CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL IMMUNIZATION PROGRAM

RECORD OF THE MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

February 10-11, 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
ABC	Active Bacterial Core (surveillance system)
ACCV	Advisory Commission on Childhood Vaccines
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
AIM	Association of Internal Medicine
AMA	American Medical Association
aP	Acellular Pertussis (vaccine)
ASCUS	Atypical Squamous Cells Of Undetermined Significance
ASTHO	Association of State and Territorial Health Officers
ATP	According-To-Protocol
BLA	Biological License Application
BRFSS	Behavioral Risk Factor Surveillance Survey
CDC	Centers for Disease Control and Prevention
CHIP	Children's Health Insurance Program
CHOP	Children's Hospital of Pittsburgh
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CSTE	Council of State and Territorial Epidemiologists
CMI	Cell-Mediated Immunity
CNS	Central Nervous System
CP	Cerebral Palsy
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
group	Glycoprotein
GSK	GlaxoSmithKline
HBIG	Hepatitis B Immune Globulin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus (Vaccine)
HCUP	Healthcare Cost and Utilization Project
HICPAC	Hospital Infection Control and Prevention Advisory Committee
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HPV	Human Papilloma Virus
IDU	Injection Drug Users
Ig	Immune Globulin (IgA, class A; IgG, class G)
IM	Intramuscular
IN	Intraepithelial Neoplasia (anal: AIN; vulval: VIN); vaginal: VAIN)

IND	Investigational New Drug
IPV	Injected Polio Vaccine
ISS	Injection Site Swelling (LISS: Large ISS)
ITT	Intent-To-Treat
LAIV	Live Attenuated Influenza Vaccine
MCV/MPSV	Meningococcal Conjugate Vaccine/Meningococcal Polysaccharide Vaccine
MD	Muscular Dystrophy
MMRV	Measles, Mumps, Rubella, Varicella (vaccine)
MMWR	Morbidity and Mortality Weekly Report
MS	Multiple Sclerosis
MSM	Men who have Sex with Men
NACCHO	National Association of County and City Health Officers
NCID	National Center for Infectious Disease
NEDSS	National Electronic Disease Surveillance System
NHIS	National Health Interview Survey
NIP	National Immunization Program
NIH	National Institutes of Health
NIS	National Immunization Survey
NMA	National Meningitis Association
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OPV	Oral Polio Vaccine (trivalent: tOPV; monovalent: mOPV)
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PRN	Protatin (antigen)
PRV	Pentavalent Human-Bovine Reassortant Rotavirus Vaccine
PT	Pertussis Toxoid (antigen)
QALY	Quality Adjusted Life Year
RCT	Randomized Control Trial
REST	Rotavirus Efficacy and Safety Trial
SIL	Squamous Epithelial Lesions (low-grade:LSIL; high-grade: HSIL)
STD	Sexually Transmitted Disease
TD	Tetanus Diphtheria (antigen)
VAPP	Vaccine Associated Paralytic Polio
VDPV	Vaccine-Derived Polio Virus
VE	Vaccine Efficacy
VFC	Vaccines for Children (Program)
VLP	Virus-Like Particles
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VZV	Varicella Zoster Virus
VZIG	Varicella Zoster Immune Globulin
WHO	World Health Organization

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MINUTES OF THE MEETING
FEBRUARY 10-11, 2005

FEBRUARY 10, 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 February 10-11, 2005. The meeting agenda was posted on CDC's Website (http://www.cdc.gov/nip/). The meeting was convened at 8:11 a.m. by ACIP Chairman Dr. Myron Levin, who welcomed all in attendance (see Attachment #1).

OPENING COMMENTS

Acting ACIP Executive Secretary Dr. Steven Hadler made several announcements:

- He welcomed Dr. Jean-Marie Okwo-Bele, Director of the World Health Organization's Immunizations, Vaccines, and Biologics office.
- The ACIP home page is www.cdc.gov/nip/acip; e-mail is at acip@cdc.gov.
- ACIP workgroups scheduled to meet were those to address influenza, the harmonized schedule, Human Papilloma Virus, MMRV, meningitis vaccine, and ACIP adult immunization.
- The next ACIP meetings will be on June 29-30 and 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 Data Safety Monitoring Boards (DSMB). Those members may provide information to the committee on matters related to those vaccines, but they may not participate in the ensuing discussion or in related votes. They may discuss other vaccines produced by the same company, but not vote on matters related to that company's vaccines.

The members and liaisons then introduced themselves (see Attachment #1). Those reporting potential conflicts of interest were Dr. Greg Poland (grants from Chiron, VaxGen, and Merck Research Laboratories), Dr. John Treanor (Wyeth, MedImmune), and Dr. Levin (clinical trials for GlaxoSmithKline [GSK], Merck, and Merck's DSMB).

AGENDA ITEMS

Hepatitis Workgroup Report
Presenter: Dr. Tracy Lieu, Workgroup Chair

Overview: Background, historical context for hepatitis B transmission elimination; draft recommendations for hepatitis B strategies, now out for public comment. An ACIP vote on the recommendations is expected in June.

Vaccination recommendations for hepatitis B elimination have been issued for high-risk adults (1982), for prevention of perinatal transmission (mid-1980s), for catch-up among 11- to 12 year-olds, and universally for all children and adolescents.

Workgroup discussions to update the complete hepatitis B virus elimination statement, which has not been updated for more than a decade, focused on three areas:

1. Policies for obstetric obstetric hospitals for prevention of perinatal HBV transmission (including standing orders). There was strong consensus supporting standing orders for a birth dose of hepatitis B vaccination as part of routine care of all medically stable infants weighing ≥2000 grams at birth. The only exception was in the case of a physician's order to defer vaccine, based on documentation of a negative maternal HBsAG test result during this pregnancy.
2. Strengthened policies to promote vaccination of adults in risk groups. This went beyond the older recommendations, to offer vaccination to all persons who appear at such selected sites as STD and HIV clinics and substance abuse programs. The previous recommendation did so only for those screened positive for risky behavior. The advantage of this approach is that it reaches adults at risk in all age groups, (>90% of those infected with hepatitis B, including >40% of cases without identified risk factors, although the other 60% remains untargeted) through existing venues. It is a feasible approach and is cost effective.
3. Increasing the recommended age for universal vaccination to include persons aged 19-25 years was not recommended by the Workgroup. Although some supported at least advising this "when feasible," the majority doubted that this would produce any major impact, as this group is much smaller than the risk groups. It may divert resources from better strategies, has no evidence of feasibility, and is unlikely to be cost effective.

Hepatitis B Vaccine Recommendations
Presenter: Dr. Eric Mast, NCID

Overview: Development time line for hepatitis B vaccination recommendations, toward an anticipated July 2005 publication; literature review about hepatitis B vaccination and multiple sclerosis (MS); management issues to prevent perinatal HBV transmission; long-term protection and booster dose issues; recommendations to prevent HBV transmission in adults; plans to finalize recommendations.

The time line for the development of the hepatitis B vaccination recommendations was outlined, form the distribution of the original draft to the Workgroup on October 22, 2004, to its presentation to the ACIP for approval in June and anticipated *MMWR* publication in July.

Perinatal hepatitis B prevention challenges include that: 1) only <50% of infants born to surface antigen-positive mothers (~22,000 annually) are identified for case management. Case management has been shown effective to ensure more often provision of hepatitis B immunoglobulin at birth and to accomplish the complete vaccination series; 2) infants born to mothers of unknown hepatitis B antigen status often are inappropriately managed (mothers not tested upon delivery; their infants not vaccinated); 3) tracking errors have prevented infants born to known surface antigen-positive mothers from receiving postexposure immunoprophylaxis. The recommendations address these issues.

Prevention of Perinatal HBV Transmission.
The recommendations for postexposure prophylaxis remained unchanged in this new draft. Rather, they focused on implementation changes, to:

- Review the surface antigen test results for all pregnant women at the time of admission for delivery; identify and administer appropriate immunoprophylaxis to infants of all birth weights and all those born to surface antigen-positive or unknown antigen-status mothers.
- Establish a standing order to vaccinate all medically stable infants weighing ≥2000 grams at birth, unless a physician orders deferral due to documented antigen-negative status
- Documentation in the infant's medical record of its hepatitis B vaccination status and maternal surface antigen test results.
- Enrollment of obstetric hospitals in the VFC program, to avoid financial impediments to a birth dose by qualifying them for the VFC's free hepatitis B vaccine.
- Implementation and maintenance of perinatal hepatitis B prevention programs in health departments. This involves policies, procedures, and regulations to ensure surface antigen testing for all pregnant women; reporting and tracking of surface antigen-positive women; and appropriate case management for infants of surface antigen-positive and surface antigen-unknown mothers. Specific program monitoring and evaluation components are recommended.
- Vaccination of household and sex contacts of surface antigen-positive women.
- Specific recommendation to vaccinate pregnant women at high risk of hepatitis B infection, as that would outweigh any theoretical vaccine risk.
- Surface antigen status testing should be done either before vaccination or at least 21 days after administration to avoid a false positive result.

Recommendations for hepatitis B vaccine booster doses.
These recommendations remained consistent with current recommendations, advising against giving booster doses to those with normal immune status who were vaccinated at any age, and to give it to immunocompromised patients and those on dialysis.

Cohort studies of long-term protection.
Studies were conducted for 15-20 years after vaccination at various ages, from infancy to adulthood. This work documented a decline in detectable levels of protective antibody (<10 million IU), ranging from 15%-76%. It also found some evidence of asymptomatic antibody hepatitis B core antigen seroconversion among vaccinees, ranging from zero to 33% in countries

with high endemicity. Such seroconversion has never exceeded 5% in the U.S.; no symptomatic infections are documented, and chronic infections are rare. That indicated persistent protection, despite anti-HBs titers.

Four booster dose studies have examined the 10-15 years post-vaccination and indicate a quick anamnestic response to a booster dose by 67%-100% of vaccinees. The clinical significance of that remains unknown. Current studies are examining CMI persistence in the absence of an anti-HBs response.

Acute hepatitis B surveillance focuses on two areas:

- Cases among children born after the 1991 recommendation for routine infant hepatitis B vaccination. Among such children between 2001-2002, CDC and state health departments recorded 19 verified cases. Eight were among children born abroad and only 3 of the 19 had received more than one vaccine dose.
- No cases have been reported among fully vaccinated health care workers who were shown to respond to the vaccine.

Strategy to eliminate HBV transmission among adults
This approach is a sub-part of the overall elimination strategy, focusing on catch-up to complement the prenatal and infant strategies. Adult vaccination in the U.S. has remained low in spite of recommendations since 1982, except for certain targeted high-risk occupational settings. It is also low in the behavioral risk groups of concern. Data were presented from demonstration projects done among MSM, IDUs, and STD clinic clients.

In 2003, reported incidence data indicate ~73,000 new infections among adults, most among those aged ≥25 years, and more in males than females. But there has been an overall decline in rates (~65%) among adults since routine infant vaccination began, with most reduction among those aged 25-39 years and those ≥40 years. Those trends have plateaued since 1999, but remained consistent among those aged ≤15 years and those aged 15-24. The decline in older age groups is expected to continue as vaccinated adolescents age.

New recommendations on vaccination of unvaccinated adults.
To accelerate the elimination of transmission among adults, the draft recommendation advises that vaccination be promoted to all adults at risk and anyone else desiring vaccination. The targeted adult groups are:

- Persons with behavioral risks (sexually active persons not in a long-term, monogamous relationship and MSM; the language is permissive for IDUs).
- Persons with medical conditions (STDs, all dialysis patients and persons with chronic liver disease, those at risk of hepatitis B virus infection and those with HIV).
- Persons at occupational risk (health care and public safety workers, staff of correctional facilities and those institutions for the developmentally disabled).
- Persons in institutional, medical, and custodial-care settings such as the above.
- Others: household and sex contacts of surface antigen-positive persons, international travelers, victims of sexual assault.

Implementation recommendations

- Offer vaccine to all unvaccinated adults seen in STD clinics, HIV testing and counseling facilities and substance abuse prevention, treatment, and harm reduction clinics and programs.
- Implement programs to ensure high vaccine coverage for persons at occupational risk of infection, and those in institutional-, medical-, and custodial-care settings such as dialysis facilities, correctional facilities, and institutions for those who are developmentally disabled; and for household contacts of surface antigen-positive persons.
- Implement targeted outreach programs, when feasible, to vaccinate at-risk persons who rarely visit traditional health care settings and public health programs (e.g., homeless persons, IDUs).
- States are encouraged to implement immunization registries for adolescents and adults to track receipt of hepatitis B vaccine, with particular emphasis on persons who receive vaccine in multiple settings. State implementation of immunization registries for adolescents and adults to track hepatitis B vaccination also was urged.
- In settings where all persons do not need to be vaccinated, clinical assessment of all patients should be done to identify those needing vaccination. Close attention to risk factors was urged, acknowledging that frequently this is a difficult task.

Vaccination of all adults aged 19-25 years was discussed. The related advantage is the ability to reach young adults without identifiable risk factors and unlikely to visit the settings cited above. But the disadvantages are that those at risk in all age groups would be missed, particularly those in the marginalized adult risk groups. The feasibility of achieving high coverage was doubted as well, since there is no platform comparable to those of youth vaccination (e.g., school entry mandates) to boost adult vaccination. There also was concern expressed that scarce resources, so divided, would risk under-attention to the target groups in high-risk settings.

The estimated incremental cost of vaccinating all adults aged ≥19-25 years was roughly estimated at ~$83,000 per infection prevented in all adults so aged (~26 million), as compared to ~$550 per infection prevented by giving 3 doses to those in high-risk groups.

The rationale for vaccination of adults target groups was provided:

1. It enables targeting of persons who account for ≥85% of persons contracting hepatitis B.
2. Prior opportunities for vaccination were demonstrated in data (2001-2003) from the Sentinel Counties Study of Viral Hepatitis . Among patients with acute hepatitis B, 40% had been incarcerated in a detention facility, jail, or prison at some point; 38% had been screened or treated for an STD; and 25% were in substance abuse treatment or needle exchange programs. Overall, 62.5% were seen in any of these settings. Data analysis by risk factor indicated that >90% of IDUs were seen in one of those settings before becoming infected, as were >80% of persons with multiple sex partners, MSM, or individuals who reported sexual contact with an infected person. About 40% had other risk factors and ~20% had none. Feasibility was demonstrated in projects conducted in high-risk settings, with vaccine acceptance ranging from 50%-86% across sites.
3. The program would be cost saving, from a societal perspective, in several CE analyses involving high-risk adults, prison inmates, and STD clinic clients. Another study in progress involves publicly-funded HIV testing/counseling sites.

Barriers to adult hepatitis B vaccination include limited public sector funding to purchase adult hepatitis B vaccine, lack of insurance coverage for adult vaccination, and limited infrastructure to support vaccination.

Conclusions were that adult hepatitis B rates dropped ~65% since 1990. This decline continues among adults aged <25 years, but has plateaued in those older; ~80% occurs among persons with identified risk characteristics. In some settings, >60% of cases could be prevented with vaccination programs, given funding.

Discussion included:

- The focus is on hepatitis B vaccination, as opposed to general immunization, but the statement's background could provide further support for vaccinating newborns.
- Appropriate documentation of birth doses needs to be stressed. Physicians often prefer to vaccinate in their own clinic to ensure they have the record and, on occasion, to save the family a higher hospital charge. Support for vaccination registries should be added to the perinatal section as well as that on the adolescent/adult dose.
- The language should be strengthened to ensure vaccination before the infant leaves the birth center. Part of the problem is the failure to re-test for HBsAg status at time of delivery. That has always been recommended, but the implementation of that has never been evaluated.
- The exception provided for physician documentation of negative maternal antigen status could weaken the recommendation and leave the door open for medical, transcription and coordination errors. Although this was designed to leave room for clinician judgment, it was also observed that that has not proven successful in achieving complete immunization. It should at least be stressed that this should be a *rare* occurrence.
- Dr. Gall noted that currently, 23 conditions are listed for pre-exposure prophylaxis and 6 are listed for post-exposure prophylaxis. That is an unrealistic mandate for busy practitioners. He felt that the use of risk factor concept had ceased to make much sense.
- Dr. Barbara Watson, of the Philadelphia health department's perinatal program, confirmed that re-screening is not being done, nor is the recommended screening for ~5% of cases. This is due to lack of insurance and patient transfers between hospitals. Chicago data show that a mother who is educated about the vaccine does return for the follow-up visits. While standing orders are generally in place, the constant rotation of residents requires that physicians should not be integral to that education. She advised against the flexible language, since often it is not the attending that decides, but a sleep-deprived resident.
- Dr. Wexler cited NIP's estimate of 22,000 births to HBsAg-positive women annually, only half of whom are reported to states. Identifying those children nationally has not achieved a good record; only 40% of infants are getting the birth dose, a decline of ~20% from 1999. She called for a strong recommendation for the birth dose.
- Dr. Temte stated the AAFP's acceptance of the wording as it is, but they also would support wording that this vaccination could be delayed *only* with physician endorsement. These problems are not an issue with women seen through delivery and thereafter, but those who arrive, deliver, and then leave the practice. Those who object in the hospital are generally long-term patients who only want to delay for a couple of months.
- Dr. Abramson reiterated that the problems of tracking remain. The antigen-positive mothers have to be identified, since the infant is best protected by vaccine and HBIG as opposed to either one alone.

Dr. Levin summarized agreement to this point, to recommend standing orders and allow an opt-out clause. He asked the Workgroup to estimate how many children might slip through with that opt-out clause. Dr. Birkhead suggested added language on pediatric care to emphasize that the physician should be sure that the patient will return if the shot is deferred.

Dr. Mast recalled data presented at the last ACIP meeting on infants identified retrospectively versus prospectively. The analysis showed that ~65% of the birth cohort retrospectively identified received the birth dose and HBIG at the time of delivery. About 70% completed the 3-dose series, versus ~95% of those prospectively identified who were vaccinated and received HBIG at delivery; ~90% completed the series.

Data comparing administration of immune globulin plus 3 doses to vaccine alone indicate that the latter is equally effective. Immunogenicity data indicate that antibody conveyed by one dose provides 50-60% protection, but there are no data on protection from perinatal transmission. Dr. Abramson recalled one study, possibly in Taiwan, that measured one dose versus HBIG and found each to be ~75% effective alone and 90% effective combined.

Discussion on revaccination included:
Dr. Turner, of the ACHA, raised the issue of vaccinated health care workers who have a positive titer but lack the required documentation of the complete series. Some are now required to have another complete series. Dr. Mast reported that there are no data to advise this question. The recommendation calls for documentation of three doses. There is also permissive statement that some medical or nursing schools will accept a positive antibody titer as well, but there are concerns about that. Nods around the table indicated general agreement that re-doing the whole series seemed unjustified. Perhaps a titer >10 might be acceptable, since booster studies indicate that a positive titer is protective. This should be clarified in the statement. Also demanding attention is dialysis patients' need for vaccination, as outbreaks in dialysis units are mostly among the unvaccinated.

High risk populations; definition; determination/justification of age cutoff.

- The big difference in the data between young adult men and women aged 20-35 years lies in the influence of MSM's higher risk. In older age groups, there has been some plateauing among men and a slight increase among women. There is some concern that a vaccine-resistant escape mutant might arise, since hepatitis B variants can replicate in the presence of surface antigen. Ongoing surveillance is needed for such mutations.
- Dr. Paul Offit noted the little impact on prevalence until the universal children's recommendation was released. He hoped for a routine 19-25 year-old immunization recommendation to achieve the second wave of impact, although that also will come with the ageing of the K-12 cohort vaccinated under school entry laws. Modeling of the impact of school entry requirements was outlined. The 40 states now with that requirement have achieved high coverage. The basic strategy is to eliminate transmission through those highly immune, and the basic question is how to accelerate that. Dr. Offit doubted that a focus on those at high risk now would work, when it did not work before.
- Dr. Poland agreed, noting that all other vaccines than hepatitis A and meningococcal vaccines (used for travel) have abandoned the risk approach. With infants and adolescents addressed, the continued increase in the 25-39 year-old age group indicates that the strategy is not working. With the lack of predictability of when a person will

become at high risk, and the need for them to identify themselves as such, it seemed that a big reservoir remains in the large adult group that is primary in transmitting the disease. ACIP should recommend universal hepatitis B vaccination for all persons aged <50 years.

- There are potential transmission risks from tattooing and acupuncture parlors, but they are uncommon.
- Dr. Schaffner, long a champion of adult immunization, strongly advocated advancing the elimination strategy in the U.S. Even a perfectly executed, targeted group strategy would only control, not eliminate, the disease. Many people acquiring hepatitis B never visit those venues and have begun at-risk behavior before coming. He compared that strategy to getting a shot only after stepping on a nail, and noted a missing mention of any funding increase to the venues catering to those at high risk. But a strong recommendation for universal immunization will prompt the private sector to respond. While success will not occur instantaneously, nothing at all will happen without a recommendation.
- Dr. Poland asked, why wait yet another generation to put all the tools in place to eliminate hepatitis B? Childhood immunization did not occur quickly either.
- Dr. Temte agreed with Dr. Gall that physicians have little time to identify those at risk of hepatitis B, and their patients may not reveal that due to the social stigma. An AAFP poll indicated ~7 minutes per year available to them to promote prevention services. Those minutes are taken up by cervical and breast cancer screening, and there are ~400 other conditions that could be screened. (Dr. Mast explained that the long list was of targeted interventions. The risk factors prompting vaccination as a standard of care are basically for only three groups: sexually active persons, MSM, and IDUs.)
- Prioritization is the issue; 19 states still do not immunize their children with PCV.
- The vaccine pilot projects proved that the targeted recommendation is feasible; the only unknown is resources to do so. Even a universal recommendation will miss a high percentage of uninsured adults who also are disproportionately in high risk groups. A strong public/private partnership is required and a recommendation will increase demand and establish the market. But the industry must be confident of the public sector's ability to target the high risk groups, reach young people, and find a way to support vaccination of uninsured adults.
- Dr. Katz asked if the intent was to control hepatitis B, eliminate it, or eradicate it? He noted that at least 3 vaccines will be recommended for adolescents: a pertussis booster, meningococcal vaccine, and hepatitis B for those who have not received it, not to mention HPV. Targeting adolescents aged 15-18 and the children covered by VFC and CHIP seemed more realistic to him in terms of funding, logistics, and the needed political and economic commitment. Dr. Turner offered ACHA's help to analyze what percentage of the 35,000 respondents to their annual student survey last year, who reported having received hepatitis B vaccine, was attributable to state laws.
- Dr. Wexler urged a recommendation to give the vaccine to those aged 19-49, as the good public health approach. They still can refuse it. Eliminating hepatitis B in the U.S. cannot be done in a fractional approach. Dr. Richard Judelson, of Erie County, NY, agreed that a universal recommendation for the 19-50 age group would be necessary for it to become a standard of care. The finances will follow, as will the private sector when they know it is in their own interest. And, as a pediatrician, he did not think that this would bleed resources from the VFC.
- Dr. Lieu called for immunization of all adults aged 18-25 years, an approach supported from the societal perspective.

- Dr. Offit found the cohort age-out approach unacceptable, urging instead that the best medical decision possible be made, and then the resources fought for.
- Dr. Scalettar pointed out the private sector's similar struggle with prioritizations and cutbacks on coverage, alongside the many already-uninsured Americans. He warned that ACIP's recommendation of many vaccines in short order would be self-defeating.
- The risk-based approach has been in place since 2002 and 2003, but the funding remains absent for these activities. Dr. Wexler suggested raising public awareness of the problem rather than focusing on congressional willingness to fund.

Revisions to the General Recommendations on Vaccine Storage and Handling
Presenters: Dr. Andrew Kroger, NIP; Dr. Ed Marcuse, General Recommendations Workgroup Chair

Overview: Vaccine administration revisions developed by the ACIP General Recommendations Workgroup, last revised in 2002.

The ACIP's General Recommendations on Immunization are revised every five years. The General Recommendations Workgroup discusses different sections in monthly teleconferences, and invited input from consultants or subject matter experts as needed. The Workgroup's draft revisions are then presented to the ACIP for its agreement, culminating in the presentation of the entire, revised document before final submission to CDC for publication in the *MMWR* (hopefully in October 2005).

The sections addressed for revision were: timing and spacing of immunobiologics, contraindications, and precautions; special situations and a subsection, altered immunocompetence; vaccination records; vaccine adverse event reporting; vaccination programs; and vaccine information sources. The incomplete sections on vaccine storage and handling were not presented. The draft revision of the vaccine administration section was presented.

The revisions to the vaccine administration section were:
1. Hygiene issues, to emphasize alcohol-based, waterless antiseptic hand rubs in addition to soap and water.
2. Needle length, to emphasize less redness and fewer local reactions when longer needles are used and to clarify that aspiration prior to injection of vaccines and toxoids is not necessary (and why).
3. A stated preference for anterolateral injection in infants and that the buttock should not be used due to concern about (documented) injury to the sciatic nerve. It is also stated that the vaccine is equally immunogenic in infants whether injected into the thigh or buttock.
4. Technique, to highlight this as the most important parameter to ensure efficient intramuscular vaccine delivery. Bunched subcutaneous and muscle tissue requires a 1-inch needle to access the muscle
5. Screening is encouraged to prevent adverse reactions; the use of standardized screening questionnaires was urged.

Discussion included:
- A suggestion to change "complications" to "contraindications."

- The anterolateral injection for infants was specified because the old document cited improved immunogenicity with buttock injection. That is not true for infants. The sections for adults, older children and adolescents, allow buttock injection. However, Dr. Neal Halsey expressed his disagreement, since there is no evidence of comparable immunogenicity whether injected in thigh or buttock. Allowing injection in the buttocks invites that for all products, and should not be done because of the risk to the sciatic nerve. He strongly favored continued prohibition of buttock injection. Dr. Marcuse agreed that the absence of evidence does not equate to absent risk, with toxoids and vaccines, but the literature has no reports of such injuries. Additionally, two methodologically strong Australian studies found buttock injection acceptable, which the Workgroup balanced against the theoretical injury risk.
- Dr. Lynn Bahta, of the Maryland health department, feared that introducing buttocks as an injection site would confuse the local level and could entail some risk, since injections are not always given by medical professionals. She also noted that, while aspiration is not a science-based practice, it is in every nursing textbook, and advising against it is close to sacrilege. She preferred to state that it is not "necessary," since not "recommended" would put nurses at a disadvantage. Ms. Stinchfield approved of the wording; a statement that it is not required allows the nurse to stop if desired, or not.
- Dr. Salisbury questioned whether the statement that screening is key to preventing the majority of serious reactions was supported by evidence. He thought the wording to be too imprecise, to raise unnecessary issues, and do little to prevent most serious adverse events. He also disagreed with all the points in paragraph 3 (lines 10-20) except for a child with cancer. Dr. Marcuse agreed that the paragraph needs review for precision and welcomed additional input.

The Workgroup will discuss these points in its monthly calls and return in June with a more extensive document (this section, modified, and 3-4 more sections), until the final document is presented in October.

ROTAVIRUS

Rotavirus Gastroenteritis: Disease Burden, New Vaccine Development
Presenter: Dr. John Traenor, Workgroup Chair

Overview: Update on disease burden and vaccine development

The Rotavirus Workgroup resumed activity in anticipation of one (and possibly more) new vaccines for rotavirus gastroenteritis. Since an ACIP recommendation and vote may be required in about a year, the Workgroup's time line is aggressive. Draft recommendations are hoped to be ready by the June meeting for discussion.

Rotavirus surveillance in the U.S.
Presenter: Dr. Umesh Parashar, NCID

Overview: Summary of two disease burden estimation techniques; CDC analysis of national data for mortality, hospitalizations, and ambulatory care visits to estimate what is attributable to diarrhea, and from that, the proportion attributable to rotavirus.

Rotavirus infection is not routinely diagnosed in children with diarrhea and testing is not routine. Since rotavirus incidence is seasonal in the U.S., CDC used epidemiologic proxies of age and seasonal disease pattern to analyze the ICD9 and -10 codes for diarrhea illness.

National data sources included data collected weekly from 19 laboratories and the mortality, hospitalization and ambulatory care data collected by the NCHS. Peak rotavirus activity occurs in winter; it always begins first in the southwest (November, December) and begins last in the northeast (March or April).

The analyses done were presented, as follow:

1. To assess rotavirus-related morbidity, National Hospitalization Discharge System data were analyzed for four periods from 1979 to 2001, using ICD-9 codes to identify hospitalizations for diarrhea. Graphically displayed data showed the distinct winter-season peak for diarrhea hospitalizations among children aged <5 years and those aged seven months to one year (the age of greatest risk for severe rotavirus disease). An extension of the analysis to include data from 1993 to 2001 remained consistent with those peaks and diarrhea hospitalizations rates.
2. Data from the Healthcare Cost and Utilization Project (HCUP, a more robust data set) presented the same pattern of geographic rotavirus progression from the southwest to northeast U.S. from 1993 to 2001, as well as rotavirus' big contribution to diarrhea hospitalizations. It accounts for an estimated one-third of the annual 160-180,000 diarrhea hospitalizations, which of themselves constitute 12% of all pediatric hospitalizations.
3. Data from Staat et al (*PIDJ* 2002;21:221-7) indicated that, of ~760 children seen for diarrhea at three study sites, 31% overall tested positive for rotavirus. For children who presented with diarrhea or vomiting, 31% and 42%, respectively, had laboratory-confirmed rotavirus disease. That offers additional evidence of rotavirus' contribution to diarrhea hospitalizations.
4. Another analysis again used ICD-9 codes to estimate rotavirus' contribution to pediatric mortality. Data from 1968 to 1991 reflected a blunting of seasonal (winter) mortality in the 1980s and early 1990s, from ~1100/year in 1968 to ~ 300/year in 1991. However, trend analysis of more recent data was challenged by coding changes when ICD-10 was initiated. The relatively stable data to 1999 then dropped dramatically (30%) for some codes that were assigned to different (in some cases, unknown) categories. But analysis of the last 6 years of HCUP data indicate a fairly stable mortality (80-100 per 100,000 hospitalizations). More intensive mortality studies done in selected states identified underlying conditions that also could have been associated with death, along with rotavirus.
5. Surveillance of emergency department visits from March 1999 to February 2000 indicated that 81% of the 1152 children seen for diarrhea and vomiting had rotavirus, as measured in bulk stool samples. A lower rate in rectal swab samples could be due to inadequate stool volume in those specimens. (Additional analyses are being done.) But, using ED visit data and applying the proportions shown in this active surveillance, rotavirus was implicated in ~ 200,000 ED visits and ~400,000 outpatient visits.
6. Data on illness episodes came from two large juvenile studies done in the early 1980s. Both indicated that ~70% of children had a symptomatic rotavirus episode by age 5, which translates to ~2.7 million annual rotavirus episodes (70% of the ~4 million annual birth cohort).

These estimates of disease burden were reasonably comparable to the original calculations presented to the ACIP in 1998, indicating that the disease burden has not changed appreciably.

Data were reviewed to determine whether the strain prevalence has paralleled the vaccine serotypes. Fecal samples collected over 6 years from 10-2 labs across the nation showed G1-P8 as the most prevalent (80%) strain globally. The balance was divided between the G2, G3, G4, and G9 strains. All but the last strain are in the reassortant vaccine.

In *discussion,* it was clarified that the ED and outpatient department visits were exclusive of each other. The OPD data included both physician visits and hospital outpatient visits.

Merck Research Laboratories, PRV Safety/Efficacy Trial
Presenter: Penny M. Heaton, MD, Merck Research Laboratories

Overview: Characteristics of the investigational pentavalent human-bovine reassortant rotavirus vaccine (PRV); primary efficacy and safety results of the large-scale Rotavirus Efficacy and Safety Trial (REST).

The characteristics of the investigational new drug, PRV, were outlined. An oral vaccine suspended in a liquid buffer/stabilizer, it has a 24-month shelf life when stored at 1º-8ºC, and does not require pre-dose feeding or antacid to neutralize stomach acid. It is provided fully constituted in a plastic dosing tube with a twist-off cap and it can be administered directly to infants. PRV is administered over 3 doses given at 1- to 2-month intervals, beginning at age 6-12 weeks. Its safety and efficacy are shown for 2-, 3-, 4-month and 2-, 4-, 6-month schedules. PRV is a pentavalent vaccine containing 5 human-bovine reassortants. Of the G serotypes for humans, it includes G1, G2, G3, G4, and the bovine G6. It also holds eight of the human P1 and seven of the bovine P7 serotypes. A picture slide presented the rotavirus and its reassortants.

An overview of PRV's development program was shared on time chart spanning from 1993-2005. Following the 1993 proof of concept study, the formulation was developed in 1999 for clinical trials of buffers and dose/reassortant composition. The manufacturing process was developed into 2001, which was also when the REST study began. REST confirmed the dosage and studied lot consistency. From 1998 into 2002, manufacturing facility design, construction, and validation was also done.

The REST study design was outlined. Its primary efficacy hypothesis was to prove the oral formulation of PRV (RotaTeq™) as efficacious against rotavirus disease caused by serotypes G1, G2, G3, and G4, occurring ≤14 days after dose 3. The lower bound of the 95% confidence interval for vaccine efficacy was to be >35%.

Clinical and laboratory case definitions for rotavirus gastroenteritis were developed and the primary analysis included only cases that occurred at least 14 days after the third dose. The primary safety hypothesis was that oral RotaTeq™ will not increase the risk of intussusception relative to placebo within 42 days after any dose. Two criteria were necessary to satisfy the primary safety hypothesis: 1) the vaccine/placebo case ratio during the study was not to reach predefined unsafe boundaries monitored by the DSMB, that is, -1 to 42 days following any dose

or -1 to 7 days following any dose. And, 2) at the end of the study, the upper bound of the 95% CI estimate of the relative risk of intussusception must be ≤10.

The DSMB included a pediatric radiologist, emergency department specialist, and surgeon. The subjects were followed for intussusception for a minimum of 42 days after their last dose, and up to one year after the first dose.

Intussusception.. The worldwide placement of the 70,301 subjects in the REST study was mapped on their 11 countries. All the subjects were evaluated for all serious adverse events, including intussusception. A clinical efficacy sub-study also vaccinated 5673 subjects. A graph charted the 27 cases (12 vaccine, 15 placebo group) observed through one year after dose 1. No case clusters for vaccine only were observed; one cluster of five vaccine- and four placebo cases occurred between 36 and 49 days. Within the 42-day period after any dose, 11 intussusception cases occurred overall, 6 in the vaccine group and 5 in the placebo group. No vaccine cases occurred after dose 1, and the distribution of cases after doses 2 and 3 was similar to that expected for background intussusception incidence. The primary safety hypothesis was satisfied, with an RR of 1.6 (range 0.4-6.4) for the 42-day period after a dose. In the 14-day period after a dose, one vaccine and one placebo case of intussusception were recorded.

VE. VE against the rotavirus serotypes (G1, G2, G3, and G4) was assessed by disease severity (symptom intensity and duration) in the first season after vaccination. VE of 74% was seen against any rotavirus disease caused by G1, 2, 3 or 4, and VE against severe disease was 98% (range 88.3%-100%). In the Phase 2 and 3 studies, VE against any rotavirus disease was 75% and 74% against severe disease, and 73% and 74%, respectively, in the Phase 3 studies. VE against severe disease was 100% in Phase 2 and one of the two Phase 3 studies. One breakthrough case occurred in the large-scale efficacy and safety trial.

Late-breaking data. The health care contacts of trial participants were followed prospectively for rotavirus gastroenteritis. A 94.4% reduction was recorded in health care contacts, including hospitalizations and ED visits for rotavirus gastroenteritis, compared to the placebo recipients.

Conclusions. RotaTeq™ is efficacious against rotavirus gastroenteritis and will improve health outcomes with respect to hospitalizations and ED visits for rotavirus gastroenteritis. The vaccine is generally well tolerated with respect to intussusception.

Discussion included report of improved efficacy against all disease, when combined with season two, up to 71%; for season 2 alone, it was 65%. There are no data available yet on the vaccine's efficacy against severe disease in season 2.

HUMAN PAPPILOMA VIRUS

HPV Workgroup Update

Presenter: Dr. Lauri Markowitz, NCHSTP

Overview: Activity of the Human Pappiloma Virus (HPV) Workgroup since February 2004 (its first meeting): Overview of HPV, data review, vaccine development, cervical cancer screening, vaccine cost effectiveness data. Future meetings will address policy issues and recommendations.

There are >100 types of HPV, which is a small, non-enveloped, species-specific DNA virus with a tropism for squamous epithelium. They cause benign and malignant proliferations in several species. Some cause common skin warts of the hand and the feet; others infect nonmucosal or cutaneous sites; and ~40 types cause mucosal or genital infection. The latter is associated with cervical cancer. Types 16, 18, 31, and 45 are high risk, able to cause low-grade cervical cell abnormalities that are genital cancer precursors. Types 6 and 11 are low-risk., mainly associated with genital warts and laryngeal papillomas.

HPV is sexually transmitted, often soon after sexual debut, and is usually transient and asymptomatic. But persistent infection with the high-risk HPV types is the most important risk factor for cervical cancer, and some types (e.g., HPV 16) is persistent. A study of college students detected HPV infection within 24 months after first intercourse among 39% of the women, and among >50% by 48 months. An estimated 20 million U.S. citizens are currently infected with HPV, including about 15% of all those aged 15 to 49 years. Prevalence is highest among those aged <25 years and decreases with advancing age. An estimated 6.2 million new infections occur each year, and an estimated 50%-80% of sexually active men and women will have ≥1 genital HPV type at some point.

Cervical cancer is the most serious sequela. HPV's role in its pathogenesis is established and there are plausible HPV mechanisms leading to its oncogenesis. Luckily, the latter is rare and, although high-risk HPV types may be necessary for the development of cervical cancer, infection alone is not sufficient. There is a loose association between HPV and nongenital cancers and some association with anogenital cancers. A slide of HPV's natural history was shared. Some 70% of infections clear within a year, some persist and develop into cervical intraepithelial neoplasia, CIN 1 or CIN 2/3. Those endpoints are being used in the vaccine clinical trials. HPV types 16 and 18 comprise ~70% of cervical cancer worldwide and account for 46%-63% of all squamous cell carcinomas worldwide. HPV 18 is the second most common.

Annually, an estimated 400,000-500,000 cervical cancer cases occur and ~250,000 die from it. It is the second leading cancer-related killer of women worldwide, 80% of these in developing countries without cervical cancer screening programs. The implementation of Pap smear screening has lowered cervical cancer incidence ~75%, but 2004 estimates indicated >10,000 cases of cervical cancer and about 3900 related deaths. There is also an impact from the ~2.8 million abnormal Pap smear tests annually, all requiring evaluation and treatment, and the estimated 500,000 to 1 million people who develop genital warts annually.

GSK HPV Vaccine Development
Presenter: Dr. Gary Dubin, Vice President, GlaxoSmithKline

Overview: Description of the GSK candidate HPV 16/18 vaccine; target vaccine profile; development strategy; overview of completed Phase I/II trials and ongoing Phase III trials.

GSK candidate HPV Vaccine The intent of the GSK HPV vaccine is to accomplish the one task the Pap smear cannot: prevent HPV infection. Specifically, the vaccine addresses HPV-16 and -18 virus-like particles (VLP). Formed spontaneously through self-assembly when the L1 protein, the major capsid protein of HPV, is expressed in a tissue-culture system, HPV VPLs cause ~70% of cervical cancers globally. The vaccine is formulated with adjuvant system

number 4 AS04 (aluminum salts and monophosphoryl lipid A[MPL]). The Phase 2 trial demonstrated that this improved the magnitude and duration of antibody responses. A schematic was shared of HPV progression from initial infection to carcinoma, over a period of many years.

Also shared was the nomenclature important to HPV and the trials' end points: precancers, cervical intraepithelial neoplasia (CIN, defined in grades 1 through 3); squamous epithelial lesions (SIL -- tested by the Pap), either low-grade (LSIL) or high-grade (HSIL).

Progression to Cervical Cancer: Persistent infection with an oncogenic HPV leads from dysplasia to carcinoma. HPV-16 and -19 cause ~70% of the world's cervical cancers, as well as about half of the HSIL and ~25% of the LSIL. The balance is caused by a heterogeneous mix of oncogenic and low-grade HPV types.

Vaccine Target Profile. The vaccine targets females from ten years of age upwards to prevent HPV-16 and -18 associated outcomes (persistent infection, cytological abnormalities, CIN), by ensuring high coverage levels in women. Modeling studies suggest this as the more effective course than vaccination of males to increase herd immunity, and more cost effective than vaccinating both sexes.

Phase I/II (safety/immunogenicity) studies were summarized on a chart. A more recent (HPV-001) study was the proof of concept for A04 vaccine. In Phase 2, the highest titers were charted after the third vaccine dose. But titers rose at each point of the 0, 1, 6-month schedule, a trend that persisted through a 3-year follow-up. Additional data comparing the immunogenicity of ASO4 versus alum formulations are in development.

HPV-001 ASO4 efficacy trial. This double-blind, randomized, controlled trial was done in North America and Brazil among 1100 women aged 15-25 years, who had ≤6 six lifetime sexual partners, were seronegative for HPV-16 and -18 and were at high risk of oncogenic HPV DNA, although negative at baseline. They were randomized to vaccine or placebo (aluminum salts) groups and followed for at least 18 months (some women were followed for ≤27 months). The end points assessed were HPV-16 and -18 incident infection over at least six months; the vaccine's ability to prevent abnormal cytologies associated with HPV-16 or -18; CIN lesions associated with those two types; vaccine immunogenicity and safety. Cervical Pap smear samples were PCR-tested for HPV DNA, as were the women's self-collected cervical vaginal samples at three-month intervals.

Safety was assessed through reported symptoms. Adverse events were about equal between the vaccine and placebo groups. There were no vaccine-related, serious adverse events; only slightly more injection site symptoms in the vaccine group. ELISA tests showed high immunogenicity in this study. Almost all subjects seroconverted to both HPV-16 and -18 within a month after dose 3. They also had high GMTs, as compared to the levels of individuals with natural HPV-16 or -18 infection. One month after injection, the antibody titers were 80-100 times higher than those with natural infection, and remained 11-16-fold higher.

VE against persistent infection. A table of data compared the according-to-protocol (ATP) cohort, which received three doses, and the intent-to-treat (ITT) cohort, which received at least one dose, but perhaps not all three. VE was high in the ATP cohort, which was marked by the absence of persistent infections still present in the placebo group. The VE point estimate was

100% in the protocol cohort and 8s7.5% in the ITT, wherein VE for each of the individual types, 16 and 18, was statistically significant.

VE was examined for LSIL and HSIL lesions, but also for atypical squamous cells of undetermined significance (ASCUS). If associated with an oncogenic HPV, a referral for colposcopy is done. Both cohorts had a ~93% VE in preventing cytologic abnormalities. A summary of the data was published in *The Lancet* in November 2004.

Vaccine impact on biopsy-confirmed HP-16 or -18 cervical lesions was also assessed. No such lesions were found in the vaccine group, while the placebo group had 3 low-grade CIN-1 lesions and 3 that were CIN-2, all associated with persistent HPV-16 infection.

Phase III Efficacy Studies. In response to the preceding, two large Phase 3 efficacy studies began in 2004. One, by GSK, follows 18,000 women aged 15-25 years for 48 months; another, by NCI, will follow ~ 12,000 subjects aged 18-25 years for the next few months. Both trials' primary end point is prevention of CIN 2, and some end points associated with HPV-16 or -18.

Summary and Conclusion. GSK's vaccine, which focuses on the prevention of cervical cancer in women, was found to induce high titer antibody responses and to protect against HPV-16 and -18 associated end points. Follow-up of the Phase 2 studies is ongoing; that for the pilot efficacy study will complete four years of follow-up later this year. The vaccine was generally safe and well tolerated in the Phase 1 and 2 studies. Phase 3 has enrolled >16,000 women worldwide aged from 15-25 years. Other vaccine evaluation studies being done involve in preteens, adolescent girls and women aged >25.

Discussion included:

- *What percentage of ASCUS is related to vaccine types?* There is some evidence that the vaccine reduces overall ASCUS rates, independent of the HPV type. LSIL would not be referred to colposcopy, so clinically, the major impact would be prevented ASCUS associated with oncogenic types. HPV-16 and -18's significance reduces with progression from cancer to low-grade lesions (~25% for LSIL and ASCUS.
- Phase II follow-up will be done through 2007 and Phase III subjects will be followed for 48 months. Planning is underway for long-term follow-up, at least for selected subsets. Also being discussed are independent Phase 4 follow-up studies.

Merck; Gardasil HPV Vaccine

Presenter: Dr. Eliav Barr, Merck Research Laboratories

Overview: Presentation of Gardasil™, Merck's quadrivalent HPV vaccine (G-6, G-11, G-16, G-18) manufactured in yeast with aluminum adjuvant. Dosing: 0.5 mL administered at zero, two, six.

This vaccine also addresses G-6 and G-11 HPV strains, which account for 90% of genital warts. Affecting men and women equally, they are painful, hard to treat, psychologically damaging, and costly. They cause CIN-1 lesions that look precancerous, so similar are they to those caused by HPV-16 and -18. Eliminating them would be very cost beneficial to the screening programs. Preventing them is also a likely incentive for the hard-to-reach adolescent/young adult population to seek vaccination and to reduce the overall risk of cervical cancer, CIN, genital

warts and other vulvovaginal HPV-related lesions, and intraepithelial neoplasia (IN), whether anal (AIN), vulval (VIN) or vaginal (VAIN).

The target population is aged 18 to 45, both genders. The endpoints are the clearance of CIN 1, 2, and 3 caused by HPV, and the moderate high-grade dysplasia and carcinoma targeted by cervical cancer screening programs. Phase 2 and 3 trials are ongoing, with follow-up of four years. Phase 2 will evaluate long-term efficacy and a booster dose in that interim time period. The centralized cervical cancer screening programs of the Scandinavian arms of the trials will follow their study populations for 10-15 years and potentially over their lifetime. That will be the sentinel cohort used to evaluate long-term duration of efficacy. Another study is evaluating VE in mid-adult women and men. GSK expects to apply for FDA licensure in the latter half of 2005.

Protocal 005 trial results (Koutsky et al, *NEJM* 2002; 347,1645-51). The HPV-16 vaccine proof-of-principal study involved 2391 non-high risk college women aged 16-23 years. Persistent HPV infection was the primary end point as a stronger predictor for development of cervical cancer; other end points were HPV-16 related CIN. Women who were naïve at baseline were evaluated to assess the vaccine's prophylactic power, and 100% VE was demonstrated against persistent disease and 94% overall at 3.5 years into follow-up. While 12 cases of HPV-16 related CIN 2/3 occurred in the placebo group, none did among the vaccinees. However, both groups reported single-time detections traced to a likely artifact of PCR-transient infections. When included in the analysis anyway, VE was 67%. In addition, when women with stable, high naturally-acquired anti-HPV levels were compared with vaccinees, the latter's antibody responses plauteaued at a level ten-fold higher, demonstrating persistent protection.

Protocol 007. The quadrivalent vaccine was tested in a dose-ranging and efficacy study. Three doses were evaluated against placebo, after which one dose was administered and the women were followed for efficacy against each of the four HPV types, for the endpoints of CIN, genital warts, and a single positive at the last recorded visit.

VE Results. The anti-HPV responses to HPV-16 were comparable to those of the monovalent vaccine. An overall VE of 90% against all four types was found, and a VE of 96% against persistent infection. Three of 4 cases in the vaccine group were due to a single positive at the last recorded visit on record, and one persistent HPV-18 infection was found. For the first time, efficacy was shown against genital warts as well as cervical cancer. The placebo group had 6 cases of HPV-6, -11, -16, and -18 related cervical or vaginal or vulvar disease, 3 genital wart cases and 3 CIN cases. All of them were in the placebo group.

Protocol 016; evaluation of adolescents' vaccine use. The target populations for this vaccine are adolescent boys and girls to age 15, the median age of sexual debut. One Phase 3 study compared immune response in boys and girls to those of young adult women. The younger individuals showed a much higher immune response than the 16-23 year-olds, the group with previously demonstrated efficacy. These high levels are likely to persist.

The Phase 3 program for young women involves ~18,000 young women worldwide, aged 16-23 years (26 in Asia). It focuses on efficacy measurement for CIN 2/3, CIN in general, and genital warts. Results are pending, as are those for mid-adult women (age ≥24). Since immune responses to natural HPV infections may wane and reacquisition may occur among sexually

active women, GSK is studying VE in women age 24-45 years, hoping to see the same benefit that emerged in the younger group.

Men have a higher rate of genital warts, transmit HPV to women, and develop anal cancer. MSM's anal cancer rates have risen. With the PACTG Group, GSK is examining the vaccine's interaction with HPV and HIV, which greatly exacerbate HPV infection. PACTG will evaluate the safety and the immunogenicity in a well-care cohort of virgin HIV-infected pre-teens (n=120).

Discussion included:

- Little is known about the role of CMI in concert with antibody and HPV infections. While CMI is important in clearing infections once they have developed, antibody is the best method to prevent infection. GSK is doing some early pilot work on CMI.
- *Is there any evidence that the older women who lost their antibody response may have actually not cleared the infection and retained some virus?* Reacquisition is likely, but reactivation of a small group of cells cannot be ruled out. In the placebo groups, once the infection was cleared, it was gone completely.

MENINGOCOCCUS

Meningococcal Workgroup Update

Presenter: Dr. Reginald Finger, Chair

Overview: Activities of the Meningococcal Workgroup in a national, multisector campaign to educate about meningococcus, formulate the policy options for prevention of meningococcal disease based on its epidemiology relative to age and serogroup, as well as safety, immunogenicity, and expected cost effectiveness of the new vaccine; development of draft recommendations for meningococcal chemoprophylaxis.

The Workgroup researched likely sites at which to reach adolescent populations, the yearly visit for some reason (not necessarily preventive) to a healthcare provider was so indicated by 7 data sets, for the majority of those aged 11-18 years. Three data sources were used to estimate age-specific incidence of meningococcus: 1) CDC's Active Bacterial Core (ABC) surveillance system, the National Electronic Disease Surveillance System (NEDSS), and the Children's Hospital of Pittsburgh (CHOP). They also assessed the likely availability of the new MCV4 vaccine to balance promotion of demand with likely production.

The topic areas and discussions of the Workgroup's multiple conference calls were summarized:

- There was consensus that MCV4's duration of protection conveys enough long-term immunity to warrant a preferential recommendation for its use over the meningococcal polysaccharide vaccine (MPSV) Menomune®.
- To balance use of the 11- to 12-year-old immunization platform, versus effecting a quicker uptake among older adolescents approaching the peak incidence period for meningococcus, the Workgroup decided to allow flexibility in the vaccination's timing.
- The importance of balancing the allocation of limited resources with the impending release of several new vaccines was emphasized.

Proposed ACIP Recommendations for Meningococcal Disease

Presenter: Dr. Nancy Rosenstein, NCID

Overview: Use of MCV4/Menactra™ (Sanofi Pasteur), and that of MPSV4: routine and permissive vaccination recommendations for specific groups; choice of MCV4 versus MPSV4; revaccination. Menactra™ was licensed based on its data showing reactogenicity, immunogenicity, and noninferiority to the polysaccharide vaccines. New efficacy data includes duration of protection, herd immunity, and economic analysis.

MCV4 reactogenicity.

- *Local reactions* (induration, swelling, redness) were seen more often from MCV4 than MPSV4, perhaps due to the former's intramuscular injection site and the conjugate's use of tetanus as the carrier protein. However, local reactions to MCV4 were less compared with Td vaccine administered to adolescents, and typhoid vaccine administered to adults. Another table charted similar rates of s*ystemic reactions* (fever, chills, malaise, rash, seizures, headache, fatigue, anorexia, diarrhea, vomiting, arthralgia*)* between the two vaccines.
- *Immunogenicity* was charted for serogroups A, C, Y, and W-135, and showed similar results. Both vaccines provided a four-fold titer to the 11-18 year-old recipients and across all four serogroups.
- *Duration of protection.* It has been shown that MPSV is protective for at least 3-5 years in adults, and that conjugate vaccines in general induce memory and higher antibody levels, which should provide longer protection. U.K. studies among adults and adolescents showed a VE of 90% at 3 years. Based on that, the Workgroup estimated that MCV4 would be protective for at least 8 years, taking the 11 year-old vaccinee through to the college years.
- *Herd immunity for serogroup C* as a result of this vaccine was determined in the U.K. The data suggest that MCV4 will reduce transmission as well.

Cost effectiveness of MCV within the routine vaccination schedule was charted. The ACIP had previously seen modeled data on policy choices relative to vaccinating infants, toddlers, and adolescents; reanalysis had raised the cost even more. However, comparison between the groups was valid, with the new adolescent vaccine and impending releases of vaccines for toddlers and infants. The infant vaccine would prevent the lowest number of mortalities and at the most cost; cases prevented by a toddler vaccine would be similar in number but have a cost similar to that of the adolescent strategy. The currently-presented adolescent strategy would prevent fewer cases and deaths, but is the least expensive program.

An analysis was charted proceeding from the group with the highest carriage rates, 11- to 17-year-olds, to assess vaccine impact on that group and its ability to promote herd immunity. A 10-year period was graphed, proceeding from the present no-vaccine baseline to immunization of all 11-17 year-olds. Even without inducing herd immunity, 10% of cases per year would be prevented. With herd immunity, as seen in the U.K., incidence would drop 32%, assuming a 93% VE and 70% coverage among those aged 11-17 years.

Cost. Lieu et al (*JAMA*, 2000) used the PCV-7 introduction as the basis from which to analyze the cost per life-year of: 1) catch-up and routine vaccination (with herd immunity),;2) routine vaccination of 11 year-olds (without herd immunity); and 3) routine vaccination in highly endemic areas. At $60/dose, the first option cost $135,000 per life year saved and the second,

$117,000. In the third, endemic case, the cost dropped to $19,000 per LYS. Compared to baseline, a table of dollars per case prevented among infants, toddlers, and adolescents estimated, respectively, $1.9 million, $629,000, and $633,000 saved per case prevented.

The Workgroup's proposed recommendation was as follows:

- Vaccination was recommended for preadolescent visit and high school entry, college freshmen living in dormitories, and other groups at high risk.
- Catch-up campaigns were not recommended
- Permissive recommendation for vaccination of other so desiring. Among those aged 11-55 years, MCV4 is preferred, but MPSV4 also is acceptable.

How to target those in the peak age of risk, 17-18 years, was debated by the Workgroup. Charted data graphically demonstrated the peak of meningococcal (A/C/Y/W135) incidence among 11-30 year-olds in the U.S., as shown by the ABC and NEDSS surveillance from 1991-2002. The related incentives to the adolescent recommendations included the opportunity to support the pre-adolescent visit platform and the wish to effect a rapid impact on disease incidence. However, the vaccine supply in 2005 and 2006 will likely be limited.

An NIP survey mailed by the University of Michigan to 587 practicing family practitioners and pediatricians included a meningococcal fact sheet. When asked to choose between different strategies, they preferred the 11- to 12-year-old preadolescent visit. However, they agreed that the scientific evidence and burden of disease supported a focus on the 14-15- and 17-18 year-old groups at highest disease risk. Their opinion of a best-fit model also equated between the 11-12- and 14-15 year-old strategies.

Based on the data and their discussions about adolescents, the Workgroup recommended:

- Routine vaccination with MCV4 of young adolescents at the pre-adolescent visit (11-12 year-olds)
- Routine vaccination with MCV4 of adolescents at high school entry (15 years old), to obtain the most rapid impact on meningococcal disease incidence.
- Vaccination of all other adolescents who wish to decrease their risk of meningococcal disease.

The ***recommendation for routine vaccination of adolescents*** read as follows:
"Introducing a recommendation for MCV4 vaccination in young adolescents (11-12 years old) may strengthen the role of the pre-adolescent visit and have a positive effect on vaccine coverage in adolescence. ACIP recommends that young adolescents see a health care provider at age 11-12 for a routine preventive visit, at which time immunization status and other preventive services should be assessed (*102*). Within 3 years, the goal is routine vaccination with MCV4 of all adolescents beginning at 11 years of age. ACIP recognizes that vaccine supply may be an issue in the first few years after licensure of MCV4."

Recommendation for college students. A table of data from Bruce et al (*JAMA* 2001; 286:688-93) was shared. This showed college students in general as not at risk for meningococcal disease, but specific subgroups were at risk, such as freshmen living dorms (elevated risk of ~5/100,000). Of a population of ~600,000, there were 30 reported cases, 66% of which were potentially vaccine preventable. The ACIP's recommendation to educate these freshmen about the risk, especially those living in dorms, and making vaccine available for them, had not worked

well. The ***current proposal*** simply recommends routine vaccination for college freshmen living in dormitories. Some colleges may target all freshmen, and other students may choose to be vaccinated. Again, MCV4 was preferred, but MPSV4 was termed as acceptable.

Other groups at increased risk were also listed for vaccination, with the same vaccine preference: microbiologists routinely exposed to isolates of *N. meningitides,* travelers to or residents of countries with epidemic *N. meningitides,* military recruits, and complement-deficient and asplenic patients.

Outbreak control language was unchanged from the last recommendation except to prefer MCV4.

Other age groups*:* Routine vaccination was not indicated but can be administered upon demand to those aged 11-55 years who are at low risk. It is not licensed for use among those aged 2-10 years and >55, so routine vaccination was not recommended for those groups.

Revaccination text stated that: 1) "Those previously vaccinated with MPSV4 may be revaccinated after 3-5 years if risk remains increased;" and 2) "ACIP expects that MCV4 will provide longer protection than MPSV4; however, studies will be needed to confirm this. We anticipate that more data will become available within the next 5 years to guide recommendations on revaccination for persons who were previously vaccinated with MCV4."

Discussion included:

- Ms. Stinchfield appreciated having these documents provided in advance for the committee's review, and thanked the families who attended to speak to the ACIP on this topic. She also saw no distinction between dorms, apartments, or fraternity houses, comparing them to military barracks.
- Dr. Michael Decker, of GSK, clarified that the "severe systemic reactions" cited were not severe in the traditional sense; they were comparable to those reported for TD, MedImmune ® and Menactra.™ The difference in local events, as mentioned, was related to intramuscular versus subcutaneous injection.
- Dr. Baker appreciated the compromise for the two groups and expressed AAP's support. She suggested inserting "with MCV4" after "vaccination" on the statement's page 29 text summarizing the recommendations.
- Dr. Marcuse respectfully disagreed with the compromise approach of giving the vaccine only to pre-adolescents and high school students. He would only support that strategy after the disease had been prevented as much as possible in the group most at risk (17-18 year-olds)
- Dr. Middleman expressed SAM's support for the recommendation, which covers a large range of issues. She reminded all that the polysaccharide vaccine will still be available and could be used to carry college students through their highest rates of risk. She advised three things: 1) strengthening the support of the adolescent visit even further by citing its ongoing recommendation by the AAP, AAFP, SAM, etc.; 2) before the footnote (102), strengthen "and assessed" to "and provided" or "and addressed (102);" and 3) clarifying whether the vaccine should be administered in the presence of minor illness, given the relative rarity of adolescent healthcare visits.
- Dr. Judelson spoke on behalf of those in the field. He hoped that the statement would strongly recommend use of MCV4 to prevent disease at the local level, and be clear why

other things that could have been recommended were not. He also hoped for uniformity in supply between the private and public sector programs.

- Data indicate a relatively flat rate of well visits in the 11-15 age group, and that routine visits then fall off to age 20. However, the reported versus written records of visits and vaccination are very variable.
- Mr. Hosbach reported that the MCV4/Menactra™ will be made in the same facility as the polysaccharide Menomune™ vaccine, so supply doubling is not a factor. He expected Menactra™ production to be ~5 million doses in 2005, 6 million in 2006, and 7 million in 2007. He did not know the amount of polysaccharide production expected. There may be >7 million doses in year three if a new production facility is completed. He stated that Sanofi Pasteur would work closely with CDC and its customers to avoid any supply issues.
- If Menactra™ parallels the experience of the hepatitis B vaccine, coverage will rise from ~15% to a high of 55% and then flatten. That seems to make an excess more likely than a shortage. There is only ~1 case per 100,000 population and only 66% of the cases are vaccine-preventable. And, since vaccination rates of high school seniors are historically poor, decreased uptake is likely at age 17. The focus should perhaps be on age 16.
- Dr. Temte reported much deliberation about this in the AAFP, particularly about changing recommendations, based on recent experiences with Td and Prevnar,® and more recently, influenza vaccine. So many changes could well reduce uptake. He appreciated the compromise offered. He expected that family practitioners would "cheat" a little on the timing (for example, giving it to a 13 year-old) to ensure vaccination when a return visit is in doubt. However, he did not expect there to be such a high demand as to affect the supply.
- Dr. Cochi expressed NIP's similar comfort with a two-cohort approach. Dr. Abramson agreed. Aside from the prioritization issue he had raised earlier, given the supply issue, he felt this to be a reasonable starting point. However, he later reiterated the importance of the prioritization issue, having personal knowledge of unvaccinated children who had died of pneumococcal disease.
- However, Dr. Turner noted that Menomune™ was not a good enough vaccine for a firm recommendation for college students years ago, which is probably still true, and that the conjugate decreases carriage.
- Another consideration is that the VFC will not pay to vaccinate 17-18 year-olds.

Public Comment

Ms. Lynn Bozof, Executive Director of the National Meningitis Association, spoke of their work to raise awareness of meningococcal vaccine and the need for vaccination. She thought that a strong recommendation would be a good first step to prevent other families and children to suffer as had hers. Routine vaccination would have prevented the death of her 20 year-old son, as well as the 5 cases recorded nationally in a recent week. She asked the ACIP to pass the broadest recommendation possible for the vaccine's use and offered the NMA's help to ACIP and CDC to broadcast their recommendations.

Mr. Richard Pasick and Mrs. Olga Pasick, of New Jersey, stated that no words can describe what it is like to lose a child. After playing one afternoon, their son developed chills and flu-like symptoms. His doctor rushed him to the hospital the following morning, and he died that afternoon. He had type C meningitis. Had he been immunized, he would have grown up to have his own family and teach his own children to skateboard and bike ride. He is enormously missed

by his family, friends, and the whole community. Everyone deserves protection from this disease.

Ms. Candy Benn, of San Diego, is one of the founders of the NMA. Her daughter contracted meningitis as a college freshman in the dorm. She became ill at home on Christmas break and entered the hospital. Her survival was not certain until 6 months and a kidney transplant had passed. She has now graduated from UCLA and won medals in the Paralympics in Greece. Ms. Benn urged ACIP to make the strongest recommendation possible to protect children.

Dr. Wexler also requested an explanation in the statement of why the ACIP does not recommend routine vaccination of adolescents of other ages. She suggested emphasis that all parents should be educated about meningitis and the vaccine. Dr. Levin confirmed that there is a mechanism in place to conduct the education campaign required.

Committee discussion, continued:

- Clarify that the vaccinated 12 year-old cohort does not need another dose when they become 15.
- Delete the specified non-recommendation of routine vaccination of adolescents of other ages, and just say that "all other adolescents who wish to decrease their risk of meningococcal disease may elect to receive vaccine."

Dr. Finger moved that the ACIP recommend the use of MCV4 as preferred and MPCV4 as acceptable for the preadolescent visit and high school entry, the preadolescent visit being age 11-12 and high school entry being age 15; for college freshmen living in dormitories; for other groups at high risk; that other adolescents and other individuals can choose to be vaccinated; that the other edits, as discussed in this meeting, be made; and that the NCID be authorized to make those minor edits. Dr. Poland seconded the motion.

VOTE

In favor: Abramson, Allos, Birkhead, Campbell, Finger, Gilsdorf, Lieu, Marcuse, Morita, Poland, Stinchfield, Treanor, Levin.
Opposed: **None**
Abstained; **None**

The vote passed unanimously.

VFC RESOLUTIONS

Meningococcal Disease
Presenter: Dr. Greg Wallace, NIP

Two votes were take relative to meningococcal disease and the Vaccines for Children program. The first VFC vote was to add meningococcal disease to the list of diseases covered by the VFC entitlement program for children aged 0-18 years. The second vote was to recommend the addition of meningococcal conjugate and polysaccharide vaccines to the VFC program, clarify the distinctions between them, and present the indications for their use.

Polysaccharide. The eligible groups for the polysaccharide vaccine are children and adolescents aged 2 to 18 years, who travel to areas that are hyperendemic or epidemic for meningococcus; children aged 2-8 years with terminal complement deficiencies; children and adolescents who are infected with HIV; and college freshmen entering dorms. The dosage is one dose; revaccination can be considered. Standard contraindication language follows.

Conjugate. Adolescents aged 11 to 18 years old are eligible for this vaccine. The groups receiving priority for administration if supplies are limited are listed: those above, plus routine vaccination of 11-12 year-olds at their preadolescent assessment visit and at high school entry, age 15. One dose is recommended. The full statement's text about revaccination will be inserted. It will also note that more study is needed to confirm the conjugate's duration of immunity and that it is recommended for revaccination of persons aged ≥11 years, with the polysaccharide as an acceptable alternative. Standard contraindication language is included.

Delineation is detailed by noting the polysaccharide's use as recommended for the listed groups at ages <11 years. The conjugate vaccine is recommended for those aged 11-18 years, but the polysaccharide is an acceptable alternative.

Discussion included a suggestion to specify that the polysaccharide is to be used for those aged 2 -11 years, but not for those <2 years.

Ms. Stinchfield moved to accept the VFC resolutions as presented with that one edit, and was seconded by Dr. Poland.

VOTE

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

The vote passed unanimously

Since release of the meningococcal conjugate vaccine for those aged 2-11 is not far off, it was agreed to leave the Workgroup intact. The full statement remained basically unchanged from before, except for the additions listed above (epidemiology, safety and immunogenicity data, and the recommendations just passed), and the need to correct a few obvious typographical errors.

To general agreement, Dr. Finger offered a friendly amendment to add the entire meningococcal statement for the ACIP's approval. **There was consensus to approve the entire statement as described.**

VARICELLA

MMRV Workgroup Update
Presenter: Dr. Judith Campbell, Chair

Overview: Time line and topics reviewed by the MMR-V Workgroup; discussions with partner organizations; current and future topics.

Formed in 2003, this Workgroup has held bimonthly conference calls and met three times a year since January, 2004. They reviewed the contemporary epidemiology of varicella and breakthrough infections, school and childcare center outbreaks, transmission in highly vaccinated populations. They discussed the correlates of protection and the data on two-dose varicella regimens. Cost effectiveness models were reviewed and revisions are in progress. Presentations were heard on the MMRV combination vaccines in development. Data were reviewed on the post-licensure VE studies and risk factors for breakthrough infection were discussed.

In fall, 2004, FDA received the application for licensure of MMRV and ProQuad® was announced. Also announced in the fall was the new long-term goal of the varicella vaccination program: the elimination of varicella. CDC was notified by the Massachusetts Biological Laboratory (MBL) that VZIG production was being discontinued, and the Workgroup reviewed and discussed alternatives for varicella post-exposure prophylaxis.

Discussions were held with partner organizations (AAP, AIM, ASTHO, CSTE) about a 2-dose varicella vaccination strategy. Concern was expressed about outbreaks and breakthrough infections in a highly vaccinated population. The organizations supported the concept of a 2-dose varicella vaccination schedule and noted the importance of an educational campaign and catch-up dose strategy. Discussion is needed of programmatic issues and the fiscal barriers to implementation.

The workgroup planned to discuss the last three at this meeting, as well as the conduct of cohort and dynamic mathematical modeling. That will include the impact of one and two doses on the epidemiology of varicella disease, the vaccine's impact on herpes zoster, and the herd immunity effect.

Current and future topics to be addressed included review of options for updating the current ACIP recommendations (1996, 1999); the two dose strategy; school and college requirements and school and child care exclusion policies (especially for outbreaks); evidence of immunity, and the validity of positive disease history in the present near-absence of wild-type disease; and alternatives for post-exposure prophylaxis when VZIG is no longer available. Finally, with an MMRV vaccine pending approval and release, its use for a possible two-dose schedule will be discussed, as will the issues and concerns about the vaccine and herpes zoster. To date, the Workgroup has focused on chickenpox, but a shift in focus to herpes zoster in the coming months is anticipated.

Varicella Epidemiology
Presenter: Dr. Dalya Guris, NIP

Overview: Updates on varicella cases from 3 states consistently reporting to CDC; from the Varicella Active Surveillance Project sites; and from an outbreak investigation in Nebraska.

Passive surveillance: A table summarized data from four states which consistently report varicella cases to the CDC. Their case reductions from 1993-95 up to 2003 have ranged from 70%-87%. The 2003 vaccination coverage rates ranged from 77%-89%.

Provisional 2004 data from Texas, Michigan, and West Virginia, indicate that children aged 19-35 months had varicella vaccine coverage of 88% in Texas and 89% in Michigan. Texas' school entry requirements now cover children in child care, kindergarten, and middle school; and by the 2004/2005 school year, grades K-4 and middle school. Michigan's schools require vaccination from child care, kindergarten and sixth grade. Nonetheless, varicella cases have not declined in Texas for five years and the 2004 rate was the highest since 2001. Michigan's reported cases declined between 1999 and 2003, but then rose again in 2004. West Virginia has required varicella vaccination only for child care entry since 2000. Coverage dropped 5% from 2002 to 2003 and incidence has been stable for four years.

Active Surveillance. CDC data from its Varicella Active Surveillance Project in Antelope Valley, California and West Philadelphia, Pennsylvania, were charted. Overall, cases declined 87% from the 1995 implementation of varicella vaccination to 2003, but they have plateaued since 1999. Details were provided about these two active surveillance sites.

Antelope Valley has required child-care centers and kindergarten vaccination since 2001 and achieved 90% coverage in 2003. Nonetheless, 2004 cases rose by 53% from 2003. West Philadelphia required vaccination for kindergarten entry in 2000 and for sixth grade in 2001. They, too, achieved 90% coverage in 2003 among children aged 19-35 months, and the steady decline of their overall cases reached a record low in 2004. Their highest incidence was among children aged 5-14 years of age, but all age groups' incidence had declined, including among school-age children.

Breakthrough cases increased at both sites, as expected with increased coverage. Vaccinees inoculated ≥42 days before rash onset during 2004 comprised 57% of all reported cases in West Philadelphia. The proportion was 45% in Antelope Valley. There, the 22 recorded outbreaks in 2004 exceeded 2003's 15 outbreaks, which in turn exceeded 2002's 7 outbreaks. Cases per outbreak ranged from 5-26 (mean of 11) and outbreak duration was 3-72 days (average ~30 days). Cases were aged 5-44 (average 9.4 years) and 17%-93% were vaccinated (average of 57%).

Nebraska. In Nebraska, the 2003 varicella vaccine coverage among children aged 19-35 months was 75% percent; in 2004, vaccination was required for kindergarten and the first and seventh grades. Nebraska's Department of Health and Human Services investigated one of several elementary school varicella outbreaks in 2004. Coverage among the 283 students was 81%, excluding children with disease history, but 33 cases occurred within two months, stemming from an unvaccinated kindergartener. The unvaccinated children's attack rate was 67% (similar to attack rates seen in previous outbreaks among highly vaccinated school populations) and 13% among those vaccinated. None of the latter had severe disease. VE was 81% (CI of 66%-89%) and 93% against severe disease.

At question was whether there was an annual variability in varicella incidence, or incidence was plateauing, or annual reporting was variable. The Texas data suggest that there may be no further reduction in varicella cases without further interventions. Further follow-up with Texas is planned to assess the impact of vaccination on varicella epidemiology there. The general lack of detailed information on age distribution and vaccination status of cases in the U.S. is a gap; more case-based surveillance is needed.

Possible reasons for the differences seen in the active 2004 surveillance data from Antelope Valley and West Philadelphia could be: 1) the lack of middle school entry requirements in Antelope Valley; 2) exclusion of susceptibles from outbreak case counts in West Philadelphia since 2002; 3) more catch-up vaccination for school-age children in the early years of the vaccination in West Philadelphia; and possibly, 4) variability annually, as well as in vaccination coverage and surveillance. Monitoring of incidence and potential accumulation of susceptibles is needed, as well as improved laboratory confirmation of the vaccinated milder cases to avoid misclassification.

Massachusetts Experience of Varicella Epidemiology
Presenter: Dr. Susan M. Lett, Massachusetts Department of Public Health

Overview***:*** Review of programmatic implementation and varicella surveillance milestones in Massachusetts; vaccine distribution and coverage; surveillance data.

Massachusetts is a universal childhood vaccine distribution state and has no county health departments. Given that, their partnerships with pediatricians, family physicians, and nurse practitioners are key to their success. Those professionals' acceptance of the varicella addition to the routine schedule was high. In fact, it was the state advisory board, which includes those professionals' associations, that requested implementation of vaccination requirements.

The state began supplying vaccine for children aged 1-19 years in 1996. They required it for child care in 1998 and for kindergarten and 7th grade in 1999. Physician verification of varicella or serologic evidence deferred the requirement. This January, that was extended to grades K-5 and 7-12. Grade 6 will be phased in during the 2005-2006 school year. Colleges do not have a requirement as of now.

Chicken pox has been manually reported (in the aggregate) on index cards by health care providers in Massachusetts since 1910. With the national recommendation and CSTE resolution in 1998, deaths also became reportable. To avoid overwhelming the single state health department and local health boards, susceptibles were excluded from clusters in 2003, and in July, 2004, electronic reporting of cases began. Providers and schools report monthly, except for unusual cases or clusters, which are reported immediately.

With the historical data, an epi curve was charted of varicella cases back to 1910. Peak incidence years occurred in the 1940s and 50s, involving 25%-40% of the birth cohort. About 2600 cases have been reported so far this year, on track with CDC's expected estimate of ~8000.

A bar chart illustrated the varicella doses distributed in Massachusetts. From a low of ~25,000 in 1996, distribution peaked in the catch-up years of 1997 and 1998, respectively, at 180,000 and 167,000 doses. It then dropped to a relatively stable rate of 100,000 doses from 2002 to 2004. Vaccine doses administered by age group were charted from the Massachusetts Vaccine Accountability Database of monthly provider reports. Catch-up is completed. Some doses are now being administered to the older age groups, but most of the state-supplied vaccine goes to children aged 1 year.

Another bar chart showed rising coverage among children aged 19-35 months, from 23% in 1997 to 89% in 2003–4% over the national average. Compared to NIS data, behind which Massachusetts lagged by 33% in 1997, the birth cohort coverage rose in 1998 to 81%. That was 38% over the NIS average of 43%, and it rose again to 95% by 2001 (NIS, 82%). A dip in 2002 reflected the varicella vaccine shortages, when orders were delayed 6-8 weeks or longer. Providers agreed to defer the dose until 24 months of age, which dropped the doses administered by 12%. They recovered thereafter.

Charted kindergarten entry coverage since the 1999 requirement showed a change in children reporting according to past history of disease (34%) versus those providing vaccination documentation (59%), for a total immunity of 93%; to, in 2003, only 3% presenting a reliable history and 95% presenting vaccination documentation, and a 98% total immunity level. In 2003, two-thirds of the seventh graders still used reported history of disease, but 97% and 98% in child care and kindergarten, respectively, had documented vaccination.

Massachusetts added a question to the BRFSS to explore history of chicken pox and shingles in the last year among its population aged ≤19 years. Data from 1998 to 2003 reflected an 80% overall reduction in varicella incidence among all age groups, most among those younger and least among adults, whose incidence dropped 30%. Reporting sources for the last 5 years were also charted, illustrating the effectiveness of combined reporting by schools and providers in identifying cases. Charted cases by age group showed an increase in the 5-9 year-old age group.

Case-based reporting is very new (6 months), but sufficient to chart illness severity from July to December, 2004. Overall, 73% of cases occurred in vaccinated individuals, 80% of whom had very mild rash illness (<50 lesions); another 18% reported 2-249 lesions. Only 4% reported 250-500 lesions and only 2 cases had > 500 lesions. The mild- to moderate cases (77% overall) were mostly among vaccinated people, who also had very few cases of severe- or very severe disease. The state is still exploring why 45% of unvaccinated cases were mild.

Of the cases that reported age, most occurred in vaccinated individuals aged 5-9 or 10-14-years. The few cases reported in older age groups are probably due to the reporting sources. Adult providers were asked to report cases, but there compliance is less complete.

Varicella workload. Massachusetts has begun a database of calls made to the on-call state epidemiologist so as to more easily track the source of and reasons for the calls. From September to December, 2004, 20% of the ~2,000 calls were related to varicella cases, or clusters, and their control. Many of these generate 2-4 follow-up phone calls and those data do not include the spontaneous inquiries to staff – and, Dr. Lett noted, it is not yet varicella season.

The data on varicella investigations do not necessarily represent the severity of the outbreak. It could, rather, represent the community's concern. The 2003 data was almost certainly an underestimate, as the sizes of the clusters or outbreaks were not known. Of 11 investigations or consultations, 64% were in schools, 18% in child-care centers, and the balance were in other (usually high-risk) institutional settings. Of the 10 investigations and consultations in 2004, 40% were in schools and 10% were in child-care centers. The median number of cases was ~3, but one outbreak in a suburban community had 39 cases, most in vaccinated children in three different community schools. So far in 2005, two clusters were reported, one with 18 cases.

Summary. Breakthrough outbreaks can be prolonged, disruptive, and take up a fair amount of staff time. They involve a lot of education and communication, some of that to relieve concerns about new strains not covered by vaccine. In fact, varicella investigation and control are placing an increasing demand on the personnel of state health and local health departments and school health staff. Current challenges include a lack of effective tools for control, since outbreaks among those vaccinated or naturally immune are not helped by isolation and quarantine. Vaccine can be used as post-exposure prophylaxis for identified susceptibles, but those are mainly school staff whose immunization history is unknown. It is not really an option for people who received one dose or have a past history of disease.

Kaiser Study of Varicella Breakthrough and Age at Vaccination

Presenter: Dr. Bob Davis, for Dr. Steven Black, Kaiser Permanente

> Overview: Kaiser Permanente/Merck study to determine whether varicella breakthrough rates vary with age of initial vaccination in the second year of life.

Study design/methods. From June through November, 1995, Northern California Kaiser Permanente vaccinated a cohort of 7585 children aged 12-23 months with Varivax® (live varicella virus vaccine [Oka/Merck]). In this post-licensure VE study, the children were followed prospectively for the development of varicella disease. Structured parental phone interviews were done every 6 months. Rates of reported breakthrough varicella were computed using first reported occurrence of varicella over the follow-up period. Subsequent analysis computed the mean age at onset of varicella, and the mean time from vaccination to varicella onset, by age at vaccination.

Results. After eight years (November 2003), 7449 (98.2%) children remained in the study. In all, 1161 breakthrough cases of varicella were reported by parents, an average breakthrough rate of 21.7 /1000 person-years over the 8-year follow-up. No trends were found in the analysis in terms of breakthrough for each additional month of age at vaccination (p=0.864), nor was any significant difference found in the rate of reported breakthrough disease across the 12 age groups (p=0.984).

Breakthrough data charted according to the age at vaccination showed a “remarkable consistency.” No single month differed statistically from the overall rate of 21.7, nor was there any trend in time. The "highest breakthrough rates" occurred both upon vaccination at 13 months of age and at 22 months of age. The reported breakthrough rates also did not differ greatly whether the child was vaccinated early or late. The rate of breakthrough within one year of vaccination was slightly increased among those vaccinated at <15 months, compared to those older, but not to any statistical significance. The time to disease onset was also stable (at ~4 years) regardless of age of vaccination.

In fact, analysis using an annualized incidence rate demonstrated a slight drop in breakthrough rates in the 12 months since vaccination, from 2.25/1000 person years to 2.1/1000 person years in those who had not had breakthrough varicella.

Superimposing those data over cumulative effectiveness, the latter appeared after ~8 years to be ~85%,but the annual effectiveness remained relatively high at 97%-98%. Cumulative effectiveness over time was also superimposed over the data of Shapiro et al (*JAMA*, February

18, 2004 – Vol 291, No. 7), which used a different metric. In this real-world, clinical vaccine efficacy study, VE appeared to decrease in the months since vaccination, but not to decrease in clinical effect relative to breakthrough rates over time. That seems to indicate that the cumulative effectiveness appears to be on a constant trend, but it is too early to draw any inferences as to whether the breakthrough rates will increase or decrease in future years.

Conclusions. Over the first 8 years after varicella vaccination, no variation in the risk of breakthrough varicella disease was seen, according to the month of vaccination among children vaccinated in their second year (i.e., children vaccinated at 12-14 or 15-23 months of age). The mean time interval between vaccination and the occurrence of breakthrough disease did not vary; if anything, the breakthrough rates appeared to decrease slightly over time. There are any number of hypotheses that could explain that (e.g., breakthrough could have been impeded by reduced disease circulation, or there may have been a reduced group of susceptibles), but the reasons remain unknown.

Discussion included:

- Dr. Plotkin raised one hypothesis that compares this to what happened with the measles vaccine in the era before dose 2 was introduced. Immunity did not wane, but the vaccine did not achieve a 100% immune response in some people, which over time produced susceptibles. He did not believe the problem to be waning immunity since disease severity does not seem to be increasing. That suggests that priming is the problem, and decreasing exposure over time also decreases boosting. From past experience, he recalled that complement fixation antibodies might be useful in identifying those with natural exposures, rather than those who have simply had the vaccine. Serologic and CMI data over time are needed to enlighten this question. He wondered if the Texas data's plateau might be attributable to the presence of Mexican immigrants, and wished to hear data on serological immunity. Dr. Guris had no data on the immigrant factor. CDC also wondered about that in Antelope Valley, where the 30% Latino population may have had more of an introduction role than seen in the Philadelphia cohort.
- Diagnostic capacity within the surveillance is needed to determine whether or not a case is chicken pox. That needs to be established, since mild chicken pox cases might be misdiagnosed as something else, or the more severe cases might not be classified as breakout disease. Some states incorporated this into their smallpox surveillance system.
- The seasonality of the cases in both vaccinated and unvaccinated persons are parallel, as demonstrated in the active surveillance sites.
- Dr. Florian Schodel, of Merck, reported that clinical trial data on antibody persistence and kinetics over 10 years indicates a slight antibody drop. It rises again upon a second dose and continues to rise for a few years, but there is no indication of waning immunity. One theory is that environmental boosting may play a role, but that cannot be determined until the circulating virus is controlled.
- Dr. Abramson stated that only a large scale follow-up of a cohort receiving two- versus one dose will be able to determine the usefulness of the second dose. Live attenuated virus that stays in the body may in itself reactivate its own immunity.
- Dr. Barbara Watson reported the openness of Philadelphia clinicians to broad diagnosis, something helpful when the PCR reports a wild type. Half their cases are lab-confirmed and most of the others are linked to an outbreak investigation.

- Dr. Judelson emphasized the need for lab confirmation, citing studies in support. He also raised Osano's caution about his own finding of persistent antibody for ~20 years, as he had identified patients who had been re-exposed.
- Dr. Barbara Kuter reported Merck's conduct of a one- versus two-dose regimen, the latter administered three months apart. They found 85% seroconversion with one dose, based on the gpELISA correlate for immunity. The second dose raised everyone to a level >5, which over 10 years involved a significant difference in efficacy, of 94% versus 98%.
- It was clarified that breakthrough disease means wild type that breaks through the vaccine, not a vaccine virus-derived outbreak.

Public Comment
Dr. Neil Halsey recalled that, when this vaccine was licensed in 1995, the AAP's Red Book committee discussed recommending two doses. Several members on that workgroup thought the epidemiological evidence sufficient to support that, and noted that the breakthrough cases threatened the credibility of the vaccine. Two doses were not economically feasible with the vaccine cost at that time. However, the last 10 years of data have reinforced the need for the second dose. While it still makes the most sense, discussion of the related economics still will be necessary.

INFLUENZA

Update on Influenza Vaccine Supply and Distribution
Presenter: Dr. Jeanne Santoli, NCID

Last November, questions were added to the BRFSS survey regarding influenza vaccine use by individuals aged ≥6 months, according to vaccine receipt, priority group status, and reasons for nonvaccination. Data collected this past January infers the success in of October 5, 2004 interim targeting recommendations: 43,1% coverage for adults in priority groups and 8.3% for nonpriority adults. In fact, coverage for all of the priority groups resembled that of the 2003-2004 season. For nonpriority groups, adult coverage dropped from the 2003-04 rate of 19.6% to 8.3%. About 16-17 million people stepped aside. Slightly more than half (50.7%) of priority children received vaccine, as did 12.4% of nonpriority children. In this, the first year of the recommendation to vaccinate 6-23 month-olds, a 57.3% coverage was achieved, even with a dramatically reduced supply.

The iterative process of vaccine distribution this season worked. Immediately identifiable orders were addressed first, doses were apportioned across the states, and then three late-season strategies were effected. After the first-identified 46 million doses were administered, state and local public health officials were key to the second stage of distribution or redistribution of the remaining ~12 million doses across the states. Of that, the first 3-4 million doses were sent to fill the remaining public health orders, after which the state/local health helped develop a formula to identify their area's unmet needs as a percentage of the nation's unmet needs. That formula was used to divide the remaining ~8 million doses across the states. The states then allocated that vaccine to their providers and facilities. Nonetheless, some states still had excess vaccine than needed for the priority groups and others were short, so three reapportionments were done. Half way through that process, ACIP advised broadening the recommendations to add two groups. Subsequent to that, ~3.5 million doses of inactivated vaccine remained.

With demand dropping but incidence rising, the three late-season strategies were announced to increase vaccine demand and make it more available. First, states were encouraged to extend vaccination beyond the January 3 ACIP recommendation as long as they had supply available; 2) Sanofi Pasteur was allowed to distribute doses from the CDC influenza stockpile to private and public providers (with unused returns allowed); and 3) unused VFC vaccine was transferred from states that met their demand to those still needing it for all priority groups.

Planning for the 2005/06 season is being done by an internal multidisciplinary CDC planning group that includes NVPO and FDA representatives. They will identify priority CDC activities, determine who will lead those, develop a time line, and monitor completion of those activities. They will help prioritize the vaccine recommendations, including considerations and process, and advise the manufacturers on their pre-booking and distribution policies if a shortage seems likely. Specifically, this group will develop scenarios as the basis of plans, and monitor vaccine production projections by current and potential vaccine providers. Sanofi Pasteur expects to have 50 million by the end of November and 60 million doses by the end of December (given sufficient strain growth); MedImmune plans to produce ~3 million doses. Planning and communication strategies for those scenarios will be developed, as will plans related to antiviral medications and infection control, evaluation will be done (e.g., the BRFSS poll already described), and related legislation will be monitored.

IND use in a routine vaccination program has been informed by this year's experience. There are challenges to this: INDs are not optimal for routine use, as they require an IRB, a co-principal investigator, and insurance carriers experienced with IND vaccine (a limited pool). Public and provider acceptance of an IND vaccine also remains an unknown.

Conclusions reached by CDC include the continuing unpredictable, seasonal character of influenza virus, vaccine supply, and demand for vaccination. Although difficult, this season CDC managed to achieve relatively high vaccination coverage among the priority groups, successfully provide interim recommendations to target the available vaccine, and strengthen some good alliances and partnerships. Good alignment of the national role with that at the local levels allowed critically important, timely decision-making and implementation.

The inescapable need for planning remains clear: starting early, anticipating multiple scenarios, and involving key stakeholders. Dr. Santoli thanked the following, who played critical roles this past season,: the citizens who stepped aside, the private provider community, public health officials, Sanofi Pasteur, MedImmune, the vaccine distributors, and FDA. Without the generous openness of all these entities and individuals to achieving what was necessary for the nation's public health, the success achieved would not have been possible.

Discussion included:

- The BRFSS data will be released by the Health Alert Network and in the *MMWR* article on the final season's results.
- Next season's supply is likely to be the same as this year's, at ~53-63 million doses. However, GSK has applied for licensure of their vaccine, so there may be some additional licensed doses available from them and other manufacturers.
- The delicate balance between promoting vaccination and handling lessened production capacity will continue for the next year. CDC will likely have to develop multiple messages to select from as the season approaches, depending on the supply status.

- Of the 61 million doses of licensed vaccine produced, 56.5 million (93%) had been distributed to this date, exceeding the average 87%-90% distribution in the past 6 years. That is a real achievement, given the circumstances, but more work is needed to prevent *any* vaccine wastage.

Neuromuscular Disorders and High Risk for Children
Presenters: Dr. Nirinjan Bhat; Dr. Carolyn Bridges; NCID

Overview: Two studies of the prevalence, among children with severe influenza outcomes, of underlying medical conditions that increase the risk of influenza complications; in this case, neurologic and neuromuscular conditions.

Study 1. CDC surveillance of pediatric-influenza-related mortality in the 2003/2004 seasons indicated 153 laboratory-confirmed cases in 40 states among children aged <18 years of age (median age of 3 years; range 2 weeks-17 years). Medical records and autopsy reports showed 45% of them to be previously healthy; a third had ACIP-defined high-risk underlying conditions (12% had only one; 20% had a combination). Another 20% had no such conditions but did have other underlying chronic conditions, such as congenital anomalies, gastrointestinal disorders, and neurologic/neuromuscular disorders.

A list of the underlying neurologic and neuromuscular disorders found was shared, which was developed after review of the data to accommodate the conditions found. Many involved both muscular and neurologic organ systems; the individual categories were not mutually exclusive. Many of the children also had an ACIP-defined high-risk condition; those overlaps were diagrammed. Of 49 children, 28 were in both categories, leaving 21 with no previously recognized susceptibility to influenza complications. The frequency of neurologic and neuromuscular conditions among all cases and those without ACIP-defined high-risk conditions were charted. This showed frequent ACIP conditions among the latter group, particularly in some of the more rare conditions, but several non-ACIP cases remained.

Conclusions. About a third of the reported fatal pediatric influenza cases had an underlying neurologic or neuromuscular condition and 14% of those had no comorbid ACIP-defined high-risk condition. These were heterogeneous disorders with multiple pathologies, ranging from the purely neurologic to the purely muscular. They frequently coexist with one another and with high-risk conditions, making it difficult to separate out the individual contributions and risks. Additionally, they were present at various levels of severity and they were from only one season; surveillance over multiple seasons will be necessary. Pediatric-influenza-related death is now nationally notifiable. Other severe influenza outcomes, such as hospitalization, should also be examined.

U.S. children/adults with neuromuscular conditions and potential impact on the influenza vaccination program (NHIS 2002 data study)
Presenter: Dr. Carolyn Bridges, NIP

Overview: Four-year retrospective study at the Children's Hospital of Philadelphia (CHOP) by Dr. Susan Kaufman, PI, using retrospective data on children with laboratory-confirmed (including by culture) influenza hospitalization.

As a means of infection control, the Children's Hospital routinely tests children admitted with respiratory symptoms for respiratory viruses. Infection control, clinical virology, and hospital discharge data records were reviewed for influenza.

Patient characteristics. Of 757 patients identified with influenza, 332 were at high risk, 58% percent were male, and most (80%) had influenza A. Of the hospitalized children, 25% were aged <6 months and 58% were <2 years (median age, 1.8 years). More than half (56%) had no ACIP high-risk conditions; of those who did, asthma was most common (24%). Ten percent had more than one ACIP high-risk condition; 3% were premature births; 12% percent had a neurologic or neuromuscular condition; and 16% had a gastroesophageal reflux. Five children died of complications; 8% had seizures, and 4% had respiratory failure requiring mechanical ventilation. A chart of the latter's predictors, based on these chronic conditions, was shared. The adjusted analysis revealed three primary causes: pulmonary conditions other than asthma, cardiac disease, and neurologic/neuromuscular conditions.

Conclusions. Preliminary data suggest that neurologic and neuromuscular conditions may increase the risk of respiratory failure in hospitalized children with influenza. The limitation of this study was its case-series basis; population-based studies are needed.

CDC analyzed the potential burden that might be added to vaccine supply if children with neurologic and neuromuscular conditions were included in those recommended for vaccination, as well as the potential impact among adults. Based on NHIS data, they estimated an additional annual vaccination cohort of 11,000 children and ~25,000 adults with these conditions. That number did not include children and adults who already have other recognized ACIP conditions. The final list of conditions included seizures in the past 12 months, with or without resulting physical limitations, mental retardation, birth defect with limitations, cerebral palsy, Down's Syndrome, muscular dystrophy, and another category with limitations.

If all those conditions are included, ~528,000-907,000 children would be added who do not have another ACIP condition. That list might be narrowed, but there are no data to indicate which neuromuscular conditions are the most likely predictors of severe disease. However, including children with only cerebral palsy (CP) or muscular dystrophy (MD), for example, would add ~269,000 children.

For adults, the list included stroke; senility; multiple sclerosis; Parkinson's; birth defects and mental retardation resulting in limitation; and other developmental problems such as CP and MD. All those categories would add 1.7 million adults aged 18-49, and ~844,000 aged 50-64. A somewhat narrower condition list, such as stroke, senility/dementia/Alzheimer's with limitation, MS or Parkinson's disease, would reduce the number to 529,000 aged 18-49 and ~571,000 aged 50-64.

The limitations of using NHIS data, however, are that rare conditions are not included, and the number of neuromuscular conditions and those with ACIP influenza high-risk conditions may be underestimated. However, in general, up to 3.5 million persons might be added by a listed broad range of neuromuscular conditions.

Discussion included a suggestion to add to the list certain levels of spinal cord injury and perhaps head injury.

Influenza Workgroup Review of ACIP General Recommendations on Influenza
Presenter: Dr. Keiji Fukuda, NCID, for Dr. Scott Harper, snowbound in Boston

Overview: Proposed changes to 2005 recommendations; proposed tiering of recommendations

On January 26-27, the Influenza Workgroup met to identify options for the prioritized use of influenza vaccine during supply shortages in normal influenza seasons. Four workgroups reported information for the Workgroup's discussions, on aspects of disease impact (led by Dr. Kathy Neuzil), disease reduction from vaccination (Dr. Kristin Nichol), herd immunity (Dr. Arnold Montos) and economics (Dr. Lisa Prosser, Harvard University). Each subgroup had spent several weeks reviewing the relevant literature, and each summarized their findings and thoughts for discussion among the entire Workgroup. Additional comments were provided by ethicists and Dr. Roger Bernier presented a model of public involvement.

The underlying considerations prompting this meeting were: 1) the influenza vaccine supply disruption in 4 of the last 5 seasons, for various reasons (production and regulatory actions), and 2) the resulting shifting communications and ad hoc interim ACIP recommendations; 3) the departure of two manufacturers from the U.S. market; 4) lingering uncertainty about the adequacy of the vaccine supply; 5) increasing concern over pandemic influenza, the most extreme mismatch between supply and demand; and 6) the desire to involve other groups in decision making process (NVAC, the ethics community, and the public). The problems of the shortage resulted in confusion, and there was concern about erosion of the progress toward good vaccination compliance.

Major points from the workgroup presentations included that:

- The elderly are at much higher risk for mortality than any other group.
- The bulk of available data addresses hospitalizations, which were elevated in all current ACIP high risk groups. Additional groups may also be at increased risk.
- VE studies indicate less vaccine effectiveness in the very young and very elderly, but there is not enough evidence to independently dictate prioritization.
- Herd immunity resulting from vaccination campaigns is supported in modeling, but data from current studies are not strong enough to support any change in the national vaccination approach. However, it was agreed that vaccination of staff would be a useful "barrier" in nursing homes.
- Vaccination is most cost effective in those aged ≥65 years and in other high risk groups.
- For optimal vaccine distribution, pre-season estimates are critical. The distribution is dictated by the market and not by any perceived need by public health. Supply inequities greatly complicated the development of and compliance with recommendations.
- Vaccine demand has historically been smaller than the size of the target group.
- Communications must be consistent with long-term goals; as simple as possible, but not simpler; and the timing of communication is important.
- The ethicists advised that, in deciding who should get vaccine, all possibilities and options should be entertained, from which to select those to discard. Broad input should be solicited and the guiding principles used to guide the selection of one strategy over another should be clear.

The Workgroup proposed a tiering protocol in the event of further shortages:

- Group 1A: Vaccinate those with co-morbid conditions and residents of long term care facilities.
- Group 1B: Vaccinate those aged 2-64 years with co-morbid conditions, those aged ≥65 who are healthy/without co-morbid conditions, those aged 6-23 months, and pregnant women.
- Group 1C: Vaccinate healthcare personnel and the close contacts of children aged <6 months.

- Group 2: Vaccinate the contacts of children/adults at high risk and healthy persons aged 50-64 years.

- Group 3: Vaccinate those aged 2-49 years without high risk conditions.

The reason for the non-consecutive numbering was to make the point that it is difficult to sub-tier within groups. This format was designed to provide some level of granularity while also pointing out how hard these fine gradations are. Many of these decisions have to be made at the local level.

Proposed Tiering Schedule.
The Workgroup's proposed tiering language was as follow:

- Priority groups in Table (XX) are ranked in three tiers based on rates of influenza-associated mortality and hospitalization in the United States.
- During periods of U.S. influenza vaccine shortfall, it is necessary to prioritize pe rsons for vaccination based on risk for serious influenza-associated complications. In such periods, the groups listed in Tier 1 should be vaccinated preferentially, followed by the groups in Tier 2, and then Tier 3.
- On rare occasions when local vaccine supply is extremely limited, state and local health officials should vaccinate groups in Tier 1A before all other groups.
- However, in all other vaccine shortfall situations, groups falling into Tiers 1A, 1B, and 1C should be considered equivalent and should be vaccinated simultaneously.
- Eligible persons in Tier 1C, Tier 2, and Tier 3 should be encouraged to receive live, attenuated influenza vaccine.

The Workgroup discussed three options of what to do with this scheme, relative to the influenza statement: 1) to not discuss prioritization; 2) to discuss prioritization and the need for it under some circumstances, in general language, and indicate that the ACIP has developed such a list; or 3) to publish the prioritized list with the regular vaccine recommendations. The caution about the third involved reluctance to invite permanent expectation of tiered vaccination. That could erode progress toward universal and broader vaccination coverage.

Discussion included:

- This scheme was similar to the tiering used when the first emergency recommendations were issued. Health care workers were added, as a particularly important group able to transmit influenza to others, and the A, B, C gives an implied separation not done before.

- Although, as pointed out, there has always been enough vaccine nationally to cover all three groups of tier 1, that may not be true locally. This kind of good guidance is needed locally and will be appreciated by practitioners.
- *Recommendation release.* There was discussion as to whether to hold back the tiered recommendations until it was known if a shortage would occur, and only then to release them, or more forthrightly issuing them, since local shortages cannot always be predicted. It the latter is chosen, they could be inserted in the annual recommendations or issued in a separate document. Local authorities should handle the tiering depending on their supply.
    - Dr. Tan reported the AMA's preference to hold back the tiering announcement, but could compromise on a separate document. Their goal was to not hazard progress toward the long term vaccination goals and to avoid practitioner and public confusion.
    - Dr. Alan Hinman advised the quick release of the recommendations, preferably with the routine immunization schedule. That has already been done for infants and for infants who needed catch-up, and this would be consistent with long term goals. It would also be encouraging to the country to know that if a shortage occurs, the challenge can be met.
- Children with co-morbid conditions were not included in tier 1A because the death data for 1A distinguishes those groups from all others; the combined evidence put them at the top of the line.
- *Who determines the timing for A, B, C group vaccination? CDC?* First, "shortage" needs to be defined. Given that, the national level could be announced with the tiering level advised, or the shortage could simply be announced and the local levels advised to assess their supply and appropriate level of tiering.
- Dr. Poland suggested a time limit for the tiering to avoid the risk of broader groups losing interest in vaccination and resulting in vaccine wastage. He also suggested a matrix to address the levels of shortage that could occur: of trivalent inactivated, of FluMist®, of the pediatric vaccine, or any combination of those for different periods of time.
- One suggestion was to set, for example, 3-4 weeks to vaccinate tier 1A, then go to 1B, and 1C, assuming the vaccine could be sent where it was needed. There may be some data to indicate that by 3-4 weeks, 90% of those needing the vaccination received it.
- There were some reservations in the Workgroup about publishing an appendix to the regular recommendations. Those focused on having two separate approaches to recommendations in a single document. But timing will be complicated; for example, the timing to develop an article about tiering will take longer than the 1-2 weeks available for placement in the next *MMWR*.
- Unlike the pandemic influenza plan, this tiering scheme did not address essential services since, in a normal season, it is unlikely that society would grind to a halt. Dr. Lynn Bhata urged that this be made clear, since the issue of vaccinating essential personnel was raised repeatedly this past season
- The pediatric flu-related deaths caused much public concern, although it turned out that >50% of those involved pre-existing conditions. The Workgroup discussed prioritizing those condition, but there was a lack of good data to inform that. More importantly, the meeting had been planned to discuss a universal vaccination recommendation, before being diverted to the emergency prioritization. It was felt that ACIP must decide whether to further define high risk groups, or just to move the whole paradigm towards universal vaccination.

- Dr. Chapman reported inquiries to NIP from injury patients (e.g., high-level quadriplegics) without respiratory complications, who could not get vaccine from their doctors. There was general agreement around the table that the "underlying conditions" could be broadly defined by whatever the respiratory impairment might be (e.g., spinal cord patients, people with seizure disorders). That would also be a much easier message for practitioners to implement. Dr. Salisbury reported that the U.K. draft influenza recommendations for next year specifically cited children with risk for aspiration with inhalation.

Dr. Levin summarized **consensus to release the recommendations in two documents.**

Development of the tiering document. Dr. Fukuda appreciated that decision, despite the wish by some to issue guidance quickly. That will allow a little more time to discuss substantive issues, an important factor, since there is more divergence of viewpoints on this than generally occurs. Among the issues needing discussion are when to implement the tiering, possible timing limitations on priority groups, etc.

Realistically, it would take at least 6-8 weeks for those discussions, development of the second document, and vetting of the text by various organizations. It could be released as an *MMWR* article or a separate ACIP document, as has been done in the past for special recommendations for antiviral use. If the document gets long and complicated enough, a stand alone document to convey all the complexities would probably be advisable. Historically, when separate documents are issued, they are subsequently combined (e.g., the influenza recommendation contains the antiviral language). This could be very time consuming, but at least provides an extra year to judge the experience and craft the language.

Ms. Nancy Fraser, of the Alabama Quality Assurance Foundation, which serves Medicare populations, urged reconsideration of the lower priority for health care workers. The Birmingham News' front page on this day reported hospitals bypassed and patients transferred to other hospitals because of staff shortages due to the flu. Multiplying the health care worker by the number of patients they would care for, and the beds that would be unusable without their services, should improve their value and prioritization.

Dr. Fukuda understood her point. However, the Workgroup's two days of discussion approached this from all angles. There was a need to make choices in the event of a low vaccine supply, and these were the ones that were made. Dr. Abramson added that this was part of the consideration when these staff were placed in the first tier to receive live attenuated vaccine. Dr. Birkhead urged the ACIP to do whatever it could to strengthen the use of LAIV among health care workers. Much effort has been exercised to get them to use it, but without much success. Dr. Marcuse commented that the same was true for healthy people aged 5-49.

It was summarized that the initial one of two documents will announce that a tiering system is being developed, that the use of LAIV needs to be strengthened and clarify this as the best option for health care workers, etc. NCID will work with the Influenza Workgroup to develop the document, distribute it to the committee members, do editing by email, and if necessary, have a vote by teleconference.

With regard to those with neuromuscular and neurologic conditions, Dr. Nichol suggested adding to the regular recommendations a statement about immunizing people at risk for aspiration or

difficulty in controlling secretions. The Workgroup agreed to work on language overnight to be presented on the following morning.

With no further comment, the committee adjourned at 6:40 p.m.

FEBRUARY 11, 2005

OLD BUSINESS

Proposed Influenza Recommendations
Presenter: Dr. Keiji Fukuda, NCID

On the following morning, Dr. Fukuda presented the suggested text to address the previous day's points about: conditions that compromise respiratory function; more strongly emphasizing the use of LAIV by healthy people aged 5-49; clarifying that the tiering which is being discussed is for inactivated vaccine and not live vaccine; emphasizing the need for health care personnel vaccination; and text on the prioritized use of inactivated vaccine during periods of shortage. This text was to go in the regular recommendation document to be issued in April, as opposed to the stand-alone document. It will be inserted in addition to the normal minor edits and technical updates made every year: replacement of older references with new ones and language on the next year's vaccine strain (A Fujian will be replaced by A California), as recommended by WHO and most likely, on the following week, by FDA's VRBPAC.

The proposed text to add to the list of high risk conditions was as follows:
"Any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration."

Discussion included:

- "Cognitive dysfunction" was felt to be too broad a term, potentially including autism, and "can" invited too many scenarios. A narrower, more specific, focus was suggested. That would be done and circulated after this meeting.

Proposed Modification to LAIV text in 05 ACIP recommendations. LAIV is currently defined as an option for vaccination of healthy persons aged 5-49, close contacts of those at high risk, and anyone wanting to avoid influenza. The new recommendation was strengthened, as indicated by the underline below:

> "LAIV <u>should be considered</u> for vaccination of healthy persons aged 5-49 years, <u>including health care personnel</u> and other persons in close contact with groups at high risk and those wanting to avoid influenza<u>. During periods when inactivated vaccine is in short supply, use of LAIV is encouraged when feasible for eligible persons (including health care personnel) because use of LAIV by these persons may considerably increase availability of inactivated vaccine for persons in high risk groups</u>."

Discussion included:

- There was general agreement to strengthen the support for LAIV use, such as "preferentially" encouraged, or "urged;" suggested language will be sent to Dr. Fukuda. Later, the following text was agreed to be stronger and was preferred for use:

  "The prioritized (tiered) use of influenza vaccine during inactivated influenza vaccine shortages applies only to use of inactivated vaccine and not to live attenuated influenza vaccine. When feasible during shortages of inactivated influenza vaccine, LAIV should be used preferentially for all healthy persons 5-49 years of age (including health care personnel) to increase the availability of inactivated vaccine for high risk groups."
- The word "feasible" was used to give latitude to some institutions that may be constrained by LAIV's cost or availability.
- Text about LAIV is scattered throughout the document; Drs. Fukuda and Harper will work to gather it in one place.
- Although this would only involve a small number of doses, the logic was questioned of not tiering the live vaccine for preferential use by health care workers, to avoid inadvertently contributing to an additional shortage of the inactivated vaccine. Dr. Fukuda explained the Workgroup's intent to "steer" people in times of a shortage, while allowing them the choice in normal supply periods.
- A typographical error indicating encouragement for those aged 50-64 years in tier 2 to receive FluMist® will be changed, as that is not FDA-approved.

Influenza vaccine use during shortages of inactivated vaccine. A subheading in the document will be inserted to indicate the advent of the larger document to come:
"Later in 2005, the ACIP will publish additional guidance on the prioritized (tiered) use of inactivated influenza vaccine to implemented only during periods when there is a shortage of influenza vaccine. Otherwise, when vaccine is in adequate supply, every effort should be made to promote and use influenza vaccine for all regularly targeted groups."

Discussion included:
- To clarify that "all regularly targeted groups" is to include the close contacts as well as those at high risk, the text will read "according to the regular ACIP recommendations."
- Work will be done with NIP to reconcile the language on "timing of vaccination" with the normal recommendation, which focuses first on risk groups and asks others to defer vaccination until November.

Proposed additional text on health care personnel vaccination. It was acknowledged that more needs to be done to increase health care worker vaccination than simply writing stronger recommendations. Text was added to specifically suggest ways of doing so, which was separated out under a new subheading to draw attention to it:

"Evidence from two studies indicates that vaccination of health care personnel is associated with decreased deaths among nursing home patients. Health care workers should be vaccinated against influenza annually. Facilities that employ health care workers are strongly encouraged to provide vaccine to workers by using approaches that maximize immunization rates. This will protect health-care workers, their patients, and communities, and will improve prevention, safety, and reduce disease burden. Health care workers' influenza immunization rates should be regularly measured and reported… organized campaigns can attain higher rates of vaccination among this population. The following groups should be vaccinated: ….."

Discussion included:

- Dr. Poland suggested adding that case reports of hospital-based outbreaks document health care workers' involvement; and adding after "organized campaigns" that "currently, several states have mandated vaccination of health care workers or required declamation."
- Inserting text to promote vaccination as a quality of care issue was suggested, based on data published in *JAMA* that reduced staffing and increased workloads on nurses can significantly affect patients' outcomes.
- Dr. Temte suggested language to state that any health care worker with a febrile or respiratory illness during confirmed flu season should not work.
- Dr. Wexler suggested moving sentence 2 up to be the lead, stating that "All health care workers should be vaccinated annually."
- Relevant language to also be reviewed was the joint ACIP/HICPAC health care worker statement under development, as well as language on the CDC Website about respiratory hygiene.

Dr. Fukuda requested that any further comments be sent to Dr. Harper by early the following week. After a final edit by CDC staff and final review by the Influenza Workgroup, the statement will be submitted in early March to the *MMWR* and for formal CDC clearance. After the statement is vetted, an ACIP vote will be done teleconference. The members will be advised two weeks in advance of that vote.

The second, tiering, document will propose tiered groups for vaccine use in periods of shortages, with a table to explain and support that approach. The next steps for that will be its drafting by CDC staff, review and editing by the Influenza Workgroup members and others, followed by ACIP's review and vote. It will be submitted for formal CDC clearance and to *MMWR* within 8 weeks, for a target publication date in mid-May to early June.

Dr. Birkhead moved to accept the 2005 influenza recommendation statement as edited, and the motion was seconded by Dr. Marcuse.

VOTE
In favor: Abramson, Allos, Birkhead, Campbell, Finger, Gilsdorf, Lieu, Morita, Poland, Stinchfield, Treanor, Levin.
Opposed: None
Abstained: Traenor

The vote passed.

PERTUSSIS

Pertussis Workgroup Report
Presenter: Dr. Abramson, Workgroup Chair

Overview: First presentation of the Pertussis (Tdap) Workgroup, formed in June 2004, with 20 members and 13 consultants. It has reviewed data on the efficacy, safety, and duration of

protection of DTaP and Tdap, cost-benefit, and strategies for Tdap use, focusing on adolescents. Future activity will address adults.

Whooping cough is caused by a gram-negative bacillus, Bordetella pertussis, that is present world-wide. It causes severe, debilitating cough illness with paroxysms lasting weeks to months (it has been called the "100 day cough"), vomiting, inspiratory whoop, and apnea among infants. Although most of its mortality occurs among young children, it also causes substantial morbidity in adolescents and adults.

With its multiple representation of disciplines, agencies and organizations, the Workgroup's charge is to consider strategies to improve prevention and control of pertussis in the U.S., using acellular pertussis vaccines formulated specifically for adolescents and adults. Since the implementation of infant and childhood vaccination with DTaP, those groups constitute the largest reservoirs of pertussis. One DTaP for adolescents and adults has already been approved, and approval of a second vaccine is likely this year. That is fortunate, since incidence has risen.

The Workgroup focused on adolescents since they have high rates of endemic pertussis and substantial morbidity. Depending on price, the use of Tdap could be cost-effective from a societal perspective, and perhaps even cost saving, as well as offer potential secondary benefits from a reduced total burden of endemic and epidemic pertussis.

Biological License Applications (BLA) have been submitted to FDA by both GSK and Sanofi Pasteur. GSK is offering Boostrix™ for use among those aged 10-18 years, and Sanofi Pasteur is offering Adacel™ for those aged 11-64 years. They will both be reviewed by VRBPAC in mid-March.

The Workgroup discussed whether to simply substitute DTaP for DT at the 11- to 12-year-old visit and conduct catch-up for those behind in their immunization; and whether to consider its administration at less than five-year intervals, the current norm, to take advantage of the first vaccination opportunity. Further information will be presented at the June ACIP meeting. If a DTaP is approved, a recommendation for adolescent vaccination will be provided with language for the statement, and a VFC vote will be held. After that meeting, the Workgroup will address the issues related to adult vaccination.

U.S. Pertussis Epidemiology; Childhood DTaP Vaccination Program
Presenter: Dr. Trudy Murphy, NIP

Overview: Background of DTaP vaccines

The five DTaP vaccines inaugurated in the U.S. in 1991-92 (for doses 4 and 5) and 1996 (for the primary series) vary by type and quantity of components: diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA), protactin (PRN), and fimbirae (FIM) antigens, adjuvants and preservatives. The product brands and their manufacturers have been: 1) Tripedia®, by Sanofi Pasteur (2 component-PT, FHA); 2) Infanrix® and Pediarix,® by GlaxoSmithKline (3 component-PT, FHA, PRN); and 3) Daptacel,® by Sanofi Pasteur (5 component-PT, FHA, PRN, 2 FIM)

The children who were the first to receive the fourth and fifth doses are now 17-18 years old; those who had the first primary series are now 8-9 years old.

Safety data. European DTaP vaccine prelicensure trials in the mid-1990s indicated lower reaction rates overall than from whole-cell DT vaccines, but also increasingly severe subsequent local reactions (i.e., >50 mm localize injection site swelling among 20%-25% after dose 4 or 5, and entire limb swelling among 2%-3%). These resolved independently but their unknown pathogenesis raises them as a concern relative to an additional acellular vaccine dose.

Efficacy. FDA approval requires demonstration of non-inferiority for immune responses to the European trials' pertussis components and, for Tdap, a significant booster response to all antigens. In prelicensure trials, the VE of three DTaP doses at 2, 4, 6 months varied with the severity of the disease. The WHO defines severe disease as 21 days of paroxysmal cough, with lab-confirmed or epidemiologic linkage to a confirmed case. The VE of the current three DTaP vaccines ranged from 80%-93%. Mild illness was defined as any cough lasting ≥7 days; for that, they vaccines' efficacy was 71%-78% in the European trials. Similar results were found in recent U.S. VE studies of children aged 7-18 months: 91% against hospitalization, 86% against outpatient treatment, and ~88% overall. As yet unpublished data also paralleled those results, and there have been no antigenic shifts of B. pertussis in the U.S. that would alter the VE.

Waning immunity does not equate to decreased protection for the three vaccines. Despite the waning antibody also seen after natural infection and whole-cell vaccine, the VE for Infanrix was 86% at age 3-6 years. Daptacel® data supported stable VE for 4-5 years with some waning immunity at six to seven years; Tripedia® maintained a VE of 91% 5-7 years after dose 4. There are no published data for longer periods.

Herd immunity. A chart was shared demonstrating the high coverage of 96% achieved by 2003 among children aged 19-35 months for ≥3 doses of DTaP (DT) Its effect to produce reduced transmission (i.e., herd immunity) is supported by some evidence. Studies in Senegal (Preziosi et al, *Vaccine*, 2003;21:1853*)* and Göteborg (Taranger et al, *Clin Infect Dis* 2001; 33:1004) indicated 85% "VE for infectiousness" in the former, although lower for less severe disease. The latter chronicled decreased hospitalizations and lab-confirmed cases among infants aged <6 months and among adults. The conclusion was that, under some conditions that are not clearly defined, a degree of herd immunity might be expected using DTaP vaccines, or possibly Tdap vaccines.

In summary, DTaP vaccines show an improved safety over DT whole-cell vaccines, although increasing swelling reactions after successive doses have remained a concern. The DTaP vaccines' VE is consistent with prelicensure estimates. Peak effectiveness was seen in the first five years and some waning immunity occurs ≥6 years after the last dose. Vaccine coverage in the U.S. is high, with three or more doses, and DTaP vaccines may provide some vaccine-induced reduction in transmission or herd immunity.

Incidence. Incidence in the 1940s dramatically dropped after introduction of the whole-cell vaccine, from a high of ~270,000 to ~1000 cases in 1976. However, charted data showed another rise in incidence in the 1980s that escalated in the 1990s. That rise has been even more pronounced recently (e.g.,. 11,647 cases in 2003 rose to 18,000 in provisional 2004 data). Most of the increases in the last 3 years have been among the adolescent (10-19 years) age group.

Among children aged <1 year, incidence has risen the most among the 0-2 month-old age group, which cannot receive vaccine and thus serves as a indicator of an increasing epidemic. Their recent incidence of ~150/100,000 was contrasted to that of the 1-4 year-old age group (18/100,000), which itself jumped from a relatively stable ~8/100,000 in the 1990s. Small increases were also documented among the 5-9 year-old group.

The reasons for these increases have been speculatively assigned to waning immunity, which is rapid 5-10 years after the last DT whole-cell vaccination. That may have been exacerbated by declining vaccination due to some safety concerns about the vaccine. One manufacturers' lots also were found to be suboptimally potent over a ~15 year period, to the mid-1990s.

The sharper rise in the last few years may be due to increased surveillance, greater access to the more defined PCR analysis, and more extensive media coverage, which raised awareness. The latter occurred in the two states with outbreaks that comprised >50% of cases, New York and Wisconsin. Cases reported by diagnostic criteria (serology, epidemiologically-linked, PCR, culture, DFA) were charted, revealing a sharp increase in these tools' use after since 2003.

Passive surveillance cannot indicate whether these rising reports reflect actual increases in pertussis or simply greater awareness of it. However, one certainty is that the current pertussis diagnostic capability still underestimates the burden of disease, particularly among adolescents and adults.

Discussion included:

- Infants too young to receive the pertussis series constitute 90% of the pertussis-related deaths, most occurring in those aged <3 months.
- Under-reporting of pertussis is due to a lack of recognition. California data indicate that only ~10% of cases are reported. Although reporting is improving to some degree, it probably remains at <50% than the reporting done for conditions of known mortality and morbidity.
- There is a good deal of literature on the organism's virulence and likelihood of vaccine escape, particularly in Dutch journals. That suggests alteration mostly in the surface marker of the protactin that does not affect the VE of pertussis toxin vaccines.
- There have been quality issues associated with commercial laboratories' pertussis PCR analyses, in the absence of standardization or QC. The data presented at this meeting likely included resulting false positives, but confirmed cases are counted if they meet the clinical case definition as well. CDC is working to improve that situation.

Pertussis in Adolescents

Presenter: Dr. Margaret Cortese, NIP

Overview: Review of Massachusetts surveillance data (considered by CDC as representative of the national situation relative to adolescent pertussis) as well as other states; data on pertussis morbidity and its impact on adolescents.

There is a large burden of pertussis disease in adolescents across the U.S. that is only hinted at by the passive surveillance data. The case reports are highly dependent on the limited availability of diagnostics and, therefore, also on awareness of the disease. Improvements in both will raise the reported incidence data.

The increased activity recognized in 2004 produced ~ 8000 cases reported in adolescents. Sixteen states reported >100 such cases, and 14 reported >500 among adolescents. Those are likely underestimates, as indicated by incidence rates.

Massachusetts presents a good example, as it has a well-established surveillance infrastructure. It is the only state whose laboratory has offered free standardized pertussis serology (99% specificity, 63% sensitivity) for diagnosis in adolescents and adults, since 1987. Its proactive outreach to local health departments, physicians and schools has heightened awareness, and it has a very high infant/childhood pertussis vaccination coverage.

Pertussis in Massachusetts. A chart of reported cases by year and age group showed increases since 1988, after diagnostic serology was offered. Most (66%) of cases were among adolescents aged 11-19 years of age. Of those adolescent cases in 2003, 85% were serologically confirmed; the rest were epidemiologically linked to lab-confirmed or culture-confirmed. The latter identified almost all the infant cases but only a fraction of the adolescent cases.

Outbreak data (defined as ≥5 linked cases) showed them ranging from 12-49 per year, of which 83%-100% were in school settings. Of Massachusetts' ~ 300/1000 adolescent cases annually, about half were detected through school outbreaks, indicating the importance of recognizing those. More than half (55%) of the adolescent cases were reported in other than school outbreaks, from smaller clusters of cases or individual cases. The average annual incidence of adolescents was charted from age 11-19, showing a steady increase from early adolescence that peaks at ~15 years of age (at 150/100,000). About 60% of the cases occur before age 16.

A chart of reported pertussis among adolescents in five states other than Massachusetts also showed rates in the high incidence years ranging from a low of 28/100,000 to 195/100,000 – and these are states without serology or PCR. In 2004, 16 states reported >100/100,000 adolescent cases.

Analyses of the morbidity and impact of pertussis among adolescents in Massachusetts and Quebec, respectively, were conducted by Lee et al (*CID*, 2204;39:1572-1580) and DeSerres (*JID,* 182:174-9). In Lee's two studies of patients aged 10-17 years, 314 cases were prospectively followed and data were collected about the illness and nonmedical costs; another 1679 cases were so analyzed from surveillance records. In Quebec, 280 adolescents aged 12-17 were investigated from case records and reinterviewed to assess disease impact. The results follow:

- *Symptomology.* These three studies revealed consistently severe and very prolonged (3 weeks to >3 months) symptomology. Most (74%-100%) of the adolescents had paroxysmal cough, difficulty sleeping and breathing or catching their breath during spasms. Most (56%-71%) also vomited after coughing spasms, a third lost significant amounts of weight, and one- to two-thirds had the classic inspiratory whoop. In Massachusetts, 39% were coughing for >1 month before diagnosis, which defeats the ability of any treatment, even antibiotics, to greatly alleviate their symptoms. More importantly, they had been transmitting infection for weeks.
- *Complications* in the three groups included pneumonia among 2%. Another 1% of each group suffered rib fractures from severe coughing, syncope after coughing spells, or hospitalization. (Passive surveillance indicates the latter at 2% outside of Massachusetts.)

- *Medical care.* In Massachusetts, adolescents made up to 15 related medical visits (median, 2), 25% made ≥3 visits. In all, 83% missed school (mean, 5.5 days); 43% of the primary parents/caretakers missed work (mean, 2.4 days), as did 14% of a second parent/caretaker (mean, 1.8 days). The average medical cost was $256, more than half of which stemmed from the medical visits.
- *Nonmedical costs* were $160/case, the vast majority of which were from missed work by missed work by parent and caregivers. The average total societal cost was >$400/case, and these estimates did not include the cost of antibiotics for the case contacts' prophylaxis, nor the public health investigation costs. The latter in particular can be substantial, to limit transmission, especially when multiplied by a school or regional outbreak that can last for months. To illustrate this, outbreaks in Pike County, Arkansas and Fond-du-Lac, Wisconsin, were presented, both settings of very high childhood pertussis vaccination coverage.

Conclusion. Pertussis in adolescents increasingly is reported across United State, and the cases reported are an underestimate of the true burden. Adolescent pertussis produces a significant impact on society in terms of morbidity, medical costs, missed school and work, and impact on the public health system.

Discussion included:

- Even in Massachusetts, there are few data on pertussis prevalence among adults; few cases are culture-confirmed.
- *Could there be bias in the response to the surveys, in that those with more severe disease may be more likely to respond?* The response rate for the morbidity and nonmedical cost cohort was ~61% of those initially contacted; the second such analysis was done from records of reported cases. Of course, the reported cases could well be more severe than the overall cases that occurred in the state.
- Some seroepidemiologic studies were done, which also indicated a great underestimation of pertussis rates in adolescents and adults.
- A recent study looked at the source of infection for U.S. infants <1 year old and could not identify a source of the pertussis for 64% whose family was asked. In 7% of the cases, the reported source was an adolescent.
- The importance was emphasized that pertussis is not a self-immunizing disease; everyone becomes susceptible again.
- Dr. Modlin asked what the expected effect of an adolescent pertussis program would be on the utility of the present assay, if many adolescents will then have a high antibody titer. Dr. Cortese agreed that a better rapid diagnostic test than that currently available will be needed, work that has been going on for some time.
- Dr. Gaston de Serres, who had conducted one of the Canadian studies presented, commented that background trends such as changes in the vaccines and their route of administration also contributed to the rise in rates, beyond recognition bias.

Epidemiology of Pertussis Disease Versus B. Pertussis Infection

Presenter: Dr. James D. Cherry, UCLA

Overview: Epidemiologic distinction between pertussis disease and infection; percentage of prolonged cough illnesses in adolescents and adults due to B. pertussis

infection; rate of B. pertussis infections in adolescents and adults; rate of B. pertussis cough illnesses in adolescents and adults

Comment. Before his presentation, Dr. Cherry offered three observations related to the previous discussions:

- The pertussis antigen declines so rapidly after vaccination that, with single-serum vaccination, single-serum serology will be usable within a year of immunization.
- The increase in incidence seen is real and is seen nationally. It almost certainly is due to increased recognition and to the fact that more vaccine failures can be expected, with only one good whole-cell vaccine in use since 1985.
- Adolescent and adult pertussis was recognized as occurring even in the prevaccine era; this is not a new occurrence.

The epidemiology of reported pertussis disease is very different from that of B. pertussis infection. In the prevaccine era, pertussis was universally present, with recognized cyclic peaks every 2-5 years. That remains true now, at about every 3 years, even with dramatically reduced prevalence. Unlike measles, which is now controlled in both disease and organism circulation, pertussis still cycles, indicating that the organism, while controlled, still circulates just as it did in the prevaccine era.

In the prevaccine era, reported cases occurred almost exclusively in unvaccinated children; >93% of cases occurred in children aged <10 years. In the 1970s, 50% of cases were reported in infants. Recently, about 50% of reported cases are in persons > 10 years of age. After the vaccine was licensed, reported pertussis in the U.S. plunged from the 157/100,000 of the prevaccine era to < 1/100,000 in the 1970s. That rose slightly, since 1984, ranging from one to 3/100,000.

Since Norton's study (*Am J Dis Child* 1978: 132; 372), interest in the transmission role of adults relative to infant pertussis has led to study. Dr. Cherry's group began study in 1986. A chart was presented of 13 studies from 1983 to 1999, which investigated people with prolonged cough illness. These assessed the percentage of prolonged cough illnesses in adolescents and adults due to infections, as measured by serologically significant ELISA titer rise or high titer to PT, FHA, PRN, or FIM, or significant agglutinin titer or titer rise. The proportion attributed to B. pertussis infection ranged from 12%-52%, with most in the twenty-percents. Some of the higher percentages were studies done during epidemics, involving that bias. Most used varying methods of serological diagnosis (e.g., just PT, FHA, protactin, and fimbriae and agglutination). In general, those using more antigens produced more cases. The other antigens invite gross reactions with other Bordetella species for FHA and protactin, and other elements that prompt antibody to FHA.

Another chart summarized seven studies, done in the last 20 years, of the percentage of prolonged cough illnesses in adolescents and adults due to B. pertussis infections. This was measured by significant IgA or IgG antibody titer rise, or high titer to PT, or positive culture or PCR. The results were amazingly consistent at ~13%, but for one outlier which had trouble with the PT analysis. Still another chart of five serologic studies done from 1984-99 illustrated the rate of B. pertussis infection in adolescents and adults. Infections were determined by the demonstration of a significant serum antibody titer rise to PT in successive serum samples. The annual rates concluded reached a high of 8%, but averaged in the 2% range.

In studies by Strebel (in Michigan) and Ward (nation-wide), rates of B. pertussis cough illness in adolescents and adults were estimated at 0.5% (5/100,000) and 0.37% (370/100,000), respectively. A study by Hodder et al in Cleveland, Ohio, was done among adults aged >65 years. That respiratory infection study collected sera every 4 months for 3 years from the participants. They found a B. pertussis rate of 1.5%, which translates to 3 million cases per year among older adults in the U.S.

Conclusions. B. pertussis infections in adolescents and adults are common and endemic, a conclusion by every researcher of the subject. Immunity after infection or vaccination is not long lasting. The outcome of an infection depends upon the time since vaccination or a previous infection. While Dr. Cherry was not certain that any data support the last statement, it is commonly agreed. Endemic adolescent and adult disease is responsible for the cyclic pattern in unvaccinated children. B. pertussis circulation cannot be controlled by present immunizations programs, but acellular vaccines make adolescent and adult booster immunizations possible. A program with adolescent and adult boosters will decrease the circulation of B. pertussis in these age groups and could lead to the elimination of the organism from the population. While that might be optimistic, it is supported by the experience of the diphtheria vaccine, which was less effective than those for pertussis, but succeeded in stopping the diphtheria circulation. The bottom line was that, to stop pertussis, it must be halted not only in children but also in adolescents and adults.

Discussion included:

- With an adult and adolescent vaccination program in place, the fourth infant dose could be dropped. In fact, that would be good to do, since infants receive more diphtheria than needed in the present vaccines.
- *Is a carrier who is so asymptomatic as to not be recognized as having pertussis still disseminating the organism?* There are many asymptomatic infections. A household contact study in Los Angeles found 42% who had titer rises but still were completely asymptomatic. They did not disseminate because one needs to cough to transmit. The ability to transmit also relates to the severity of illness. Although adults are relatively less contagious than children, there are more adults. Many hospitalized infant cases are traced to a parent as the source, many of whom had relatively trivial illness but had close contact with the child. While asymptomatic infections are not an issue, mild infections are a relative issue, and serious infections are a big issue.
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APERT Trial of Immunogenicity/Safety

Presenter: Dr. Joel Ward, UCLA

Overview: NIH APERT trial conducted at eight centers across the U.S.; a population based prospective trial to estimate the incidence of pertussis disease and infection, to assess the safety/efficacy of the trivalent GSK acellular pertussis (aP) vaccine, and to characterize pertussis immune response.

Study design. This randomized trial provided hepatitis A vaccine to half the cohort and acellular pertussis vaccine to the other half. The study end points for efficacy were to define the incidence of prolonged cough illness, clinical pertussis and pertussis infection; assess aP vaccine

safety and efficacy for prolonged cough illness, clinical pertussis and asymptomatic infection, and characterize immune responses (naturally acquired levels in older persons; immunity to aP vaccine and to natural infection and illness [diagnostic utility], and to assess antibody correlates of protection).

Active surveillance involved phone calls to all subjects every two weeks for two years. Upon any cough illness of ≥5 days, a clinical evaluation was done via nasal aspirate for PCR and culture and sera at that time and 30 days later. Multiple pertussis case definitions were used. The cohorts' age distribution ranged from 15-65 years old, representative of the nation across that age range.

Comparability of study groups. When randomization was broken, no significant differences were seen between the two study groups. Most of those who received aP vaccine were female; about a third were health care workers, another third were students, and the balance were community volunteers.

Safety results were examined for severe adverse events; differences in safety by vaccine; differences in reaction rates over time, 14 days after immunization; and gender-specific differences in reaction rates. Adverse events differed little between the cohorts. Data were charted showing minimal reactions for each vaccine group according to incidence of temperature >101ºC, redness and soreness at the injection site. Of interest was that, given the very moderate reactions seen, all the occurrences were among women.

Pertussis antibodies. A table charted the prevalence of detectable pertussis antibodies in unimmunized adolescents/adults for IgG and IgA to PT, FHA, PRN, and FIM. Of those subjects without detectable IgG pertussis antibody, 5.4% were above the minimum level of detection (MLD) and 1% were above the limit of quantitation (LOQ). There was little difference seen by sex, area, age, or race. A minimum of 2-5% had no detectable immunity.

Immune response to trivalent aP vaccine was charted on a table. Significant response was seen to the vaccine's 3 antigens. The rises, measured by IgG and IgA were: PT, 15-fold and 4-fold; FHA, 27- and 18-fold; and PRN, 25- and 15-fold. FIM was not in the vaccine. Decay analysis indicated that the antibodies of shortest duration were the PTs, the longest were the PRNs. This is of interest to booster vaccines.

APERT Results

- *VE/impact on duration of cough (2577 subjects)* A range of 1%-7% of prolonged cough lasting ≥5 days was found to be due to pertussis. When stratified by duration of cough divided by vaccine groups, no difference was found, suggesting that pertussis represents a small proportion of a large number.
- *Pertussis infection rates* were estimated based on seroconversion data between the 1-month and 12-month specimens in the control group (receiving hepatitis A vaccine). A variety of sensitivity analyses were done, using different antibodies, antibody levels, and cutoffs, regardless of clinical status. A complex table charted the number and rate of antibody increases among the non-vaccinated subjects during the APERT study. The final estimate during this time period was a 1%-2% infection rate. To assess the rates among those vaccinated, decay rates were analyzed across serial sera samples, which indicated a <2% infection rate in this group.

- *Proportion of subjects with antibody increases over an 11 month period*, by vaccine group, showed a statistically significantly lower FIM antibody response in the vaccine group than the control group, suggesting a vaccine response.
- *VE/prevention of pertussis with aP vaccine.* Using a very stringent serologic diagnosis that required a two-fold or greater rise in PT or 2 other antibodies, this analysis produced an efficacy of 92% (CI of 32%-99%).
- *Proportion of patients with pertussis by duration of cough/vaccine group.* This analysis divided the number of pertussis cases by the number of subjects who had prolonged cough to determine the proportion of individuals with pertussis and prolonged cough, stratified by duration of cough. All the results were statistically significant between the two groups, rising to 5.7% for those who had cough at ≥2 months.
- *Estimated pertussis incidence by vaccine group and by pertussis case definition*. The incidence rate observed for the primary case definition, of 3.7 cases per 100,000, translates to ~674,000 cases per year in the U.S., among only adolescents and adults. Including pediatric cases raises the incidence, to a total very close to that of the Strebel study, and suggesting ~1 million cases of clinical pertussis annually. And, based on the numbers of this study, an infection rate of 20/1000 and a disease rate of 4/1000, indicates one case in every five asymptomatic infections.

Conclusions. Pertussis wanes after 5-10 years; complete control requires immunization boosters. The current vaccine booster doses are not administered to persons aged >5-7 years. The evidence shows that older persons have asymptomatic infections as well as mildly symptomatic, and, less commonly, classical pertussis illness. Interpreting serologic responses, especially in immune individuals, is difficult. PCR and cultures are rarely positive unless they are done early. Prolonged cough illness (>5 days) is extraordinarily common in adolescents and adults, affecting >50% of persons per year. Culture and PCR are relatively insensitive in diagnosing pertussis in adults, even at 5 days of cough. Approximately 1%-5% of the population is without detectible pertussis antibodies. The annual infection incidence is probably five time the pertussis illness rate, at ~1%-2% per year. The incidence of clinical pertussis in adolescents and adults is at least 4 cases per 1000 person years. This incidence represents 800,000 to 1 million U.S. cases per year. Such illness is often long lasting and not benign. The risk of pertussis increases with duration of cough: 0.7% with cough >5 days; 1.75% with cough >21 days; and 4.0% with cough >42 days.

Discussion included:

- Dr. Poland was interested to know if the gender or body mass index related to reactogenicity data shared. His studies involving a deltoid injection have been affected by the larger size of the deltoid fat pad in women, which he thought also may have affected the results in this study.
- About a third of the cases occurred among adolescents and those in their 20s, and another third were aged >20. Only about 13% of those enrolled in the trial were adolescents.

Tdap Vaccine (Boostrix™) Presentation

Presenter: Dr. Leonard Frieman, GlaxoSmithKline (GSK)

Overview*:* Presentation of the reduced-antigen content tetanus toxoid, diphtheria and acellular pertussis, adsorbed (Tdap) vaccine, Boostrix.™ FDA is reviewing GSK's license

application. It has been licensed abroad since 1999 and is now used in 42 countries.

Vaccine Composition/Indication. The components and excipients of Boostrix™ are the same as those of Infanrix® and Pediarix® vaccines. But, for use as a booster vaccine, all the antigens are lowered: 50% of the tetanus, 10% of the diphtheria, and 33% of the pertussis antigens of the other two vaccines. The anticipated indication is as an active booster immunization against diphtheria, tetanus, and pertussis in adolescents aged 10-18 years. Boostrix™ will be administered as a single-dose booster after a minimum of 5 years from the last dose received of any diphtheria- and tetanus-containing vaccine. VRBPAC will discuss its application on March 15 and licensing is hoped for in May.

Adolescent pertussis vaccination. The recent increases in reported cases have occurred largely among those aged ≥10 years. A May licensure of Boostrix™ would be timely, as most routine Td boosters are administered to adolescents in the spring and summer months for back to school requirements. The current immunization platform and health economic data support universal adolescent immunization at the recommended 11-12 year-old visit. A combined Td-acellular pertussis vaccine will provide pertussis protection for adolescents without requiring an additional injection

Over 1.9 million doses of Boostrix™ have been distributed abroad. That antigen formulation is the same, but for a 0.5mg level of aluminum and a preservative (2-phenoxyethanol). The U.S. product is preservative-free. The clinical trial data in the U.S. were presented; concomitant vaccine studies were not required for licensure.

Pivotal Study 001 compared Boostrix™ to the U.S.-licensed Td vaccine for both immunogenicity and safety, and pertussis response in infants for immunogenicity. This was a randomized, observer-blinded study conducted in 45 U.S. centers, involving 4114 adolescents aged 10-18 years (75% were aged 10-14). They received a single dose of Boostrix™ or a single dose of the Massachusetts Biologic Laboratory's U. S.-licensed Td vaccine. The two cohorts were matched for age, gender, race, and type of pertussis vaccine priming history. The subjects were randomized 3:1 for one of three manufacturing lots of Boostrix™ or one lot of Td. They had previously completed DTP vaccines on the recommended schedule and received their last DTP vaccine at least five years earlier (85% did so in the last 5-10 years). Most were primed with whole-cell pertussis vaccine.

Results. As measured by ELISA one month after vaccination, antidiphtheria and antitetanus antibody concentrations were ≥0.1 UI/ml, the recognized seroprotective level, among ≥99.9% in both groups, and ≥97.3% of both groups achieved antibody concentrations ten times above ≥0.1 UI/ml. A four-fold rise in antibodies over prevaccination levels was shown in booster responses to diphtheria and tetanus. Diphtheria booster responses occurred in 90.6% of the Boostrix™ group and 95.9% of the Td group; tetanus boosters were seen by 89.7% of the Boostrix™ group and 92.5% of the Td group.

The noninferiority of Boostrix™ compared to Td was demonstrated for diphtheria and tetanus seroprotection rates and booster responses, meeting the predefined criteria of ≤10% percent for all parameters. Since there has been no serologic correlate of protection to pertussis found, a bridging analysis was done to demonstrate pertussis efficacy.

Another comparison of this study's results was done to a previous GSK immunogenicity study of infants (Study 039), for the DTaP vaccine Infanrix®. That study produced 88.7% efficacy against the WHO-defined "typical" pertussis and 81.3% VE against a German study's milder pertussis definition. This study required the upper limit of the 95% CI of the GMC ratio to be <1.5 when the VE of Infanrix® was divided by that of Boostrix.™ That was achieved, demonstrating the noninferiority of Boostrix™ antibody responses. GMC responses after Boostrix™ in adolescents compared to Infanrix® in infants were 1.8-fold higher for PT, 6.9-fold higher for FHA, and 3.8-fold higher for PRN.

The antibody distribution was displayed via reverse cumulative distribution curves (RCC). The curves for the adolescents in Study 001 before vaccination with Boostrix™ showed, for all three pertussis antigens, lower levels than those of the infants after three doses of Infanrix® in the infant efficacy trial. One month after vaccination with Boostrix,™ the curved levels of the Study 001 adolescents showed similar or higher pertussis antibody concentrations than those of the infant efficacy trial.

Study 001: Safety and reactogenicity incidence data.

- *Injection site pain.* Any injection site pain was reported by 75.3% and 71.7%, respectively, of the Boostrix™ and Td groups. Grade 2 pain (interferes with activities) or Grade 3 pain (prevents activities) was reported by 51.2% and 42.5%, respectively. The differences of the incidence of any pain and Grade 2 or 3 pain are statistically significant, although the incidence of Grade 3 pain alone was <5% and not statistically significant. Incidence of injection site redness, swelling, and increase in mid-upper arm circumference of the vaccinated arm was similar between both groups, as was the incidence of solicited general adverse events of fever, headache, fatigue, and gastrointestinal symptoms. They were not statistically different except for Grade 2 or 3 headache, which was reported by 15.5% and 12.7%, respectively, of the Boostrix™ and Td groups.
- *Injection site swelling (ISS)* after repeat vaccination with DTaP, DTPw and Td has been well described. Rennels (*Sem Ped Inf Dis* 2003;14:196-198) reported occurrence of entire proximal limb swelling in 2%-6% of children upon their fourth and fifth consecutive DTaP doses. Study 001 also assessed large swelling with daily mid-arm circumference measurement. Most of the study subjects had been primed with at least 3 doses of DTPw. The Large Injection Site Swelling (LISS) criteria required >100mm selling, and/or a >50 mm increase in the mid- to upper arm circumference compared to the pre-vaccination baseline, and/or diffuse swelling that interfered or prevented normal activities.

Results. LISS was reported in two of the 4047 study participants. That low incidence does not signal a new or unexpected safety issue. U.S. adolescents primed throughout life with DTaP vaccine will not be evaluable until 2007. GSK recently conducted a study with a cohort of 300 German adolescents who received a sixth consecutive dose of acellular-pertussis containing vaccine. Results are being prepared for submission to FDA and for publication

Study 030/Duration of Protection. Study 030 assessed D, T and P antibody persistence in a serological follow-up of Finnish adolescents aged 10-14 years who, five years earlier, were vaccinated with the .5 milligram non-U.S. formulation of Boostrix™, or Lederle's U.S. licensed Td vaccine.

A logarithmic curve demonstrated the progression of the anti-D and the anti-T GMCs over the 5 years of follow up. The levels of both the Boostrix™ and Td groups remained ≥0.1 IU per mL, and the GMCs for both antigens had declined only slightly in the two years since their last follow up sample. A similar chart was shown to illustrate the evolution of the pertussis antibody. There are no immunologic correlates of protection for pertussis, but 5 years after vaccination, the GMCs elicited by FHA and PRN antigens were still higher than the prevaccination levels, and the GMCs for PT approached those levels. Again, the GMCs for all three antigens had declined only slightly since the last follow-up sample two years earlier.

Conclusion. At five years post-vaccination, GMCs to diphtheria, tetanus, FHA, and PRN remained higher than the prevaccination levels, and the GMCs to PT approached those levels.

Additional data were presented that compared the Study 030 results to follow-up data from an NIH study of Italian infants vaccinated with the primary series of Infanrix® and without a booster dose in their second year of life. That efficacy trial demonstrated that, at 6 years post-vaccination with the primary series, Infanrix® maintained efficacy against the WHO-defined "typical" pertussis at 86% efficacy (95% CI 79%-91%; Salmoso, *Pediatrics 2*001;108:81). Those data, and the adolescent bridging presented, suggest that Boostrix™ will afford protection against diphtheria, tetanus, and pertussis through at least 5 years after vaccination.

Conclusions. The immunogenicity of Boostrix™ is comparable to that of the U.S.-licensed Td vaccine. It will confer protection against pertussis. Its safety and reactogenicity profile is also comparable to the U.S.-licensed Td vaccine. Boostrix™ offers adolescents needed protection against pertussis with no additional injection, and no additional office visit is necessary if the vaccination is coupled with the ACIP-recommended 11-12 year adolescent assessment.

Discussion included:

- *The entire limb swelling occurred mostly in children who were primed with acellular vaccine, and was significantly different from those primed with whole cell vaccine. When will the sixth-dose study be available for evaluation?* GSK plans to present that information at the fall meetings and after that to publish them, but FDA has not yet reviewed that study report. Of 319 children aged 9-13 years who received a sixth dose of DTaP, 3 had large injection site swelling within 0-2 days of vaccination. None had such swelling upon the fifth dose of DTaP. All resolved 4-5 days later. The children who did have LISS on their fifth dose of DTaP, none had it upon their sixth dose. GSK plans to share these data after FDA's review.
- Dr. Neal Halsey asked why the upper age limit was being set to 18 years, as that would eliminate young mothers and impede the vaccine's use to protect very young infants under 6 months. There seemed to be no biological data to suggest that that use at age >18 years would be inappropriate. Dr. Friedland agreed that it is safe and effective and is licensed for use in adults abroad. It was simply that GSK's first approach to U.S. licensure was to focus on adolescents.
- Of the 4114 vaccinated adolescents, there were no reports of serious adverse events within 30 days after vaccination. A subsequent 5-month safety follow-up found 22 serious adverse events reported in the Boostrix™ group, for an incidence of 0.5%, and 0.2% in the Td group. All the serious adverse events were found to be unrelated to vaccination.

Adacel™ Presentation
Presenter: Dr. Michael Decker, Sanofi Pasteur

Overview: Safety, efficacy and immunogenicity of Adacel,™ Sanofi Pasteur's Pasteur adolescent pertussis formulation.

All components of Adacel™ are U.S.-licensed immunogents of Daptacel® or Td adsorbed. Adacel™ is produced in the same manufacturing facility as Daptacel® and the testing methods used for Adacel™ were the same as for those two vaccines. The main difference between the two vaccines is the reduced concentrations of pertussis and diphtheria toxoids in Adacel.™ More than 5 million doses of Adacel™ or Adacel™-based vaccines have been distributed worldwide. It is designed for use in an adolescent/adult population.

Clinical trials. Immunogenicity was demonstrated by comparison to Td vaccines or T and D components, and to Daptacel® for the pertussis components. The safety evaluations were based on comparison to the Td standard of care in the adolescent/adult populations. Sanofi Pasteur's four U.S. clinical trials were supplemented by Canadian licensure data. All the Adacel™ trials involved ~7000 subjects. *Efficacy* was first demonstrated in an NIH-sponsored trial in Sweden. The Sweden-1 study was a randomized, double-blind placebo- and whole-cell-controlled comparative trial. Two aP vaccines were evaluated, one whole cell and Td, administered at 2, 4, and 6 months of age to Swedish infants. That study supported Daptacel's™ efficacy of 85% against the WHO-defined classic pertussis and 78 percent against any pertussis, whether culture-proven or epidemiologically linked, with at least one day of cough.

Trial Td506. The pivotal trial, Td506*,* was done at 39 U.S. sites and involved ~5000 vaccinees. Subjects were stratified equally into five age groups: adolescents young and older, and adults young, middle-aged and older. The diphtheria sero response and booster response rates for adolescents were charted, demonstrating essentially the same response rates for Adacel™ and Td, and for adults when Adacel™ was compared to tetanus. When the sera from this trial were compared to those of the Sweden-1 efficacy trial, at the same laboratory under the same conditions and using the same validated assay, one dose of Adacel™ generated substantially more antibody in adolescents and adults than did 3 doses of the highly efficacious infant vaccine to infants. Adacel's™ noninferiority to Td vaccine for diphtheria and tetanus immune responses was proven, as was its immunogenicity for pertussis responses compared to the Sweden-1 trial.

Trial Td501 examined the co-administration of Adacel™ with hepatitis B vaccine to explore its suitability to the adolescent catch-up recommendation. Adacel™ and hepatitis B vaccine were given to 400 adolescents, either concomitantly or one month apart, to assess the equality of response. The two groups' responses for simultaneous and sequential administration of diphtheria and tetanus were virtually identical, proving the ability to concomitantly administer Adacel™ with hepatitis B vaccine.

Trial Td502 was an analogous study of ~700 adults who received Fluzone™ influenza vaccine either simultaneously with, or consecutively to, Adacel™. The diphtheria response rates were essentially identical across the two groups, as were the response rates for the three influenza strain antigens. The pertussis responses seemed to be systematically lower in the concomitant group than the separate administration group. Nonetheless, antibody levels were dramatically

higher than those seen in Sweden-1, suggesting that Adacel™ can be administered concomitantly with influenza vaccine with no diminution of protection.

Reverse distribution curves (RCC) were used to demonstrate the Adacel™ trials' responses among adolescents for PT, FHA, protactin, and FIM rate. The Adacel™ curves dominated the results from Sweden-1, demonstrating substantially superior immune responses. The RCCs for adults were very similar.

Canadian data. Three of the Canadian licensure trials conducted long-term follow up of patients provided Adacel.™ Data points were charted for the periods of preimmunization, and after vaccination at 1 month, 1 year, 3 years and 5 years (2006 will the eighth year). Every data point showed Adacel™ to be equal to or superior to those of Td, and similar results for both diphtheria and tetanus seroprotection for adults and adolescents.

The pertussis results were graphed for PT, FHA, protactin, and FIM. The RCCs reflected the Sweden-1 efficacy data for antibody levels at 1, 6, and 24 months after immunization. This was the antibody associated with 85% efficacy against classic pertussis for 2 years after vaccination. The RCCs for Adacel™ extended to 60 months, and paralleled the Sweden-1 curves, inferring the possibility that Adacel™ could be administered at the same ten-year interval now used with Td. The eight-year data will further enlighten this question.

Safety data. Td506 also assessed *local reactions* (erythema, swelling, and pain). The charted data for Adacel™ versus Td were very similar overall for adolescents and adults. There was some increase in limb swelling among infants and adults, and some injection site swelling, but none to a significant degree and no differences between the two groups. Adacel™ recipients had slightly more of the moderate pain than in the Td group, but not to any significance. For *systemic reactions*, there was an increase in mild fever among the adolescents given Adacel™ versus those receiving Td, but none was seen in the adult groups.

Unsolicited adverse reactions were reported by 36% adolescent of the Adacel™ recipients and 51% of adolescent Td recipients. But again, there were no differences reported among adults given Adacel™ or Td. The U.S. trials had no reports of whole arm swelling nor of limb circumference and swelling, even with additional analyses done. *Severe adverse events* occurred in ~1% of both groups, with no significance in the rate differences. Two of these SAEs could have been related, both in Adacel™ recipients. One severe migraine, beginning one day after vaccination, required hospitalization of a person with a family history of migraines. The second involved ridiculer pain in the left upper arm 12 days after vaccination. Both cases recovered without sequelae. One death occurred, a suicide 70 days after vaccination.

Conclusion. Adacel™ is safe and well tolerated among adolescents and adults, with a safety profile very similar to that of licensed Td vaccine. Adacel™ achieved all prespecified noninferiority criteria for immunogenicity versus Td, and can be given concomitantly with hepatitis B vaccine or influenza vaccine. One dose of Adacel™ in adolescents and adults produced much greater pertussis antibody levels than those following three doses of Daptacel® in infants. The antibody responses for all components persist at elevated levels for at least five years.

Discussion included:

- An immunogenicity study comparing Adacel™ to Menactra™ is underway. Since Menactra™ showed no interference administered concomitantly with Td, interference with pertussis is thought to be even more unlikely.
- A follow-up study in Germany is in planning, to give a sixth dose via Adacel™ to a group that received five consecutive doses of Tripedia® in the past.

Canadian Adacel™ Clinical Trial

Presenter: Dr. Scott Halperin, Dalhousie University/IWORK Health Centre, Canada Clinical Trials Research Center

Overview: Data from the Canadian Adacel™ clinical trials done by Dalhousie University, the Prince Edward Island (PEI) Department of Health and Community Services, and Sanofi Pasteur.

Background. Pertussis is increasing among adolescents and neither the disease nor the vaccine will convey lifelong immunity, resulting in a large pool of susceptible individuals. Canada's routine schedule includes a Tdap booster in place of Td equivalent for all adolescents. That will be fully implemented across the provinces by the end of this school year. This study was to determine a safe interval between Td vaccines, as frequent doses of tetanus toxoid can cause arthus-like reactions due to antibody excess. That excess causes complex deposition of antigen/antibody in blood vessels and resulting damage, with a rapid onset reaction that can occur within several hours.

The Canadian Adacel™ prelicensure studies had a <5-year interval exclusion, but they were not evaluated for intervals since the previous dose. In fact, there are no data to support that a dose at <5 years after a previous dose will cause substantial reactions, and most of the data on arthus reactions involved hyperimmunization by multiple tetanus toxoid doses given in EDs after injuries.

This study was to develop data for catch-up programs and for use of Tdap vaccines in outbreak situations. The primary objective was to compare Adacel™ reactogenicity to that of Tdap after intervals of 2-9 years, compared to ≥10 years since receiving a Td or a Td-containing vaccine. The study was conducted in Prince Edward Island, where the routine schedule provides a pentavalent DTaP-IPV-Hib, given at 2, 4, 6, and 18 months of age, and then DTaP-IPV at 4-6 years. Universal Tdap adolescent immunization has been done since autumn of 2003 and achieved 95% coverage in the first year.

Study design. Any child could get the vaccination in the school system. Exclusions to the study involved any known or suspected allergy, planned receipt of any other vaccine within the 14 days after administration of Adacel,™ and the cohort that had already received Adacel.™ The hypothesis was that injection site reactions and fever in individuals given Adacel™ 2-9 years after a previous DT-containing vaccine would be noninferior to rates in a control group immunized after a ≥10 year interval. Proof would be the difference in rates, which were ≤10% for injection site reactions and 5% for fever, within the 95th CI. The comparison was to Pentacel™, the Canadian name for Adacel.™ This was an open label, nonrandomized, province-wide study that offered a single dose of Adacel™ to all participants, and adverse event collection was via diary or Web entry for days 0-3, 4-14, and 15-28 after immunization.

Preliminary data on adverse events showed more common injection site reactions with decreasing interval, but the vaccine was still well tolerated. Redness and swelling appeared to be related to a prior dose of acellular pertussis vaccine, while pain appeared to be related to the recent Td vaccine. Fever was infrequent and unrelated to the interval since the prior immunization. Serious adverse events, including arthus reactions, were not observed in any frequency related to the vaccine in the study.

Conclusion: The Tdap Adacel™ vaccine was well tolerated by adolescents who were immunized after intervals of ≥2-10 years since previous vaccination with a diphtheria/tetanus- or diphtheria/tetanus/pertussis-containing vaccine. There was only a modest increase in injection site events with decreasing intervals since a previous immunization. Adacel™ can be used safely when administered in intervals ≥2 years (i.e., 18 months to 2.5 years) since receiving a previous diphtheria/tetanus-containing vaccine.

Discussion included clarification that decisions on using the 10-year minimum interval will be local, until the Canadian National Advisory Committee on Immunization reviews the data.

Cost Implications of Pertussis Vaccination
Presenter: Dr. Tracey Lieu

Overview: Dynamic modeling of the health benefits and costs of adolescent & adult pertussis vaccination in the U.S., jointly conducted by Harvard Pilgrim Health Care and Harvard Medical School, the Massachusetts Department of Public Health, and CDC, in the Joint Initiative in Vaccine Economics Project

Analysis assumptions: Pertussis in adolescents and adults is increasing and is costly. Pertussis vaccination of adolescents is an effective strategy that is likely to be beneficial and relatively cost-effective. However, the results depend greatly on pertussis incidence and vaccine cost. The risks should be weighed. Since pertussis immunity wanes, boosters may be required, and the vaccine price is as yet unknown. Achieving vaccine coverage can be a challenge, even more so for adults than adolescents, so the best strategy for vaccine use should be chosen. To best create that strategy, better data on pertussis incidence is needed.

Possible programmatic strategies include: 1) vaccinating during adolescence at ~12 years of age; 2) vaccinating adolescents and providing boosters every 10 years thereafter; 3) vaccinating young adults ~20 years of age; 4) vaccinating young adults and providing boosters every 10 years thereafter.

Analysis/model. The analysis addressed three questions: 1) Do the health benefits of vaccination outweigh the vaccine risks?; 2) will vaccination save money?; and, 3) if it does not save money, will it be cost-effective, relative to other health interventions? The dynamic model used puts hypothetical groups of people through a framework from being susceptible, to infected, to having natural immunity which wanes. Some will be vaccinated and receive immunity, which also wanes. Different age groups such as infants, adolescents, and adults are assumed to have different characteristics, and they mix with one another at varying rates.

Health benefits. A dynamic model utilized by a study led by Van Rie and Hethcote (*Vaccine,* 2004) indicated that a 75% vaccine coverage among adolescents will not simply shift the disease

to older age groups, thereby increasing infant disease. Rather, they found that vaccinating adolescents reduced overall pertussis burden by 13% and reduced infant pertussis 17%. Adding 10-year boosters would improve those numbers by 30% and 35%, respectively. A strategy of simply "cocooning" (i.e., vaccinating contacts) would reduce the burden by only 9%, but would reduce infant disease by 70%. A recent NIP analysis reached similar conclusions.

Economic benefits. From that, the next question relates to interventions' cost effectiveness (CE). "cost effective" does not equate to "cost savings." While the latter is optimal, almost all U.S. health services are not so; they improve health outcomes, but they also increase net costs. The exception is immunizations, which are often cost saving as well as cost effective. To illustrate this, the Lee et al study for the Joint Initiative (publication pending, *Pediatrics)* was presented and then compared to that of Purdy and Ward (*CID,* 2004) and Iskedjian (*Vaccin*e, 2004).

A decision tree of the computerized decision analysis model illustrated possible vaccination strategies versus no vaccination, in which pertussis happens (or does not) in any given year. The disease outcomes in adolescents or adults could be mild or severe cough illness or pneumonia; for infants, respiratory or neurologic sequelae, or, rarely, death. The population probably will not be 100% vaccinated; those who are could have no reaction, or a reaction that is local, or systemic or, rarely, anaphylactic.

Data sources were, 1) for incidence: Massachusetts enhanced surveillance system (incidence among adolescents of 155/100,000and 11/100,000 for adults, with post-pertussis pneumonia rates of 1% and 3%, respectively; 2) national vaccine coverage data; 3) adverse events, the literature and expert opinion; and 4) cost of pertussis cases: Harvard studies of Massachusetts enhanced surveillance data. For these, adult costs were higher than those of adolescent cases (medical costs and work loss). *Assumptions* included a VE of 87% in year one that wanes to zero over the next 15 years, and a pertussis vaccine incorporated with Td for both adolescents and adults, that adds $15 to the price per dose.

Outcomes measured were pertussis cases prevented; cost of vaccine adverse events; total cost; life years saved; quality adjusted life years saved (QALY). Dollars per QALY was the primary CE measure. One quality-adjusted life year could equate to one year of perfect health; illness reduces QALYs. This suited a pertussis vaccination analysis because: 1) QALYs allow value to be assigned for prevented morbidity in adolescents and adults; mortality is generally among infants; 2) QALYs allow valuation and measurement of vaccine reactions prevented; and 3) QALYs are standardized measures allowing comparison of pertussis vaccination's CE to other vaccines and preventive services.

The time-tradeoff method was used to determine how many QALYs a case of pertussis is worth. Adults in Massachusetts who had had pertussis (or an adolescent with pertussis) were asked, hypothetically, the number of days or weeks of their life they would trade to avoid a particular illness scenario (e.g., severe cough for weeks). The answer to that one was 90-100 days at some point before the end of life.

Strategies on which to base the analyses were refined to two:

1. Vaccinating adolescents once, to prevent 31,000 cases of pertussis (36% of potential cases without vaccination). The modeled vaccination program costs were ~ $44 million, which was offset in part by the savings from prevented pertussis of $11 million.

2. Vaccinating in adolescence and boosting every ten years through adulthood would prevent 40% percent of all potential cases. This would cost $74 million and would save only $12 million in prevented pertussis.

Clearly, adolescent vaccination was the most cost-effective strategy in terms of cases prevented and QALYs saved, at $1100 per case prevented and $20,000 per QALY saved. Beginning immunization in adulthood was less effective due to lower incidence, and might in fact be cost-productive due to the effects of possible vaccine adverse events. A chart was shared of annual benefits for the U.S., assuming no change in infant transmission. No vaccination would result in 85,000 cases per year. One vaccination of adults, or vaccination of adults every ten years wound up producing *negative* QALYs when cost was considered with cases prevented, while vaccination of adolescents alone or in concert with adults produced QALYs saved >1600. Another chart showed similar results in terms of savings per pertussis case prevented, with adolescent and adolescent/adult benefits an order of magnitude higher than adults alone.

Comparison to other vaccines/preventive services. These CE results for adolescent vaccination were compared to other vaccines and charted. Varicella (one dose) and hepatitis B vaccination are cost saving per case prevented and QALY. Per case prevented, pneumococcal conjugate vaccine costs $200, and $4700 per QALY or life year saved. Pertussis does better in terms of cases prevented, at $1100/case, but worse in QALYs saved, at $20,000. Meningococcal conjugate vaccine costs $61,000 and $92,000, respectively.

When compared to other preventive health services, the cost of vaccination fares well. "Reasonable" CE is generally accepted as ≤$50, less per QALY saved (some say $100,000). From a societal perspective, pertussis vaccination's cost of $20,000 per QALY saved is well below the benchmark, and more CE than, for example, HPV testing with Pap smears ($80,000/QALY saved).

Sensitivity analyses were done in which key assumptions were estimated over plausible ranges to see if the findings would change.

- Base-case analysis. This did not assume that adolescent or adult vaccination would prevent any disease in infants. The results indicated that, with a low vaccination cost ($15/dose) and double the pertussis incidence as first assumed, adolescent vaccination could be cost-saving. If the cost is higher or disease incidence is close to the Massachusetts data, it could be cost-effective but not cost-saving.
- An alternative analysis assumed the prevention of some percentage of infant disease and the results of Van Rie's model. The added infant benefits improved the desirability of the adolescent strategy, but the results changed little. They were very sensitive to pertussis incidence as well as vaccine costs.
- A two-way sensitivity analysis raised the incidence rate and the cost of vaccination. Adolescent vaccination was still fairly CE, with a dose cost of $25. Raising disease incidence can make adolescent vaccination cost saving, but would require at least a two- to five-fold increase, and the vaccination cost would have to be <$15.

Comparison to other studies was done with the Purdy et al study, which used far higher incidence rates for adults from the APERT study as well as higher costs. His findings paralleled those of this study in indicating adolescent vaccination as the most attractive option and adult vaccination somewhat less so. The study by Iskedjian in Canada used five-fold higher incidence

rates and a lower vaccine cost. It suggested that adolescent vaccination would lead to cost savings for society, although not for the health care system.

Conclusions. Pertussis vaccination of adolescents is an effective strategy. It is likely to be relatively cost effective compared with other strategies, vaccines, and preventive health services, although the results depend a great deal on pertussis incidence and vaccine cost. Continuing studies of pertussis epidemiology are needed.

Discussion included:

- Dr. Baker encouraged analysis of approaches for infants aged <6 months who cannot have the primary series. One strategy is to immunize pregnant women to prevent mortality in that age cohort. The diagnostics seems to be better for young infants and the case fatality rate is high.
- There was confusion about the difference between direct and indirect costs. Most of the savings with pertussis are in indirect costs, which are lower than those of many other diseases. But traditionally, ACIP has taken a societal perspective and included in its analyses the cost of work lost by parents. There is some question if the future productivity costs of an infant who dies of a disease should be included, as that could entail double counting in both the denominator and numerator. The Ward et al study included those productivity costs because it was a cost-benefit analysis, while this study was a cost-effectiveness analysis.
- Dr. Plotkin reported a data review by a group of pertussis experts. This will be published in summary in *Clinical Infectious Diseases* and in detail in *Pediatric Infectious Diseases.* They calculated that the cost per life year gained could be as low as $6000 or as high as $22,000. But they cited the effect of vaccination on herd immunity as a critical factor that, by reducing incidence in other age groups, would greatly increase its public health value.
- Dr. Cherry found the 30% immunization coverage rate for adults to be reasonable, but critical to raise to be successful in eliminating both flu and pertussis. Immunizing adults at a reasonable rate should equalize the CE between adolescents and adults. A focus on any one sector, even adolescents, will not succeed; the problem has to be addressed holistically.
- *With the uncertainty expressed in earlier presentations about incidence, what effect would only 50% of that used in this analysis have?* That was done and of course lessened the attractiveness of the vaccination program. It did not exceed $50,000/QALY saved.

Physicians' Perspective of a Pertussis Vaccination Program
Presenter: Dr. Karen Broder, NIP

Overview: Report on an NIP national survey conducted with the University of Michigan, of U.S. physicians' willingness to accept the Tdap recommendation under discussion.

A survey was done to explore physicians' current Td vaccination practices, and their beliefs about adolescent Tdap and pertussis. Specifically, their willingness was explore to replace Td in the routine 11-12 year-old immunization, to catch up adolescents aged 13-18 who missed their Td dose, and to vaccinate adolescents with Tdap who already received a Td booster >5 years earlier (the "first-opportunity" strategy). Initially, the latter would add a vaccination at age ~16-18 years. Estimates of adolescent Td coverage range widely, from 33% (NHIS data based on

vaccination cards) to 97% (Florida review of school immunization certificates). Regional variation in Td coverage is likely.

The one-page survey was sent with a fact sheet about pertussis to ~300 pediatricians (57% response rate) and 300 family physicians (55% response rate) who are AMA members. They provide outpatient primary care to at least one adolescent patient per week in private, independent office settings. Half the pediatricians saw ≥10 patients/ week. The preliminary data indicated that:

- Most pediatricians (83%) and family physicians (79%) vaccinate adolescents with Td as part of routine practice. Pediatricians were more likely to vaccinate at the recommended 11-12 year-old visit, but both they and family physicians were equally likely to vaccinate during the 13-18 year-old visit. This suggests that family physicians might still be vaccinating at the 14- to 16-year age group, the ACIP recommendation until 1996.
- The major barriers to Td vaccination were listed as a lack of patient visits by 40% of pediatricians and almost half of family physicians. Family physicians were significantly more likely to report barriers, including reimbursement, than pediatricians
- Of both groups, <25% disagreed that pertussis is "a serious enough disease" to warrant administering Tdap rather than Td to adolescents. However, 70% of pediatricians would use Tdap in place of Td; only 42% of family physicians would, and the other 38% were neutral.
- The physicians were asked how they felt about new adolescent vaccine recommendations in general and how they should be structured: 1) with all vaccine consolidated at a single age group; or 2) each vaccine targeted to specific ages based on disease incidence. There was a slight preference to consolidate vaccinations by age group. But the preferred age was not indicated and, as seen earlier, the two groups may prefer to vaccinate at different age groups.

A meningococcal survey also was sent to a different group of physicians during the same time period, with a >55% response rate. The results were as follow:

- Pediatricians were more likely to report that most (63%) of their patients have an 11-12 year-old preventive visit than older adolescent preventive care visits. Family physicians reported that for the 11-12 (35%) and 14-15 (27%) year-old visits.
- Both groups agreed that there are less adolescent (17-18) preventive visits than those of the other age groups; ≤30% of the physicians reported seeing that group.
- Both reported Td coverage at age 11-18 years, by 84% of the pediatricians and 59% of the family practitioners.

Conclusions. These data suggest that: 1) physicians will likely accept routine adolescent Tdap vaccination instead of Td at 11 to 12 years of age; 2) routine Tdap vaccination for older adolescents who received Td more than five years earlier might pose challenges due to lack of preventive care visits by the 17-18 year-old age group; and 3) adolescent Tdap vaccination practices will likely differ between pediatricians and family physicians.

Potential Strategies to Reduce U.S. Adolescents' Pertussis Morbidity
Presenter: Dr. Trudy Murphy, NIP

Overview: Possible strategies for Tdap vaccination; further information needed for a decision in June.

The Pertussis Workgroup preferred an initial use of Tdap in adolescents before addressing adults, due to the high rates of endemic pertussis and substantial morbidity among adolescents, as well as a potential secondary benefit of reducing the total burden of disease and the cost of endemic and epidemic pertussis. Possible strategies included:

1. Routine use of Tdap at age 11-12 years, substituting Tdap at for Td, and catching up Tdap at age 13-18 years for a missed Td dose or a missed Tdap dose age 11-12. This was the Workgroup's preference. The primary objective was to reduce morbidity from pertussis in adolescents, which provides the following advantages:
    a. conveying individual protection against pertussis, simplicity, in that it simply substitutes Tdap for Td on the familiar schedule
    b. there is an established well visit for children aged 11-12 years and catch-up for those 13-18
    c. eventual protection against school outbreaks;
    d. some states already have Td laws that couldn't be modified;
    e. This is expected to eventually reduce some of the total burden of disease.

    However, the disadvantages include:
    a. older adolescents would not have very high coverage;
    b. initial impact on school outbreaks would be limited;
    c. little anticipated benefits for infants;
    d. a potential shift in age of peak disease to the childbearing years. (There are few data on this, but the model makes it seem unlikely).
    e. unknown initial impact through herd immunity since the level of coverage needed for that is unknown, as are the dynamics necessary.

2. Increase the number of adolescents who are protected against pertussis. The advantages to this would be to protect more, older, adolescents, and increase the potential impact on school outbreaks. The disadvantages include the added injection and cost for some older adolescents, a potential (but perhaps unlikely) increase in the risk of adverse events, and issues of record-keeping to know when the last Td was given.

3. Conduct Tdap vaccination campaigns or recalls to vaccinate older adolescents at the first opportunity, assuming an interval >5 years from the last Td shot. The latter is a point of discussion. The advantages include more rapid reduction in the pertussis morbidity among adolescents and possible increased benefits in the community. Related issues include feasibility (the lead to conduct the campaigns, venues at which to do them; cost),

Other considerations not yet addressed in detail include the use of Tdap for wound management; the minimum interval from the last Td; Tdap for the primary or booster immunization during pregnancy (a safety issue); and Tdap for primary immunization of children ≥7 years of age who may not have an immunization history for diphtheria, tetanus, and pertussis.

Discussion included:

- Information is needed of any available data (e.g., the European experiences with similar vaccines) to inform the issue of vaccine dose administered in pregnancy, as pregnant

women are a high risk group. Pregnancy was an exclusion in the prelicensure trials, although some women became pregnant thereafter. There are no data on this, and that is an important knowledge gap to fill.

- Data on postpartum or targeted immunization of the family is hoped to be ready to present in June. Also hoped to be presented then, or in October, are data on other options, such as vaccination of those with cardiovascular or pulmonary disease, similar to those for PCV; and data hoped to soon be released from ~3 studies of pertussis immunization in newborns. It may be possible to piggyback the adult immunization process onto the upcoming recommendations for influenza and PCV.
- There are data on 60 peripregnancy immunizations, 20 within 14 days, and no problems reported from any of them. Dr. Decker reported similar experience in his studies of at least 12 women who were vaccinated unaware that they were pregnant, and who had no adverse effect. However, again, there are few data on this.
- Dr. Murphy agreed to provide information for the ACIP's consideration of any concomitant vaccine combinations might be given at the age 11-12 and catch-up visits. Special situations like health care worker issues also will be reported.
- There are no data on college students, and this is an enormous issue on campuses. It is hoped that the adolescent data will help to address that.
- Dr. Marcuse believed that the seriousness of pertussis is not widely appreciated in the field. Until such data as Massachusetts' is made "real", even a pertussis campaign is unlikely to be successful.
- Dr. Birkhead drew a parallel between pertussis and the meningococcal vaccination discussion, to catch up adolescents and college students.
- Although it makes sense that, as soon as Tdap is shown to be safe, immunogenic and effective in any age group, the Td would be dropped, Dr. Chen also cautioned that several years had to pass before Td itself was recommended.
- Dr. Marcuse added that, since pertussis vaccine has not been given to children aged <7 before, this would not be a simple substitution; it will require an educational effort.
- Dr. DeSerres suggested that, depending on the epidemiology, administering Tdap vaccine at age 14 years may be even more effective, given the little knowledge about the acellular vaccines given as a booster dose before school entry.
- Dr. Middleman reported a 2004 survey by SAM of parents of adolescents. They found that only about 25% could name only one symptom of pertussis and about 85% did not know that the vaccine's immunity wanes. Parents will need a lot of information.
- Dr. Marcuse advised, in the baseline period, also collecting data on what the public thinks about pertussis and pertussis immunization, before launching the vaccine or a vaccination campaign out. That should include benefits and risks.

Dr. Murphy summarized her understanding of what ACIP wanted: new information on pregnancy and how to protect the newborn, separate from the adolescent dose; additional information on combination vaccine administration; how to address the huge gap in educating the public; subset populations needing attention, such as college students; and education extending to wound management and other settings where health care practitioners think of tetanus, but not pertussis. Education is also needed on Tdap should *not* be given, and the best age period in which to give it.

Evidence-Based ACIP Recommendations
Presenter: Dr. Dan Fishbein

Overview: Rationale for and proposal of an analytic framework with which to craft evidence-based recommendations for ACIP approval.

The purpose of issuing recommendations based on evidence is to ensure that the process of their development and the evidence base is transparent; that they are complete, based on individual, public health and economic outcomes; consistent over time and across ACIP recommendations; and compatible with the evidence-based recommendations of CDC's partners.

To achieve systematic review and aid the prioritization of considerations, an analytic framework is used, which examines three aspects relevant to the recommendations: 1) individual health outcomes, 2) public health outcomes and 3) economic evaluation.

An analytic framework mapping the components to be considered for a recommendation on the individual health outcome aspects of vaccination was shared. Each step of the framework considers the quality and consistency of both individual studies and over all the studies, leading to the recommendation. The quality of evidence is rated from the strongest and highest quality (1) to the weakest (5). The delineation of the quality of research designs is generally as follows, with the letter assignations indicating the strength of the research design:

1A. Systematic review of randomized controlled trials (RCTs)
1B Individual RCT (with narrow confidence intervals (C.I.)
1C All or none

…. The list proceeds down to:

5. Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

There is some flexibility possible to assign strength to a study that is not, an RCT; for example, something generally accepted as historically and clearly effective, but without RCTs.

Once an intervention's effectiveness has been demonstrated, "benefits" and "harms" are identified. Those were translated on this framework to "positive and negative externalities" to refer to the public health benefits and harms. These "externalities" generally pertain to economic analysis, but are used more broadly here to avoid the inference of "harms," when associated with vaccines, such as side effects.

Positive externalities offer potentially favorable outcomes to society beyond those protecting the individuals (e.g., interrupting disease transmission, herd immunity, etc.) Negative externalities are potentially unfavorable outcomes to the society beyond the adverse events experienced by the individual (e.g., vaccine-associated paralytic polio), or the potential interference of one vaccine or new recommendation on another (e.g., crowding the routine schedule).

Then, the issues of feasibility and implementation are considered (e.g., again, the crowded schedule), and the finally, the economic analysis, which also distinguishes the benefits/harms to the individual and public health (e.g., herd immunity for pertussis vaccine). The economic analysis also rates the quality of the evidence.

Finally, the overall recommendation emerges from the synthesized evidence of individual and public health benefits, cost, and feasibility of implementation. Those overall recommendation are generally presented in a letter-grade system such as used in school, from the strongest (A) to (D), Poor, and I (Insufficient evidence). Subgroups can be created for any of these categories to ensure the maximum usefulness and transparency. For vaccination, these would translate to:

A Vaccination is recommended for the target group, however defined.
B Vaccination is considered an option
C No recommendation for or against vaccination.
D Vaccination is not recommended (e.g., not licensed for an age group, or other contraindications such as for persons with known egg allergy not taking egg-cultured vaccine).
I Insufficient evidence

The committee was asked to direct its comments on this framework to Ms. Megan Lindley (MLindley@cdc.gov) to be conveyed to the Evidence Based Workgroup's attention.

Discussion included:

- Dr. Scalettar stated the AAHP's appreciation of this plan. The more credibility and transparency, the better. Such recommendations are essential to facilitate evidence-based benefit design, and they will prove the value of immunizations.
- *When a recommendation is made, will there be evidence ratings for individual components, as well as overall, published?* It will be up to the ACIP to decide if they will be separated and/or combined into an overall letter grade, as well as how much the committee wants the consistency of the evidence to affect the rating decision. Each new statement could have a table rating the research design quality, one for the economic analysis quality, and another with the overall recommendation. Once the ACIP approves the overall framework, the Workgroup will return with specific examples. An example could be provided using a present recommendation or a new one being developed.
- A rating can be changed in future, just as the statements are now updated or changed with new information.
- Still to be determined is how to address the varying range, for example, of large and small public health impacts, and those in between. That may have to be done on a case-by-case basis. Dr. Lieu appreciated the framework, its intent and many of the steps, but agreed with concerns about trying to quantify the magnitude of the benefit. She suggested unlinking the two steps, as rating the strength of the evidence will require extended staff resources, and quantifying the benefit will be very difficult and will require value judgments. The U.S. Preventive Services Task Force has been doing such ratings for years and found it to be very difficult even from just an individual perspective, let alone a public health perspective. She questioned if the letter ratings needed to be tied to the magnitude of the benefit, and agreed to discuss this off-line.
- Dr. Chapman requested the ACIP's judgment about testing this analytic framework, which depends in part on resources and staff available to apply the necessary time and effort. She welcomed the help of anyone interested.
- Dr. Levin urged that the ratings remain as simple as possible so as to not confuse the intended audience further.
- Dr. Tan explained the Workgroup's main intent to keep the recommendation development process transparent. For areas where there is insufficient evidence, ACIP is

the expert group that can advance its expert opinion, if necessary, that an intervention will have an impact, being clear that there is no empiric data to indicate that. The recommendation will acknowledge where the strengths and weaknesses are.

Dr. Levin summarized the ACIP's consensus for the CDC to proceed with a pilot program to use this evidence-based framework.

Update on Yellow Fever Vaccine Safety
Presenter: Rachel Barwick Eidex, PhD, for the Yellow Fever Vaccine Safety Workgroup (not an ACIP Workgroup)

Overview: Update on sequelae of vaccination against yellow fever.

Since 1996, VAERS has received reports of yellow fever vaccine-associated viscerotropic disease and neurologic disease after vaccination. Vaccine-associated viscerotropic disease is a potentially fatal adverse event. There were no cases in the U.S. since the mid-1960s until two cases appeared in both 2001 and 2002. ACIP recommended enhanced surveillance and establishment of the Yellow Fever Vaccine Safety Work Group, both of which were effected. The ACIP yellow fever vaccine recommendations were updated in 2002 and identified advanced age as a potential risk factor for both of these adverse events.

Using VAERS data as the numerator and the number of doses sold by Sanofi Pasteur (the sole U.S. manufacturer) as the denominator, data were charted showing an overall risk for yellow fever vaccine-associated viscerotropic disease at 3 cases per million doses sold in the U.S., and 4/1 million doses for neurologic disease.

Two risk factors were reported: elevate risk for those aged >60 years (~15-20 cases/million doses sold) and a history of thymus disease. Details of the cases were outlined. Four of the 28 (14%) related cases reported globally of viscerotropic disease after yellow fever vaccination had a history of thymus disease. That rate greatly exceeds the 1% expected rate of thymoma in the general population. While thymus disease history may be a confounder with age, CDC urged that these risk factors be treated independently when a health care provider is assessing a person for vaccination.

The Workgroup meets monthly. Enhanced surveillance continues, with a CISA protocol in place to help obtain or collect samples and analyze them. The Workgroup is also developing, and hopes to put through the Brighton Collaboration process, standardized case definitions for yellow fever vaccine-associated viscerotropic disease and yellow fever vaccine-associated neurologic disease.

The cases identified to date under this neurologic umbrella have revealed three distinct syndromes: 1) viscerotropic disease which presents as an encephalitis, 2) autoimmune disorder with peripheral nervous system involvement, which generally presents as Guillain-Barre Syndrome; and 3) autoimmune disorder with CNS involvement, which generally presents as acute disseminated encephalomyelitis.

A subgroup also meets once a month to review VAERS report of adverse events after yellow fever vaccine. The members classify them according to the case definitions, identify research

gaps, and review protocols. Ten cases, and perhaps an eleventh, of yellow fever vaccine-associated viscerotropic disease have been reported in the U.S., two with a history of thymectomy. The case fatality rate is high, at ~60%. Brazil, which has active surveillance during mass vaccination campaigns, has identified eight cases. One in particular, in 1975, was the first recognized case of vaccine-related viscerotropic disease. Other countries with cases were listed with the same case fatality rate as that in the U.S.

Another listing was shown of the 14 cases identified in the U.S. of yellow fever vaccine-associated neurologic disease. The cases include both the neurotropic peripheral nervous system and CNS involvement. The neurologic disease had a longer period (3 weeks) of days to onset than did the viscerotropic disease (~1 week). And, although it can be fatal, none of these 14 cases were.

Among the research needed is surveillance. A pilot program has been proposed using Telewatch, the system proposed for smallpox surveillance, to do active surveillance for adverse events after yellow fever vaccine. Also proposed has been to use VSD and Air Force data to retrospectively follow a cohort for such adverse events.

Wild-type disease surveillance remains a challenge. CDC will continue to warn providers of the risk factors identified so that they can weigh the vaccine's risk against that of the disease. A Web-based yellow fever vaccine provider registry was created that is on CDC's Traveler's Health Website. A protocol is also being finalized to compare healthy primary vaccinees, who receive yellow fever vaccine alone, to those who receiving it in combination with immune globulin, to see if the IG inhibits viremia without inhibiting the immune response.

Remaining challenges include identification and specimen collection. Clarification of ACIP yellow fever vaccine recommendations is needed to ensure that their misinterpretation does not prevent researchers from getting the vaccine. ACIP's concurrence on that would be helpful. Workgroup publications issued include a Yellow Fever Vaccine Information Sheet, chapters and journal articles and reports.

Discussion included note of a problem encountered by Acambis, which wished to use it for a placebo group. That required an FDA IND, but FDA felt the vaccine may be too risky for that use. ACIP's statement advises against giving it to people not at risk of wild type disease. That advice is a legitimate role, but advising on what should be on an IND, or on vaccine use in studies, is not. Great caution is needed in commenting on such areas. Dr. Baylor agreed to follow up on this particular case.

Update on Polio Outbreak Response
Presenter: Dr. James Alexander, NIP

Remarkable success has been made world-wide toward polio eradication, but it has spread in African and Southern Asia in the last 2-3 years. Decreased geographic distribution of virus, fewer cases, and decreased virus diversity, came with the elimination of Serotype 2 in 1999. Intensified polio eradication activities in the endemic countries of Egypt, Afghanistan, Pakistan, and India also reduced cases and increased the focal distribution of wild polio. However, Nigeria's internal troubles resulted in the suspension of oral polio vaccination from mid-2003

until mid-2004. That caused a big outbreak in Nigeria and Niger, which then spread Types 1 and 3 to other countries, some of which now again have internal ongoing transmission.

Wild virus is again circulating internally in India, in the provinces of Utar Pradesh and Bihar, as well as in Pakistan's provinces of Sind and Gujrat. Egypt and India have increased the intensity of vaccination and surveillance. They are planning immunization campaigns that will use the monovalent OPV Type 1, to take advantage of its greater immunogenicity and boosting effect.

Despite these setbacks, polio eradication is advancing. Wild virus transmission is hoped to be halted in 12-18 months. But once eradicated, polio risks remain from the continued use of OPV. That risks the renewal of polio from vaccine-associated cases (cVDPV), and immune-deficient persons who excrete wild virus may contribute to ongoing transmission. The second category is the mishandling of the wild polioviruses, either in diagnostic labs or in vaccine facilities. Revertant vaccine poliovirus is rarely seen, but does occur, and it is a potential problem in the post-eradication era.

In view of these risks, WHO and its partners decided that OPV use must stop and cannot be used for routine eradication in the post-eradication era. That has to occur at a very critical time, when population immunity from the mass campaigns and high routine immunization coverage is still high, and surveillance sensitivity is also high. The key prerequisites to ending OPV use are: containment of all polioviruses, including at vaccine production facilities, diagnostic labs, and clinical samples that might contain them; global surveillance and notification capacity to rapidly detect and respond to cases and outbreaks; a polio vaccine stockpile (most likely, monovalent OPV [mOPV] as the primary vaccine), and coordinated cessation of OPV over a one-year period. Since most of the world currently uses OPV, this is a breathtaking challenge to change immunization practice.

One component of this preparedness for the post-eradication, post-OPV cessation period is to establish a stockpile of monovalent OPV, for which licensure is pending. That will be used to complete eradication in Egypt, India, and elsewhere, and will be the principal stockpile vaccine.

However, as interest grows among manufacturers in the developing world to produce IPV, the risk exists of wild polioviruses replication in inappropriate manufacturing facilities. The use of Sabin stocks as starter for IPV could resolve that, to facilitate containment of wild polioviruses and to use for outbreak control in a ring vaccination strategy. Sabin strains in IPV also could be a basis for restarting OPV production if necessary.

There is no currently licensed, effective antiviral drug for poliovirus. Research and development are needed. Such a product could have multiple uses (e.g., to clear chronic excretion in the immunodeficient, for postexposure prophylaxis of persons during an outbreak, or as part of the ring vaccination strategy). A time line was shared of the likely post-eradication events to address an undetected wild poliovirus outbreak, which would probably happen shortly after eradication.

U.S transition to IPV. The U.S. has eliminated both indigenous and imported wild polio. However, the use of OPV has caused cases of vaccine associated paralytic polio (VAPP) by ~9 cases/year. That risk was accepted for many years, since OPV provided both visceral and humoral immunity. The rapid decline of polio cases with OPV use in the 1960s was charted, with the related VAPP cases. The latter predominated by the 1980s and, with the progress of the

global program in the 1990s and lower risk of imported wild polio, OPV's benefit-risk ratio changed. With a move to a sequential IPV/OPV schedule and then and all-IPV schedule, the last VAPP cases occurred in 1999. High vaccination coverage has been maintained, as has high sero immunity to all three poliovirus types. The risk remaining in the U.S. comes primarily from imported wild virus, most likely a risk to under-vaccinated children in urban areas and vaccine decliners in religious groups.

Stockpile. In 2004, NVAC recommended acquisition of ~8 million doses of IPV for use either alone or with OPV for outbreak control. They also noted the need for a licensed and uncombined IPV. Funding has been allocated and contracts signed to do that, but <4 million doses are actually stored to date. That is due to financial disincentives to the manufacturers to have an uncombined product versus rather than a multiantigen one, and financial disincentives to have a vaccine not in rotation. Work to further develop the stockpile is ongoing, through the pediatric vaccine stockpile mechanism and other options.

With ACIP's expressed preference for mOPV for outbreak use, a draft IND was prepared. Regulatory options will be discussed with FDA, as work will continue with WHO and manufacturers on the monovalent product in the licensure process.

The committee's opinion was asked if, in the short interim, work on a trivalent OPV (tOPV) should be done, or if work should continue on an mOPV stockpile.

CDC and WHO staff have been collaborating on stockpile and outbreak response issues, and CDC continues to work with FDA on the regulatory issues. CDC will continue to support WHO's efforts to license mOPV and to develop that stockpile, to evaluate the utility of Sabin IPV, and to assess the potential use of antiviral drugs and work with WHO to determine the appropriate global stockpile size, the composition, and its regulation. CDC thinks the Sabin IPV product has real potential, but its efficacy and safety still need evaluation. Work continues to license an antiviral drug with WHO and the NAS; the ACIP's thoughts on that will be welcomed as well.

Finally, CDC has developed a draft polio outbreak response plan, which will be developed with ASTHO, CSTE, NACCHO, and others.

Conclusion. The U.S. stockpile is not ready in either composition, size or use. The IPV stockpile is affected by economic issues, which are being worked on. CDC is very interested to follow and work with its WHO colleagues on potential products. The OPV stockpile is still pending, but it seems that mOPV will be the direction to take without an intermediate trivalent product. The big issue is how to use an unlicensed product.

Discussion included:

- The current inactivated polio vaccine is made from wild viruses which grow vigorously, are killed, and whose antigenic mass is put into the inactivated vaccine. The Sabin strains are temperature-sensitive variants, and that sensitivity, the growth characteristics, and neurovirulence are quite linked. If not grown under the right conditions, reversion to neurovirulence could occur. Manufacture in inappropriate facilities could redistribute wild polio all over again.

- The mOPV referenced would be all three serotypes to handle any vaccine-strain related outbreaks.
- The WHO is pondering how to maintain the needed skills for an OPV stockpile, such as batch and neurovirulence testing and who will maintain the required monkey colonies. However, alternative neurovirulence tests to correlate them with monkey neurovirulence are being sought now. FDA is involved in this as well.
- Dr. Clem Lewin, of Chiron, the OPV manufacturer, stated Chiron's willingness to supply it through OPV cessation, but manufacture of the product after that is an open question. Dr. Alexander cited, as part of the planning difficult, the need to ensure supply before OPV cessation, in a bulk form that is storable at -20ºF for a very long time, because it will not be able to be replenished.

There was some further discussion, given that the joint ACIP/NVAC Polio Eradication Workgroup had been disbanded, of who would be making such decisions as pursuing the mOPV or tOPV. Dr. Cochi cited the existing de facto stockpile of trivalent OPV managed and overseen by WHO and reported that discussion of long-term future issues are proceeding. There is no longer a joint workgroup, but NIP wished to keep the NVAC and the ACIP informed of the progress made. Dr. Marcuse thought these stages to be an NVAC issue, creating or addressing collaboration between industry and government for non-economically viable vaccines.

Dr. Mawle reported legislation pending to update Bioshield that is similar to that for pandemic influenza and bioterrorism vaccines. One issue that has arisen is the difficulty of using a vaccine under an IND. Bioshield has some provision for that and perhaps polio could be put under that. It may be that the ACIP/NVAC Workgroup should be reconstituted. Dr. Seward reported CDC's work on this with other agencies.

Dr. Levin summarized that the ACIP had been informed of the polio eradication campaign and the stockpile issues, and that ACIP held no opinions to the contrary of what had been told to the members.

Public Comment
Public comment was solicited, to no response.

Agency Updates
Agency updates had been distributed. Further comment was provided by the following:

VICP. Dr. Evans circulated charts of the status of the Trust Fund He reported that legislation passed after the last meeting created excise taxes for hepatitis A and trivalent hepatitis A vaccines, at 75 cents each. The trivalent vaccine was added retroactive to September 4, 2004. But for the influenza vaccine, Congress let the DHHS Secretary set a different date. That will be July 1, 2005, so that when this season's supply expires on June 30, there will be a clean break in terms of excise tax collection. The Department is considering that now; he expected to be able to report the final disposition in June. The ACCV also will discuss what industries should be added to the VIT for those vaccines at it next meeting in March, and probably the June meeting as well.

FDA. Dr. Baylor reported VRBPAC's next meeting to be on June 16-17 to decide the influenza vaccine strains for the coming season.

NCID. Dr. Mawle updated the committee on the rabies vaccine, which also encountered supply issues this year. When the last rabies recommendations were issued in 1999, there were 3 vaccines being produced. One manufacturer had contamination problems and dropped out of the market. The supply is probably satisfactory, but it is never certain how much post-exposure prophylaxis might be needed. There also are recommendations for PEP after bat exposures, which are now the #1 human exposure, and those recommendations need to be updated. She asked the ACIP to form a workgroup to update the rabies vaccine statement.

Dr. Levin planned to take that up at the next meeting, when new members will be seated who could staff that workgroup. With no further comment, the meeting then adjourned at 3:33 p.m.

Certification

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

Myron J. Levin, MD, Chair

Date

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
Patsy Stinchfield, NP
John J. Treanor, MD

Members absent were: Mr. John B. Salamone, Dr. Robin J. Womeodu

EX-OFFICIO MEMBERS

Centers for Disease Control and Prevention
Stephen L. Cochi, MD, MPH
Stephen C. Hadler, MD, Acting Executive Secretary
Alison Mawle, MD
Gina Mootrey, DO, MPH
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, and Amy Groom, Indian Health Service (IHS)
Barbara Mulach, MD (for Dr. George T. Curlin), National Institute for Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
Geoffrey S. Evans, MD, National Vaccine Injury Compensation Program (NVICP)
Bruce Gellin, MD, Director, National Vaccine Program Office (NVPO)
Linda Murphy, RN, Center for Medicare and Medicaid Services (CMS)
Kristin L. Nichol, MD, Department of Veterans' Affairs (DVA)
Stephen Phillips, LTC, DO, MPH, Department of Defense (DOD)

Liaison Representatives
Carol J. Baker, MD, and Margaret Rennels, MD, American Academy of Pediatrics (AAP), Committee on Infectious Diseases (COID)
Nancy Bennett, MD, MS, National Association of County and City Health Officials (NACCHO)
Damian A. Braga and Peter Paradiso, PhD, Pharmaceutical Research and Manufacturers of America (PHARMA)
Dennis A. Brooks, MD, MPH, National Medical Association (NMA)
Linda Murphy, RN, Centers for Medicare and Medicaid Services (CMS)

Stephan L. Foster, PharmD, American Pharmacists Association (ApharmA)
Stanley Gall, MD, American College of Obstetrics and Gynecology (ACOG)
Nancy Bennett, MD, MS, National Association of County and City Health Officers (NACCHO)
Samuel Katz, MD, Infectious Disease Society of America (IDSA)
Clement Lewin, PhD, MBA, Biotechnology Industry Organization (BIO)
W. Paul McKinney, MD, Association of Teachers of Preventive Medicine (ATPM)
Amy B. Middleman, MD, MPH, Society for Adolescent Medicine (SAM)
Kathleen M. Neuzil, MD, MPH, American College of Physicians (ACP)
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)

Laison representatives absent:
Richard. Clover, American Association of Family Physicians (AAFP)
Steve Gordon, MD, Hospital Infections Control and Prevention Advisory Committee (HICPAC)
Charles Helms, MD, National Vaccine Advisory Committee (NVAC)
Monica Naus, Canadian National Advisory Committee on Immunization
David A. Neumann, PhD, National Coalition for Adult Immunization (NCAI)

AGENCY STAFF

DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS)

Office of the DHHS Director: Julie Schafer

Centers for Disease Control and Prevention (CDC):

Office of the CDC Director: Kevin Malone, Office of General Counsel

Staff, no C/I/O identified:

Raine Alexander
Rachel Barwick
Rich Besser
Joseph Bresea
Traci Camilli
Scott Campbell
Richard Dixon
Kashif Iqbal
Thea Fischer
Demetria Gardner
Pauline Harvey
Rita Helfand
Julie Kanne
Mark Katz
Kristen Kenyan
Nicole Liddon
Eva Margolis
P. Nuorti
Mac Otten
Linda Quick
Umeshi Parashar
Brian Pascual
Christie Reed
Michelle Russell
Colin Shappard
Barbara Slede
Margarita Sniadack
Stephanie Steele
M.A. Widdowson

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

National Center for HIV, STD and TB Prevention: Eileen Dunn, Michael Greenberg, Dale Hu, Lauri Markowitz

National Center for Infectious Diseases (NCID):

Larry Ander
Stephen Benoit
Stephanie Bialek
Lynette Brammer
Martin Cetron
Mitch Cohen (CCID)
Rosamond Dewart
Keiji Fukuda
Roger Glass
Erin Goldman
Allison Greenspan
Eileen Lau
Anna M. Likos
Joe Perz
Alicia Postema
Catherine Rebmann
Elizabeth R. Unger
Susan Wang

National Imunization Program (NIP):

James P. Alexander
Carolyn Bridges
Karen Broder
Angela Calugar
Bob Chen
Susan Chu
Bo-Hyun Cho
Amanda Cohn
Margaret Cortese
Gayle Daniels
Gustavo Dayan
Chris Duggar
Rex Ellington
Gary Euler
Gabrielle Farler
Paul Gargiullo
Edith Gary
Jane Gidudu
John Glasser
Holly Groom
Dalya Guris
Penina Haber
Sonya Hutchins
Lisa Jacques
Archana Joshi
Katrina Kretsinger
Andrew Kroger
Laurie A. Johnson
Broch Lamont
Pengjun Le
Jessica Leung
Megan Lindley
Tasneem Malik
Stacey Martin
Mark Messonnier
Elaine Miller
Trudy Murphy
Rick Nelson
Carolyn O'Mara
Dennis O'Mara
Ismael Ortega-Sanchez
Bette Pollard
Vitali Pool
Krista Powell
Susan Reef
Lance Rodewald
Alison Rue
Tammy Santibanez
Jeanne Santoli
Judy Schmidt
Kris Sheedy
Tom Shimabukuro
Barbara Slade
Nicole Smith
Pamela Srviastava
Shannon Stokley
Peter Strebel
Ray Strikas
Tejpratap Tiwari
Ron Van Duyne
Donna Weaver
Bruce Weniger
Skip Wolfe
Surasak Youngpairo

National Immunization Hotline*:* Ada de la Vega

National Institutes for Health (NIH): National Institute for Allergies and Infectious Diseases (NIAID): Phil Brunell, David L. Klein

National Vaccine Program Office (NVPO): Kenneth J. Bart, Sarah Landry, Ben Schwartz

DEPARTMENT OF DEFENSE (DOD): John D. Grabenstein

FOOD AND DRUG ADMINISTRATION (FDA): Bob Ball, Milau S. Blake, Lucia Lee; Bruce Meade, Rosemary Tieman

MEMBERS OF THE PUBLIC OR PRESENTERS TO THE COMMITTEE:
Vincent Ahonkhai, GlaxoSmithKline (GSK)
Arthur Allen, Washington, D.C.
Jennifer Allen, Merck & Co, Inc.

Donna Ambrosino, Massachusetts Biological Laboratories
Kate Arnold, Georgia Division of Public Health
Phyllis Arthur, Merck Vaccine Division
Mark Bagonazzi, Merck
Lynn Bahta, Minnesota Department of Health
Eliav Barr, Merck Research Laboratories
K. Bash, Baxter
Joe Beaver, Tennessee Immunization Program
Candice Benn, National Meningitis Association (NMA)
Joan Benson, Merck & Co., Inc.
John W. Boslego, Merck
Andrew Bowser, Brooklyn, NY
Lynn Bozof, NMA
Carol Bryan, Sanofi Pasteur
Dirk Campens, Sanofi Pontave MSD, Belgium
Dan Casto, Merck
Jim Cherry, UCLA
Lenore Cooney, Cooney-Waters Groups, NYC, NY
Noreen Dahill, GSK
Lisa Danzig, MD, Chiron
Anna DeBlois, Association of State and Territorial Health Officers (ASTHO)
Michael Decker, Sanofi Pasteur
Gaston De Serres, Quebec Insitute of Public Health
Richard Dinovitz, Wyeth
Renee Dougherty, Merck
Gary Dubin, GSK
Mark Feinburg, Merck
Brian Ferguson, GSK
Betsy Frazer, AQAF, Birmingham, AL
Jeffrey Fu, Merck
Diane Gaffoglio, CCR, CVR-CN
Kathy Garrett, Merck Vaccines
Matt Garrett, Wyeth
Donna Gaskins, Georgia Immunization Program
Ruth Gilmore, Georgia Immunization Program
Greg Gilmet, Sanofi Pasteur
Cleveland Grady, Jr., GSK
Eric Greenbaum, Merck
Jesse Greene, South Caroline Department of Health
Jill Hackell, Wyeth
Scott Halperin, Dalhousie Universtiy
Neal Halsey, Johns Hopkins University, Baltimore, MD
Claire Hannan, Association of State and Territorial Health Officers (ASTHO)
Ann Harris, Sanofi Pasteur
Rick Haupt, Merck & Co., Inc.
Penny Heaton, Merck & Co., Inc.

Philip Hosbach, Sanofi Pasteur
Barbara Howe, GSK
Jeff Huckman, MedImmune, Inc.
Melonie Jackson, Georgia Chapter, AAP
Shirley Jankelevich, South Carolina Department of Health and Environmental Control
David R. Johnson, Sanofi Pasteur
Richard Judelsohn, Erie County Department of Health, NY
Karen Kessnick, Acambis
Saloh Kivlighn, Merck & co.
Julie Klim, Houston, TX
Rachel Knowlton, Sanofi Pasteur
Trisha Korioth, AAP`
A.N. Krishnaj, Chiron
Charlotte Kroft, GSK
Barbara Kuter, Merck
Fred Lake, NMA
Len Lavenda, Sanofi Pasteur
Susan Lett, Massachusetts Department of Pubilc Health
Christian Loucg, Acambis
Harold Lupton, Sanofi Pasteur
Lori Lush, JK Associates, Inc.
Raymond MacDougal, Sabin Vaccine Institute
Andrew MacKnight, GSK
Susan Malone, Chatham County Health Department
Patrick Maroney, Sanofi Pasteur
Jill Marette, Minnesota Department of Health
Susanna Matter, Leerink Swann, NYC, NY
Ed McCarthy, CNN Radio Network
Maryn McKenna, Atlanta Journal-Constitution
Anita Manning, USA Today
Michelle Marill, Hispital Employee Health
Christopher Meneely, Sanofi Pasteur
Jacqueline Miller, GSK
John Modlin, Vermont Department of Health
Marie Murray, Recorder, Atlanta, GA
John Neal, GlaxoSmithKline
Bridget Newberry, Merck Vaccine Division
Karen Nielsen, GSK
Paul Offit, Children's Hospital of Philadelphia
Jean-Marie Okwo-Bele, MD, WHO Office of Immunizations, Vaccines, and Biologics
Walter Orenstein, Emory University Vaccine Center
Will Page, GSK
Greg Parro, GSK
Olga Pasick, NMA
Richard Pasick, NMA
Diane C. Peterson, Immunization Action Coalition

Stanley Plotkin, MD, Sanofi Pasteur, Doylestown, PA
Geoff Porgess, Alliance Bernstein, NYC, NY
Jane Quinn, GSK
James R. Ransom, National Association of City and County Health Officers (NACCHO)
Judith Rusk, Infectious Diseases in Children
Lolita Robinson, MedImmune
Fred Ruben, Sanofi Pasteur
Debbi Saslow, American Cancer Society
Carlos Sattler, Merck Research Laboratories
Cathy Schmid, Chatham County Health Department
Florian Schödel, Merck
Anne Schuind, GSK
Jerry Shelton, Merck Vaccines Division
Judith Shindman, Sanofi Pasteur Ltd.
Janet Skidmore, Merck
Dr. Alan J. Sievert, AAP, East Metro Health District, Lawrenceville, GA
Eric Skjeveland, Merck & Co., Inc.
Ben Sloat, Georgia Division of Public Health
Mike Smith, Children's Hospital of Philadelphia
Parker Smith, PCS Photo for IMN
Matther Staley, Constella Group, Atlanta, GA
Brad Staller, Houston, TX
Nanette Stoback, Geneva, IL
J. Stoddard, MedImmune Vaccines
Stacy Stuerke, Merck Vaccine Division
Lamont Sweet, Prince Edward Island Department of Health
Michelle Tidwell, Georgia Chapter, AAP
Miriam E. Tucker, Elsevier
Thomas Vernon, Philadelphia, PA
Peter Vigliarolo, Cooney-Waters Groups, NYC, NY
Beth Ward, Georgia Division of Public Health
Joel Ward, UCLA
Martin Wasserman, GSK
Barbara Watson, MD, Division of Disease Control, Philadelphia, PA
Cole Weible, Dalrymple & Associates
Wayde Weston, GSK
Deborah Wexler, Immunization Action Coalition, St. Paul, MN
Celia Woodfill, California Department of Health Services
Carol Wu, Merck
Terry Yamanchi, University of Arkansas, Medical Sciences
Greg Yoder, Merck
Laura York, Wyeth
Daniel Yu, AP
John Zahradnik, Sanofi Pasteur