa, the only continuing transmission is in Sudan, Nigeria and Niger. WHO has a continuing will to persist. Public comment was invited, to no response, and the meeting adjourned at 3:55 p.m.

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

Myron J. Levin, MD, Chair

Date

ATTACHMENTS

Attachment #1: Attendance

ACIP Members

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

Dr. Robin J. Womeodu was absent.

Ex-Officio Members

Centers for Disease Control and Prevention
Louisa Chapman, M.D.
Stephen L. Cochi, MD, MPH
Alison Mawle, MD
Gina Mootrey, DO, MPH
Larry Pickering, MD, Executive Secretary
Charles Vitek, MD

Ex-Officio Representatives of Other Federal Agencies
Norman Baylor, MD, Food and Drug Administration (FDA), for Dr. Karen Midthun
James Cheek, MD, Indian Health Service (IHS)
Barbara Mulach, for George T. Curlin, MD, National Institute for Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
Geoffrey S. Evans, MD, National Vaccine Injury Compensation Program (NVICP)
John Folkemer, for Linda Murphy, RN, Center for Medicare and Medicaid Services (CMS)
John Grabenstein, MD, for Stephen Phillips, DO, MPH, Department of Defense (DOD)
Benjamin Schwartz, MD, for Bruce Gellin, MD, Director, National Vaccine Program Office (NVPO)

Ex-officios absent: James Cheek, MD, Indian Health Service; Kristin L. Nichol, MD, Department of Veterans' Affairs (DVA), was absent.

Liaison Representatives
Carol J. Baker, MD, and Margaret Rennels, MD, American Academy of Pediatrics (AAP), Committee on Infectious Diseases (COID)
Dennis A. Brooks, MD, MPH, National Medical Association (NMA)
Richard Clover, MD, and Jonathan Temte, MD, American Academy of Family Practitioners (AAFP)
Stephan L. Foster, PharmD, American Pharmacists Association (ApharmA)
Stanley Gall, MD, American College of Obstetrics and Gynecology (ACOG)

Andrea Gelter, MD, American Association of Health Plans (AAHP)
Steve Gordon, MD, Hospital Infections Control and Prevention Advisory Committee (HICPAC)
David Johnson, MD, MPH, Pharmaceutical Research and Manufacturers of America (PHARMA)
Samuel Katz, MD, Infectious Disease Society of America (IDSA)
Clement Lewin, PhD, MBA, Biotechnology Industry Organization (BIO)
Amy B. Middleman, MD, MPH, Society for Adolescent Medicine (SAM)
Monica Naus, MD, National Advisory Committee on Immunization, Ontario, Canada
David A. Neumann, PhD, National Coalition for Adult Immunization (NCAI)
Kathleen M. Neuzil, MD, MPH, American College of Physicians (ACP)
Margarita Nava, MD, National Immunization Council and Child Health Program, Mexico
David M. Salisbury, MD, London Department of Health
Robert Scalettar, MD, MPH, American Association of Health Plans (AAHP)
William Schaffner, MD, Infectious Diseases Society of America (IDSA)
Litjen Tan, PhD, American Medical Association (AMA)
James C. Turner, MD, American College Health Association (ACHA)

Liaison representatives absent: Charles Helms, MD, National Vaccine Advisory Committee (NVAC); W. Paul McKinney, MD, Association of Teachers of Preventive Medicine (ATPM); and Jonathan Temte, MD, American Academy of Family Practitioners (AAFP)

Agency Staff

Agency for Toxic Substances and Disease Registry: Kris Bisgard

Department of Health and Human Services (DHHS)

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

No C/I/O identified: Don Blackman, William Boswer, Crystal Calloway, Scott Campbell, Pam Cassiday, Eric Comfort, Shuvro De, Irene Dunn, Lynn Finelli, Beth Hibbs, Sonya S. Hutchins, Richard Keenlyside, Cindy Knighton, Katrin Kohl, Laurel Leudel, Lucia Pawloski, Kelly Robison, Allison Rue, Meredith Reynolds, Michelle Russell, Gary N. Sanden, Mona Saraiya, Kate Shaw, David Shay, Margarita Sniadack, Stephanie Steele, Alice Steward, Jennifer Tsui, Marc-Alain Widdowson

Office of Media Relations: Kathy Harben

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National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP): Herschel Lawson

National Center for HIV, STD and TB Prevention (NCHSTP): Kristen Suhr

National Center for Infectious Diseases (NCID):

Miriam Alter	Niranjan Bhat	Kaafee Billah
Beth Bell	Stephanie Bialek	Joanna Buffington

Maria Cano
Rachel Barwick Eidex
Rima Khabbaz
Eileen Lau
Mehran Massoudi
Eric Mast
Martin Meltzer
Scott Schmid
Elizabeth R. Unger
Susan Wang
David Warnick

National Immunization Program (NIP):

James P. Alexander
William Atkinson
Melissa Barnett
Michelle Bashu
Achel Bhatt
Carolyn Bridges
Karen Broder
Krinstin Brown
Amanda Cohn
Margaret Cortese
Natalie Darling
Jill Davila
Gustavo Dayan
Chris Duggar
Gary Euler
Susan Farrell
Mark Frank
Sandra Gambescia
Paul Garguillo
Penina Haber
Jonelle Harrison
Stacey Hoffman
Sonya S. Hutchins
Lisa Jacques-Carroll
Kristen Kenyan
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National Institute for Allergies and Infectious Diseases (NIAID): Carolyn Deal, Jean Hu-Primmer

National Vaccine Program Office (NVPO): Kenneth Bart, Emma English

Members of the public or presenters to the committee in attendance were:
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http://www.cdc.gov/vaccines/recs/acip/downloads/min-archive/min-jun05.pdf