

CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICE

Records of the Meeting Held on

June 20-21, 2001

Atlanta Marriott North Central Hotel
Atlanta, Georgia

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ATTENDEES:

Committee Members

Dr. John Modlin, (Chair)
Dr. Dennis Brooks
Dr. Richard Clover
Dr. Jaime Deseda-Tous
Dr. Charles Helms
Dr. David Johnson
Dr. Myron Levin
Dr. Paul Offit
Dr. Margaret Rennels
Dr. Natalie Smith
Dr. Lucy Tompkins
Dr. Bonnie Word

Ex Officio Members and Liaison

Representatives

Dr. Jon Abramson (AAP)
Dr. Benedict Diniega (DOD)
Dr. Geoffrey Evans (NVICP)
Dr. Eric France (AAHP)
Dr. Stanley Gall (ACOG)
Dr. Amy Groom, IHS
Mr. Randolph Graydon (HCFA)
Dr. Randolph Jackson (NMA)
Dr. Samuel Katz (IDSA)
Dr. Sara Landryan, (NIH)
Dr. Martin Mahoney (AAFP)
Dr. Karen Midthun, FDA
Dr. Martin Myers, NVPO
Dr. Margarite Nava (NIC, Mexico)
Dr. Kathy Neuzil (ACP)
Dr. Kristin Nichols, (VA)
Dr. Georges Peter (NVAC)
Dr. Gary Overturf(AAP)
Dr. Kevin Reilly (PhARMA)
Dr. William Schaffner (AHA)
Dr. Jane Siegel, (HICPAC)
Dr. Richard Zimmerman (AAFP)

Executive Secretary

Dr. Dixie E. Snider, Jr.

Office of the Director

Sylvia Powell
Barbara Reynolds

Office of General Counsel

Kevin Malone

Epidemiology Program Office

Amy Khan (EPO)

National Center for Infectious Diseases

Carlos Alonso
Miriam Alter
Larry Anderson
Michael Bailey
Lynn Brammer
Carolyn Bridges
Mrtin Cetron
Nancy J. Cox
Roz Dewart
Keiji Fukuda
Alexander Klimor
Andrea Krull
Anthony Marfin
Allison Mawle
Linda McKibben
Ann Moen
Nancy Rosenstein
James Sejvar

**National Center for HIV, STD and TB
Prevention**

Marta Ackers
Brad Bartholow
Timothy Mastro
Eleanor McLellan
Allyn Nakashima
Ida Onorato

National Immunization Program

**Joseph Alen
Curtis Allen
William Atkinson
Roger Bernier
Achal Bhatt
Victor Caceres
Sarah Ceaser
Scott Campbell
Lynn Carroll
Bob Chen
Susan Chu
Joanne Cono
Frank Destefano
Gary Euler
Dan Fishbein
Karin Galil
Jayne Gaskins
Ramshidar Goli
Stephen Hadler
Beth Hibbs
Penina Haber
Anne Huang
Marika Iwani
Alison Johnson
Laurie Johnson
Sharon Katz
Duane Kilgus
Katrin Kohl
Maureen Kolase
Martin Landry
Kim Lane
Charles LeBaron
Dean Mason
Emily McGinley
Nazune Menka
Elaine Miller
Gina Mootrey
Trudy V. Murphy
Serigne Ndiaye
Rick Nelson
Bill Nichols**

**Glen Nowak
Ron Nuse
Dennis O'Mara
Chima Ohuabunwo
Walter Orenstein
Pata Palihaardana
Larry Pickering
Jeri Pickett
Yaler Pleer
Robert Pless
Bette Pollard
Pam Protzel-Berman
Lance Rodewald
Kari Sapsis
Susan Schmidt
Susan Scheinman
Ben Schwartz
Jane Seward
Kristine Sheedy
Abby Shefer
Diane Simpson
Jim Singleton
Vishnu-Priya Sneller
Ray Strikas
Pamel Srivastava
Shannon Stokley
Natarsha Thompson
Diane Urban
Turas Verstracten
Charles Vitek
Donna L. Weaver
Meghan Weems
Melinda Wharton
Craig Wilkins
Skip Wolfe
Lynn Zanardi**

**Other CDC
Jo Jones (MASO)
Peng-yun Lu
Mark Papanier
Susan Riley
Jennifer Robinson
Renee Ross (MASO)**

National Vaccine Program Office

Steven Sepe

Food and Drug Administration

C.D. Atreya

Norman Baylor

National Institutes of Health

Albert Kapikian

Linda Lambert

Others Present

Betsy Alueham-VanPays, Wyeth

Bascom F. Anthony, Biologics Consulting Group

Lynn Bahta, Immunization Action Coalition

Joseph Beaver, TN Department of Public Health

Bryan Bechtel, Infectious Disease News

Noelle Broadnax, Northeast Health District

Pat Cannon, Wyeth

Dan Casto, Merck

Jill Chamberlain, Vaccine Bulletin

Dack Dalrymple, Bailey and Dalrymple

Michael Decker, Aventis Pasteur

Carmen Deseda, San Juan, PR

Richard Dinovitz, Wyeth Lederle

Craig Engesser, Wyeth

Stephen Fields, Becton Dickinson

James Froesh, Aventis Pasteur

Bruce Gellin, Vanderbilt University

Jayne Gilbert, Chiron Corp.

Ruth Gilmore, Georgia Immunization Program

Jesse Greene, SC Department of Health

P.G. Gromi, Duhalle Polize

Neal Halsey, Johns Hopkins Univ.

Claire Hannan, ASTHO

Scott Harward, Glaxo, Smith Kline

Bill Hausdorff, wyeth

Philip Hosbach, Aventis Pasteur

Dominick A. Iacuzio, Roche Lab, Inc.

Matthew Kempf, Baxter Hyland

Luc Kuykens, Merck

Tom Lale, Merck

**Len Lavenda, Aventis Pasteur
Edgar Ledbetter, San Antonio, TX
Scott Litherland, Parallax Communications
Bill Mackey, Merck
Susan Malone, Chatham County Health Department**

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Others Present (continued)

**Nestor Molfino, Baxter
Stan Musci, Merck
Maria Nicholas, Virgin Island Department of Health Immunization Program
Marie Murray, Atlanta, GA
Patricia Nolan, Rhode Island Health
Peter Paradiso, Wyeth Lederle
Tima Parisi, C & W Helathcare
Diane Peterson, Minnesota Department of Health
Stanley Plotkin, Aventis Pasteur
Jane Quinn, Galxo, Smith Kline
Cassandra Richards, Infectious Diseases in Children
Steven Rifkind, Physicians World
Jorden Robinson, Glaxo, SmithKline
Zeil Rosenberg, Becton Dickinson
Fred Ruben, Aventis Pasteur
Brent Rutland, Aventis Pasteur
Georgia Seibert, GA Immunization Program
Kristine Severyn, Vaccine Policy Institute
Elizabeth Shea, Ketchum, Washington, D.C.
Judith Shindman, Aventis Pasteur
Alan J. Sievert, Cobb County Board of Health
Nanette Stoback, Aventis Pasteur
Matt Strasburger, Merck
Kathleen Stratton, Institute of Medicine (IOM)
Stacy Stuerke, Merck
John Talarico, NYS Department of Health
L.J. Tan, American Medical Association
Dirk Teuwen, Aventis Pasteur
Lonnie Thomas, Bastian, VA
Eric Tischler, Aventis Pasteur
Ted Tsai, Wyeth Pharmaceuticals
Miriam Tucker, Pediatric News
Theresa Turski, DHR, GDPH
Carmen Vanterpool, Virgin Islands, St. Thomas Department of Health
Thomas M. Vernon, Merck**

Peter Vigliarolo, Cooney Waters
Tom Waytes, BioPort
Deborah Wexler, Immunization Action Coalition
Jocelyn Wright, Glaxo, Smith Kline
Laura J. York, WLVI
John Zahradnik, Aventis Pasteur
Thomas Zink, Gaxo, Smith Kline

CENTERS FOR DISEASE CONTROL AND PREVENTION
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

Marriott Century Center

Atlanta, Georgia

October 17-18, 2001

Agenda Item

Purpose/Action

Presider/Presenter(s)

October 17

8:30 Welcome Disclosure by Committee Members		Dr. J. Modlin (Chair, ACIP) Dr. D. Snider (CDC, OD)
9:15 Report of the Rotavirus Vaccine and intussusception working group	Information	Dr. S. Katz (Duke Univ.) Dr. M. Levin (Univ. of Colorado) Dr. G. Peter (NVAC)

10:00 BREAK

10:30 Issues related to Influenza Vaccine Burden of influenza Summary of VRBPAC / possible time frame for LAIV Summary of TIV safety and efficacy Summary of feasibility/implementation issues Summary of program funding issues	Information Discussion	Dr. K. Fukuda (NCID, DVRD) Dr. K. Midthun (FDA, CBER) Dr. K. Neuzil (Univ. of Wash) Dr. K. Nichol (VA) Dr. B. Schwartz (NIP, ESD) Dr. N. Smith (CA Dept. of Hlth) Dr. T. Uyeki (NCID, DVRD) Dr. B. Word (ACIP)
12:15 Update on 2001-2002 influenza vaccine supply	Information	Mr. D. O'Mara (NIP, ISD)

12:30 LUNCH

1:30 Hepatitis B Recommendation	Discussion Decision/Vote	Dr. H. Margolis (NCID,DVRD) Dr. Wm. Schaffner (Vanderbilt) Dr. J. Siegel (Univ. of Texas)
2:30 Inclusion of Twinrix in the VFC Program	VFC Vote	Dr. M. Wharton (NIP, ESD)
2:45 Childhood Harmonized Immunization Schedule	Discussion Decision	Dr. M. Cortese (NIP, ESD) Dr. N. Smith (Ca. Dept. Public Hlth.)

3:30 BREAK

4:00 Adult Harmonized Schedule	Information Discussion	Dr. B. Schwartz (NIP, ESD) Dr. V. Sneller (NIP, ESD)
4:45 Use of OPV to Control Outbreaks of Poliomyelitis	Information	Dr. B. Schwartz (NIP, ESD)

<u>Agenda Item</u>	<u>Purpose/Action</u>	<u>Presenter(s)</u>
5:15 IOM Recommendations on Thimerosal	Discussion	Dr. M. McCormick (IOM) Dr. K. Stratton (IOM)
6:45 Public Comment		
7 :00 ADJOURN		
<u>October 18</u>		
8:00 Unfinished Business from Previous Day		Dr. J. Modlin (Chair, ACIP)
8:30 Updates	Information	
National Immunization Program		Dr. W. Orenstein (NIP, OD)
Food and Drug Administration		Dr. K. Midthun (FDA, CBER)
Vaccine Injury Compensation Program		Dr. G. Evans (HRSA)
National Institutes of Health		Dr. C. Heilman (NIH, NIAID)
National Vaccine Program		Dr. M. Myers (NVPO)
National Center for Infectious Diseases		Dr. A. Mawle (NCID, OD)
9:45 BREAK		
10 :15 Proposal to decrease the time interval recommended to avoid pregnancy after receipt of rubella vaccine	Discussion Decision	Dr. S. Gall (ACOG) Dr. S. Reef (NIP, ESD)
10:45 Pneumococcal conjugate vaccine: effect of the Vaccine on invasive disease during 2000 and plan for tracking vaccine failures Update on vaccine supply	Information Discussion	Dr. C. Van Beneden (NCID, DBMD) Dr. C. Whitney (NCID, DBMD)
11:15 Update on varicella disease and varicella vaccine in the United States Vaccine coverage Status of child care and school requirements Vaccine effectiveness Varicella disease surveillance	Information Discussion	Dr. K Galil (NIP, ESD) Dr. A. Jumaan (NIP, ESD) Dr. J. Seward (NIP, ESD) Dr. R. Vessey (Merck)
12:15 LUNCH		
1:15 The OSHA requirement for using safety engineered needles and implications for childhood immunization delivery	Information Discussion	Ms. L. Chiarello (NCID, DHQP) Ms. A. Hogan (OSHA) Dr. H. Yusuf (NIP, ISD)
2:15 Adaptation of vaccine formulary selection algorithm to web-accessible tool	Information	Dr. S. Jacobson (Univ. Ill.) Dr. E. Medina (Austral Eng. & Software) Dr. B. Weniger (NIP, ESD)
2:30 Public Comment		
2:45 ADJOURN		

**ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
MINUTES OF THE MEETING**

JUNE 20-21, 2001

JUNE 20, 2001

OPENING COMMENTS/DISCLOSURES

Chairman Dr. John Modlin convened the meeting at 8:36 a.m., and introduced Dr. Dixie Snider, the ACIP Executive Secretary. Announcing liaison representatives changes, Dr. Snider welcomed Dr. Gary Overturf of the University of New Mexico Medical Center, as the liaison for the American Academy of Pediatrics; and Mr. Kevin Reilly, President of Wyeth Vaccines and Nutrition, liaison for the Pharmaceutical Research and Manufacturers of America. He announced that Dr. Larry Pickering had joined the National Immunization Program staff. Dr. David Salisbury will serve as the Ex-Officio representative from the London Department of Health and Dr. David Wilson will serve for the American Medical Association, but neither were present at this meeting.

ACIP terms were completed for three members, who may return to the October meeting if the current federal hiring freeze prevents seating their replacements. Certificates and a letter of appreciation from CDC Director Dr. Jeffrey Koplan were presented to retiring members Drs. Richard Clover, David Johnson, and Chuck Helms.

He announced the ACIP home page (www.cdc.gov/nip/acip), the October 17-18 date for the next meeting, and those for 2002: February 20-21, June 19-20, and October 16-17.

Dr. Snider reviewed the rules pertaining to the ACIP's function. The amended (December 2000) committee charter's addition of three new ACIP members raised the membership to 15 and, therefore, the quorum to 8. As the Executive Secretary, Dr. Snider may appoint Ex-Officio members as voting members in the absence of a quorum. Public comment is solicited at regular intervals of the agenda, but the Chair frequently recognizes brief comments from the floor.

Dr. Modlin drew the members attention to information distributed and announced this meeting's scheduled workgroup meetings. The Committee members and those attending in the audience then introduced themselves (see the attached list). The members also indicated any conflict of interest that may prevent them from voting or seconding a motion or a VFC resolution, but their participation in discussion of all issues was still allowed. Such disclosures from ex-officios, liaisons, and public attenders were welcomed as well.

Committee members present reporting potential conflicts were:

Dr. Myron Levin: Merck, Glaxo SmithKline (GSK) research support; GSK stock

Dr. Margaret Rennels: trial support from Wyeth Lederle, Aventis Pasteur, GSK, and Merck.

Dr. Richard Clover: Merck, Wyeth Lederle, GSK, and Astra Zeneca.

Dr. Paul Offit: co-inventor on a patent for a bovine human resortant rotavirus vaccine in development by Merck and Company.

Of the liaisons present:

Dr. Eric France, AAHP liaison: Wyeth and by Merck funding for vaccine trials he oversees.

Dr. Stan Gall: ACOG conducts vaccine trials for Merck and Glaxo SmithKline.

Dr. Kathy Neuzil, ACP liaison: research funding from Merck and Aventis Pasteur.

Dr. Benedict Diniega, Department of Defense (DOD): owns Bristol Meyers stock.

UPDATE: TETANUS TOXOID VACCINE SHORTAGE/DTaP SUPPLY

Mr. Dean Mason updated the committee on the shortage of tetanus and diphtheria toxoid vaccine. In the event of a critical shortage, the ACIP members had already supported a CDC recommendation on prioritization of Td use according to indication.

DTaP Supply: Prioritization: A March 16, 2001 *MMWR* article recommended DTaP usage according to certain priorities: first priority to vaccines to infants to complete the primary series (doses 1, 2, and 3 at 2, 4, and 6 months of age). In the event of shortages, the fourth dose would be deferred; in the event of a greater shortage, the fifth dose would be deferred. Those deferred children would be called back when vaccine supply was more adequate. The deferral decision was left up to the programs and providers.

Supply. The back orders (defined as CDC contract orders not filled by 14 days) reported at the February meeting had improved. Aventis Pasteur's 579,000 doses on back order shrank to 268,600; GlaxoSmithKline (GSK) had almost none as of June. Manufacturer reports were matched with CDC records to confirm the supply status.

Public Health Response to Shortage. The National Immunization Program (NIP) asked for state reports of the central inventory of their total DTaP doses, and all DTaP vaccine orders placed through CDC's contracts were closely monitored. Twenty states had central DTaP inventories with a <30 day supply; 23 at 31-60 days (probably the most any state would need); 9 at 61-90 days; and 4 with a >91-day supply. Some state orders were modified to ensure equitable distribution, considering the population base, number of children served in the public sector, inventory, doses on back order, and special needs/circumstances. The states were also urged to downsize their central inventories to <30 days. Weekly or semi-weekly communication was held with vaccine manufacturers and with the FDA.

Shortage Impact. In the last month, of CDC's 60+ grantees, 48 states (84%) had sufficient supply for the 5-dose series; 12 (21%) were cutting product supply to providers; 8 states had formally changed their policy; and 11 states (19%) indicated awareness of spot shortages. Currently, of the total back order of 424,500 doses, ~156,000 doses are <14 days on back order and are of less concern. The public and private sectors' vaccine need is ~17.3 million doses per year. The distribution is uneven (more needed during school-entry vaccine drives, etc.), but if evenly spread, it would be ~1.44 million doses/month. The two manufacturers, Aventis and GSK, project a supply of 10.4 million doses of DTaP for the balance of this year (1.733 million doses/month), and Glaxo could supply the U.S. with an additional 3.9 million doses. That extra production would total 14.3 million doses (2.383 million/month).

NIP estimates that 1.73 million doses/month are sufficient to return to the 5-dose schedule for all children, as long as the DTaP orders through the CDC contract remain closely

monitored to ensure equitable distribution, the state inventories gradually build up to 30-day maximums, and a steady vaccine supply of the projected amounts is maintained. Glaxo's additional 3.9 million doses would also allow catch-up for children's missed booster doses, perhaps eliminate the >15 day DTaP vaccine back orders, improve supply for school drives, and could allow state inventories to build up to 60 days.

In discussion, Dr. Katz commented that the problem of such recall of children for missed doses supports the development of a registry system. Dr. Orenstein stated the NIP's comfort with the supply's adequacy to ensure that five doses are available for all.

Tetanus/diphtheria (Td) Supply. Mr. Dean Mason, of the NIP, recalled Wyeth Lederle's announcement in December 2000 of its intent to stop production of tetanus, diphtheria, and tetanus toxoid vaccines due to production and thimerosal issues. Their provision of 32% of all diphtheria and tetanus products for the U.S. market in 1999 dropped to 19% in 2000. Aventis Pasteur is now the sole national producer of tetanus and diphtheria, aside from the small production at the University of Massachusetts Medical School.

The ACIP and AAP recommend on the use of Td, but CDC has no contract for Td. During the January through May 2001 shortage, Aventis established screening criteria and prioritized product according to the ACIP's guidelines (hospitals, emergency rooms, and public clinics, focusing on wound management, travelers, persons with <3 doses, pregnant women without vaccination within the past 10 years). In the first part of the year, hospitals received only 50 doses/week unless more were justified. The new Aventis policy allows 300 doses/month and more with appropriate justification. Individual practitioners are not receiving their previously-allocated 20 doses/month, and Td booster vaccine is not supplied. The Immigration and Naturalization Service suspended Td boosters for immigrants. Reserved product for natural disasters is kept in a central public health inventory station.

Mr. Mason summarized that the outlook for Td is of demand exceeding supply. The vaccine requires an 11-month production time and Aventis is working at full capacity. Tetanus is the limiting factor in producing DTaP, Td, T, DT, and DTaP/HBV. Improvement is not expected before early- to mid-2002.

MMWR Notice to Readers. Dr. Lynn Zanardi updated the committee on the recent *MMWR* Notice to Readers, which recommended: 1) delay of all Td booster doses until vaccine supplies are restored in 2002; 2) clinic implementation of a callback system for those patients with booster doses deferred to next year; 3) re-emphasis of Td use for priority indications, for which the Td supply should be adequate. The article reminded readers that the ACIP recommendations for wound management had not changed (in response to some practitioner inquiries about using DT and DTaP as a substitute for Td) and reminded health care providers to ask when the last Td was received by the patient to avoid unnecessary vaccinations. Institutions were asked to order vaccine for only their anticipated priority indications. Aventis can ship quickly upon emergency situations.

Aventis Pasteur Status Report. Dr. Philip Hosbach described Aventis Pasteur's production status. Their first priority is to produce more vaccine (a challenge with the unexpected status of sole manufacturer and the 11-month production cycle), manage the

current supply and build inventory to avoid further shortages. He expressed Aventis' appreciation of the ACIP recommendations of prioritization to avoid any further run on the available Td stocks, and requested its continuing help in communicating the necessary further steps to state health departments. Td demand is currently high, with warm weather, increased outdoor activities, and more natural disaster emergencies due to recent unpredictable weather. The current shipping policy targets only public health clinics and urgent care facilities. Production is now a 24/7 operation. Aventis expects to ease the supply restrictions in 2002, and perhaps later this year, and is seeking an FDA license for a Canadian Td facility to double the production capacity.

Current Aventis outreach includes a letter issued to 400,000 health care providers through the Postgraduate Institute of Medicine, summarizing the current recommendations for Td, and defining wound management and the related ACIP guidelines. A recall reminder letter and recall materials will also be sent this summer.

Discussion included:

- Dr. Smith: *How is Aventis addressing potential gaps, such as rural areas with relatively inaccessible hospitals?* Aventis is communicating with those health departments as well as medical societies to explore potentially necessary adjustments. At this time, the people are asked to come to the vaccine, if possible, and the health departments are notified of where the vaccine is shipped. Dr. Smith suggested that the Aventis cover letter include mention of travel to "diphtheria-endemic" areas.
- Dr. Abramson: *North Carolina is ignoring the recommendations since they have an adequate supply.* Mr. Mason knew of this; CDC is working with them.
- Dr. Deseda asked for Aventis' attention to Puerto Rico, reporting that in metropolitan San Juan, patients have been referred to some large pediatric groups by emergency rooms with short Td supply.
- Dr. Levin: *What planning is needed to ensure coverage if another vaccine ends up with a sole manufacturer?* Dr. Modlin responded that this is being studied by an NVPO/NVAC workgroup. The Secretary has requested a report. Dr. Orenstein cited the past use of vaccine storage and rotation contracts to deal with short-term interruptions. This is still in place for single-manufacturer vaccines (e.g., MMR and inactivated polio vaccine), and now is being reconsidered to include all the routine recommended vaccines.
- Ms. Diane Peterson: *What is the recommendation for routine vaccination of persons with occupational risk, not mentioned in the last MMWR?* Mr. Mason confirmed that there is no current such provision, but any wound trauma commands product use.
- Dr. Clover: *What percent of the historical total distribution went to private physicians?* Mr. Mason reported 20 doses/month and more as justified, as well as through the public supply system. Mr. Hosbach agreed to check on the market percentage. Since they have only recently directly distributed the vaccine, they do not have those historical numbers, but current data are available.
- Dr. France: *Kaiser Permanente Colorado, has ~700 doses left now and expects to run out of tetanus by October or November. They have been limiting its use to dirty wounds and even prioritizing those.* Mr. Hosbach appreciated Kaiser's compliance with the recommendations, but prioritizing wounds should not be necessary. Aventis will work with its customers to avoid the need for such decisions.

INFLUENZA VACCINE

Influenza Workgroup Report. The Influenza Workgroup reported on their review of the issues related to live-attenuated influenza vaccine (LAIV) and pediatric influenza vaccine. Dr. Bonnie Word summarized the ACIP recommendation to delay initiation of major campaigns, and providers' focus on vaccinating high-risk patients and deferring until December vaccinations of those aged 50-64 years and other healthy individuals. However, since many of those who deliver most vaccine to high-risk individuals reported not receiving the vaccine, the manufacturers were involved to find a solution.

The LAIV Workgroup sponsored an influenza workshop in May, to identify and address the concerns/issues related to LAIV, particularly its use among children; to review the current efficacy and safety data of the inactivated influenza vaccine; and to identify any knowledge gaps that could prevent formulating future options for using either live or inactivated influenza vaccine. Although intertwined, the issues of these two vaccines are still separate.

The meeting convened experts for general discussions of the impact of influenza on children, reviewing rates of pediatric infection and hospitalization, clinical complications and mortality among children. One issue to be discussed further is of unusual complications of acute necrotizing encephalopathy reported in Japan. The development of an LAIV was described for the workshop, and data were presented on the LAIV effectiveness/efficacy studies for children, healthy adults, the elderly, and high-risk adults (e.g., asthma, CF).

Four subgroup presentations provided literature reviews on:

1. The overall safety, effectiveness, and efficacy of vaccinating young children with inactivated influenza vaccine, and specifically its application to herd immunity, day care settings, and selected high-risk populations.
2. The potential for reversion of LAIV vaccine strains and potential for recombination of vaccine strains with wild viruses.
3. The potential biologic issues related to co-administration of LAIV with other childhood vaccines. It can be given with almost every pediatric immunization, while adult co-administration involves consideration of pneumococcal vaccine.
4. The potential for adverse immunologic effects in children who are repeatedly vaccinated against influenza.

Research gaps were identified for safety, feasibility, and economic issues. A second workshop is planned in September after the FDA review of the live attenuated vaccine license application.

Influenza Vaccine Workshop. Dr. Fukuda applauded Drs. Edwards, Brian Murphy, Wendy Keital, and Ruth Karron for the workshop, which he termed as the best scientific meeting he had attended in recent years. Each subgroup identified and reviewed the literature, and decided its presentation at the meeting in preconference calls, ensuring that ample time was allotted for discussion.

The impact of influenza in children was reviewed by Drs. Tim Uyeki and Bill Thompson.

Influenza morbidity is substantial, and is probably generally under-reported and underappreciated in the medical community and the literature. Children's attack rates exceed those of adults in several different studies, and related hospitalization rates are higher in younger children than those older, as well as in children with high-risk conditions versus age-matched healthy children. The highest complication rate is in children aged <6 months, for whom vaccine is not approved. Vaccination rates among high-risk children are low (10-30%). Among the outstanding questions left from this group was whether vaccination of pregnant women really confers any protection to infants. Primary outpatient complications are otitis media and asthma. The very severe influenza-associated encephalopathy reported from Japan is of unclear etiology, although the data are impressive. That outcome has not yet been seen in the U.S.

Vaccine Safety and Effectiveness Review. The study exclusions of the literature review of the safety and effectiveness of inactivated vaccine use among young children were those of whole virus vaccine (not recommended for young children), foreign trivalent inactivated vaccines incompatible with U.S.-approved ones, and those of pre-1981 vaccines, which were lower in antigen than modern vaccines. The topics reviewed were trivalent inactivated vaccine and the possibility of herd immunity, and safety and immunogenicity in day care settings. Most of these studies supported the vaccine's effectiveness and immunogenicity with only local adverse reactions. The findings of the sparse literature of studies among high-risk populations (sickle cell anemia, asthma, diabetes) generally paralleled those for healthy children. The literature on the development of live-attenuated vaccines (LAV) and their effectiveness/efficacy indicate complex immunity issues. For example, post-vaccination immunity differs between live-attenuated vaccines and trivalent inactivated vaccines according to the naivete, sero-negativity or sero-positivity of the population. Studies sponsored by NIH, Wyeth, and Aviron demonstrated the effectiveness and efficaciousness of LAVs.

The literature on the potential reversion of LAIV strains to wild-type strains and that of vaccine strain gene reassortment with wild viruses indicate genetic stability in susceptible persons by both the A and B cold-adapted reassortant strains. While cold-adapted viruses also can reassort (exchange genes with other influenza viruses), they generally do so less often than wild-type viruses. In addition, there are no foreseen unique consequences from combinations of live-attenuated and wild-type virus genes. Nonetheless, the use of LAVs with novel hemagglutinin or neuraminidase antigens is not indicated if an aborted pandemic occurs, to avoid releasing those antigens and genes into the population. Similarly, it would not be used in such scenarios as that of the Hong Kong H5 outbreak, because the LAV virus genes could recombine with the H5 virus to produce one more transmissible than the native virus.

The biologic issues related to the co-administration of LAV and other childhood vaccines are major, but still largely unstudied. The literature on adverse immunologic effects in children vaccinated annually was approached from two perspectives:

- The risk of reduced immunogenic response to future influenza vaccination or infection. One focus was on the Boskin hypothesis of a reduced immune response against influenza. The group found that repeat immunizations in children and adults were safe and well-tolerated for both trivalent inactivated vaccine and LAV. However, there are

theoretical risks associated with repeat immunizations (e.g., from repeated exposure to egg proteins). Further evaluation is needed of the safety, tolerability, and efficacy of both trivalent, inactivated, and live-attenuated influenza vaccines in young children. Particularly if LAV is recommended for routine use in young children, Phase IV studies of adverse events are definitely needed.

- The potential for unforeseen aberrant immune responses, as seen to the early RSV vaccines. No aberrant immune responses have been identified, but more data are needed. This is particularly true for young, unprimed children, for outpatient settings, and particularly for risk conditions such as asthma, and as related to encephalopathy and meningococcal infections. Updated dose-ranging studies are needed to explore, among other things, the protection conferred by maternal vaccination with trivalent inactivated vaccine to their infants. And for both LAV and trivalent vaccines, further safety studies would be welcome.

FDA's VRBPAC will review the Aviron live-attenuated product in July, hopefully allowing the review of Aviron's unpublished safety data at the September Influenza Workgroup meeting. That meeting will also address other important outstanding issues of annual influenza vaccination: its economics, logistic and feasibility issues for providers, the potential impact on programs and their funding, and the crowding of the immunization schedule.

Discussion included:

- Dr. France: *Rare adverse events linked to trivalent inactivated vaccine cannot be explored with a cohort of only ~200 families.* However, the Vaccine Safety Datalink (VSD) program will examine their data sets for anything unusual and hope to report by September or October.
- Dr. Levin: *Is there a meeting report, and among what immunocompromised groups was these vaccines' use discussed?* The extensive meeting notes are being compiled and edited and will be made available to the Committee. While there was some discussion about the vaccines' effects in HIV-infected and other immunocompromised children, the meeting's focus was on healthy rather than high-risk children, nor are there much data. What exists is mostly unpublished. Whether LAV vaccines pose a risk for that group, in particular, is a research need, and will be discussed in September.

Influenza Vaccine Utilization/Supply. Dr. James Singleton of the NIP provided updated data on influenza vaccine utilization. He shared a graph of vaccine coverage trends for those aged ≥ 65 years, 50-64; and 18-49, as measured by the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS). The NHIS data showed a 69% coverage rate in 2000 among people ≥ 65 and ~23% in those aged 18-64. The 1998 vaccine coverage for high-risk groups was 43% among those aged 50-64 and 23% for those aged 18-49. Coverage may be plateauing among older people after the doubling of rates between 1989-1995.

Vaccine production. *Manufacturer data* of net doses distributed in the U.S. in 2000 indicates that 60 million adults were vaccinated. Compared to prior vaccination years, Northern California Kaiser data showed a drop in vaccination rates of those aged ≥ 65 years (whose numbers increased by ~30,000) from 70% to 60% from September through March. However, some vaccine may have been received outside of Kaiser. The rate for high-risk

children dropped somewhat, from 31.5% to 29%, perhaps due to Kaiser's reduced focus on this group in favor of targeting the older adults. Similar results occurred for high-risk adults age <65.

The Influenza Branch's Food Net Survey of 2000 included influenza vaccine questions. The FNS is an ongoing random monthly telephone survey of the rate of self-reported diarrhea and risk factors for food borne illnesses, across ~11% of the U.S. population. Preliminary unweighted data indicate, among 2,011 persons with complete data, influenza vaccination rates of 60% in those ≥ 65 , ~28% in high-risk people aged <65, and 12% in non-high-risk persons. November or December vaccination last season was reported by 71%. Although these are preliminary findings, it seems that those at high risk received a higher proportion of doses in December 2000 than in December 1999.

The BRFSS data of those interviewed in December 2000 was compared to those interviewed a year earlier in 18 states. It showed reduced coverage (~67% to 62%) among those aged ≥ 65 , and a smaller drop among those with diabetes than those without it. The impact of the ACIP recommendations was assessed by calculating the percent of vaccine given to high-risk people in December 1995, '97, '99, and 2000. Vaccination was provided to ~45% of those in two high-risk groups, as opposed to 38% in 1999. However, the years before 1999 showed a similar ratio to those of 2000 (43-44%). Vaccination sites reported to the BRFSS in the 1998-99 influenza season included the use of physician's office by 63% of those aged ≥ 65 , and the workplace by ~33% of those aged 18-49. In 2000, analysis of people with diabetes indicated vaccination as more likely in their doctor's office than at the workplace.

Of the 60 million adult doses received overall, the 46-47% were provided in their doctors' offices, and 19% in the workplace. Of those aged ≥ 65 , >50% were vaccinated in their doctors' offices, only <3% in the workplace, and ~33% in health departments, other clinics, and stores. The use of such nontraditional sites may increase in future. By the 2002 BRFSS, data on vaccination sites in all 50 states will be available. Data from one large national commercial provider indicate that 64% of their influenza vaccination clinics in retail settings were provided to those aged ≥ 65 , and 23% to those aged 50-64.

Mr. Dennis O'Mara, of the NIP, discussed influenza vaccine production, distribution, and administration; lessons learned, and preparations in process for the upcoming season.

Lessons Learned. The vaccine supply is fragile, and only three manufacturers produce influenza vaccine. The vaccine is essentially new every year, and takes about a year to produce. A failure of any component of the multifaceted production process can greatly reduce or totally jeopardize the production. Regulatory and Good Manufacturing Practice (GMP) guidelines must be followed. Vaccine production is based on egg culture, a difficult and complex process, which is followed by a similarly complex distribution process.

Primarily delivered to the private sector through vendors, the vaccine is subject to many market forces that can mis-match supply and demand. Distribution is uneven because companies produce and distribute vaccine at different rates. But the unevenness varies from year to year, and can create chaos in times of shortage. The crucial nature of good communication was emphasized from this last season.

The public sector has limited involvement in purchasing, distribution, and administration. Targeting vaccine to high-risk groups will involve changing the behavior of both vaccine providers and recipients. Providers will need to get accustomed to serving only their high-risk patients first and deferring the rest; recipients who are not high-risk will need to learn to wait for vaccination until the supply is more plentiful later in the season. State and local public health departments have tried to help, but are limited by a lack of infrastructure, and many providers do not have reminder-recall systems.

Preparations In Process. This year, the CDC is developing voluntary approaches throughout the entire system of production, distribution, and administration to target high-risk patients early in the vaccination season. The options include:

1. *Distribution.* Shipping vaccine directly to providers with high-risk patients, perhaps as identified by the vaccine companies and distributors. Aventis Pasteur will fill at least 25% of every order to ensure their customers have vaccine early for high-risk patients.
2. Collaborate with mass clinic operations to encourage them to follow the ACIP/ NIP best practices, which were updated and widely distributed. This includes a patient self-screening form that can help identify those at high risk.
3. The states have been asked to develop a contingency plan for a vaccine delay, with criteria to guide redistribution of vaccine where appropriate and possible, focusing on the high-risk groups.
4. Provide more clear and explicit recommendations.
5. Strengthen existing partnerships and develop new ones as appropriate. This already has aided planning, communication, and monitoring efforts. A partial list of the partners involved was distributed.
6. A meeting with the AMA may be held in August before the vaccination season begins, to ensure that all plans are in place.
7. Increase CDC's contracts for vaccine through-purchase by state and local health departments, if needed to better help them to fill the gaps.
8. Plans to meeting with the distributors' trade organizations are being discussed, and with the vaccination contractors who immunize at nontraditional sites.
9. *Communication:* A letter from Dr. Orenstein was widely distributed in May to providers, and a similar one will go to pharmacists. Biweekly bulletins will be sent to all partners, who in turn are asked to re-convey this information to members/constituents. The NIP Website will post information, and the calls and partner meetings will continue on an ongoing basis, either regularly or *ad hoc* as needed. A mass media campaign will inform the general public again. The NIP Communications Office tracks news media coverage of stories to assess the communication with the public and to adjust as needed.
10. *Monitoring.* Communication about monitoring is frequent with the vaccine manufacturers, the FDA, and the Centers for Medicare and Medicaid Services (formerly HCFA).

Distribution. Mr. O'Mara shared data and information from the vaccine companies to discuss the 1999 and 2000 aggregate monthly distribution of influenza vaccine. The 2001 figures were projections. Distribution analysis used 1999 as a benchmark year, acknowledging that no single year is actually "usual" or "average." He emphasized that these figures served only as a rough guide with which to project.

Based on data provided by the vaccine manufacturers, CDC anticipated a less extensive distribution delay than in 2000. The projected production for this season will be ~ 84 million doses. The delay is attributed, in part, to the retooling time required by the manufacturers to compensate for the dropout of one manufacturer. The monthly projected vaccine distribution for 2001-02 was charted, beginning in August and peaking from September through November. About 64% is expected to be distributed in October. Charted distribution data from 1999, 2000, and 2001 showed the previous delays. Where slightly more than a third was issued in October 2000, this year about two-thirds should be issued. Nonetheless, Mr. O'Mara cautioned again that other factors could exacerbate the delays, including production difficulties, uneven vaccine distribution, some early vaccination of young healthy individuals, and price speculation.

AMA Statement. Dr. L.T. Tan, of the American Medical Association (AMA), related their House of Delegates' Substitute Resolution 416 in December 2000. It included that the AMA will 1) "work all with appropriate agencies and organizations, including vaccine manufacturers, to prioritize the distribution channels for influenza vaccine to assure the vaccine is available to patients in accordance with CDC guidelines for high-risk patients;" and 2) "explore options for appropriate oversight of the supply, distribution, and marketing of influenza vaccines by appropriate agencies."

The large AMA/NIP joint meeting on March 27 resulted, which involved almost all the stakeholders of the production, distribution, and/or administration of the influenza vaccines. It was held to help the participants understand influenza vaccine supply, distribution, administration, and why influenza vaccine availability was delayed in 2000-2001. Many of the viewpoints expressed by the AMA physicians have already been addressed by the NIP, including:

1. The uneven distribution starved vaccine supply to physicians serving high-risk populations while supplying those who were not; they were caught between the distributors' shipment delays and their patients' demands for vaccine, forcing embarrassing referrals to the local food store vaccination clinic. The physicians felt they should be first to receive vaccine shipments, since they deliver to 60% of those at high risk.
2. Not only were the physicians notified too late of the revised ACIP recommendations, they felt that communication in general completely failed. Reading media accounts of the delay was the first notice to some providers.
3. Many providers knew that other physicians were not adhering to the guidelines, despite the release of the best practices late last season.
4. The terminology used in communicating the problem was ambiguous, which led some to a conspiracy theory. When "delay" actually translates to "shortage" regionally, credibility is lost, paranoia escalates, and such AMA resolutions are advanced which the organization must then act upon.

Perhaps the meeting's most important finding was the need to communicate to physicians when the vaccine supply is sufficient, and that, while not perfect, the current production and distribution system is adequate. The AMA supported development of a contingency plan for when the vaccine supply is delayed or insufficient, which should be voluntary for both public and private sectors. They urged that as soon as manufacturer projections are available,

they be issued to all involved to allow the coordination of messages to the public and providers. CDC was felt to be best suited to do this and to implement the contingency plan.

Improved communication is critical among all the stakeholders involved with influenza vaccine production, distribution, and delivery. Although it is improving, the fact that a problem will again exist this season had led to a Board of Trustees Report (#36) on the previous day. The Board committed to: 1) work on the second CDC/AMA meeting on influenza vaccine; 2) to communicate current ACIP recommendations, etc. to physicians and to assist CDC's dissemination of information on their Website; 3) to monitor progress in developing the contingency plan and an influenza pandemic plan which should involve the physicians on the front line as much as possible; and 4) to support mechanisms to include influenza vaccine supply in ensuring achievement of the Healthy People 2010 goals. This last is critical to the AMA, in view of many reports that reimbursement levels for influenza vaccine have not kept pace with its cost. Many now intend to refer healthy patients to public health departments.

Unfortunately, this report was received by the House at a time when the physicians, following Dr. Orenstein's advice to order vaccine early, were told that pre-orders had closed and further orders were not being taken. This contributed to the conspiracy theory, and resulted in a fifth resolution:

5. The AMA will immediately investigate issues, including cost, reimbursement, availability, and distribution, which may adversely affect the ability of physicians to provide influenza vaccine to their patients in the upcoming 2001-2002 influenza season.

Dr. Tan noted that this automatically involved the AMA's Washington D.C. office. However, the AMA is trying to work with CDC to keep response to these issues voluntary.

February 2000 ACIP Recommendation. Dr. Ben Schwartz presented the draft influenza recommendations developed by NIP, the NCID Influenza Branch, and the CDC Office of the Director, with input from the FDA and the ACIP Influenza Workgroup. He first reviewed the previous year's recommendations, which focused on high-risk patients and health care workers, determining local priorities to match those local needs, continuing vaccination beyond December, beginning with vaccination of those not at high risk in November, providing pneumococcal vaccine, and continuing focus on high-risk children. Two recommendations addressed mass campaigns to focus them on those at high risk, and those for health care organizations urged the use of proven effective techniques to increase vaccination of high-risk persons.

Little data from the last season has been analyzed to assess vaccine use, but some things have become clear: 1) stronger and more definitive recommendations are needed earlier in the season than the October publication of ACIP recommendations; 2) providers' ability to focus vaccination to high-risk individuals may be limited, and the growing nontraditional settings primarily service lower-risk individuals; 3) providers complained of distribution not matching the need of high-risk patients. Of concern to both their professional societies and Congress, that led to proposals of a greater government role, including legislation. Vaccine redistribution as a rule did not occur last year, despite a CDC pilot-tested Website to facilitate such communication and exchange; and 4) finally, while late

(November/December) vaccination increased, data suggest a drop in overall coverage, and little vaccine was ordered for December delivery. Of the 9 million CDC-guaranteed vaccine doses, only ~1.5 million were distributed.

Supplementary Language, Draft Recommendations. The primary goal of the draft recommendations is to create a prioritized system in which those aged ≥ 65 years who have chronic illnesses, and the medical personnel who care for them, are vaccinated early. Other goals are to maximize coverage of those at highest risk of severe influenza complications and to increase coverage in high-risk and targeted groups. As opposed to last year's focus on providers, this new approach is one of collaboration between providers, the public, manufacturers, distributors, and vendors, and health departments.

The draft statement summarizes the recommendations, outlines the reasons for the 2000-2001 season vaccine delay and the related manufacturing issues, as well as the projections for 2001-2002. The recommendations are specific for the various participants in the immunization system:

Providers

- "Providers should actively target vaccine available in September and October to persons at increased risk of influenza complications and to medical people who care for them." A table defines high-risk conditions and reminder recall systems are promoted.
- "Providers should continue vaccinating patients, especially those at high risk and in other target groups, through December and later as long as vaccine is available." The targeted groups are defined, including those aged 50-64 years old. Data are cited to support substantial duration of protection from a December vaccination. Health care organizations' assessment of influenza vaccination practices is urged, as is ensuring feedback to providers on coverage.

Public

- "Persons who are at high risk, including those who are ≥ 65 years of age or < 65 who have underlying chronic illnesses, should seek vaccination in September and October or as soon as vaccination is available with their provider." Communication to encourage patients to seek vaccination throughout the season is urged.
- "Persons who are not at high risk are encouraged to defer seeking influenza vaccine until November and later when additional supply will become available." This is a new recommendation. Consultation with their provider is advised for those unsure of their status. Again, providers are encouraged to adopt a reminder/recall system for those who defer vaccination until later in the season.

Manufacturers/Distributors

- "Distribution of vaccine to work sites should be delayed until November." The worksite is a site where those at high risk or elderly are less likely to be vaccinated. This delay should make substantially more vaccine available early to providers of high-risk patients. Manufacturers are encouraged to identify worksite orders placed by the doctor's name rather than by company name. The latter are urged to self-identify and indicate their willingness to receive vaccine later.
- Since vaccination campaigns often occur early, this recommendation could apply every year rather than only this influenza season.
- Apportionment of vaccine available early to ensure equitable distribution to all providers who ordered was encouraged.

- Manufacturers, distributors, and vendors were advised to inform providers of the amount of vaccine and the date of shipment so that they can contact their high-risk patients first.

Health Departments/Organizations

- "Groups that provide influenza vaccine services should develop contingency plans responding to a delay in vaccine distribution." Communication among partner organizations and the potential for redirection of vaccine to high-risk persons in the community was emphasized.

Mass Vaccination Campaign Sponsors

- Organizers of mass immunization campaigns not conducted in work places (e.g., senior centers, clinics, retail stores) should make special efforts to vaccinate the elderly and those at high risk of influenza complications. CDC offered materials that define high-risk groups and support a tiered approach, as well as useful screening forms.

Discussion included:

- Dr. Smith: *There may be undue pressure on providers and health departments from patients wanting vaccination; and add text about delaying mass campaigns till mid-October.* High-risk individuals seeking vaccination are advised to ask their providers about vaccine availability before going for vaccination. A recommendation for health departments, HMOs, and other mass vaccinators to wait and ensure vaccine availability before publicizing a mass campaign is reasonable.
- Dr. Offit: *Please summarize why vaccine distribution is delayed, since the scale-up problem from seed stocks was resolved last year.* Mr. Kevin Reilly, PHARMA liaison, cited the standard complexity of developing a new vaccine annually, and the reduction to three manufacturers from four in 1999, the benchmark year. Each manufacturer needs time to add more capacity/volume into their systems.
- Dr. Fred Rubin: *Replace the term "delays" in the title of the recommendations to avoid an implication that this is another bad year, since the vaccine supply will be good. However, the term "delay" is appropriate in the text where now used.*
- Dr. Abramson: *Cite the reasons for the delay, particularly if a new framework for timing is advanced.*
- Ms. Linda McKibbin, CDC Office of Health Care Partnerships: *Were recommendations considered specific to managed care organizations (MCO), and were standing orders programs considered?* Standing orders are specifically addressed in earlier ACIP publications. Managed care organizations are addressed under the recommendation for mass immunizers. MCOs are uniquely well positioned to respond to the recommendation for assessment and feedback.
- Dr. Schwartz: The only way to reach HP 2010 goals is to increase supply, which likely will require a longer period of production and administration of vaccine. He supported Dr. Abramson's suggestion of using this recommendation as a new a new norm of timing rather than a contingency plan or a single season model.
 - *Discussion of this as a new timing framework* included the following: Shifting the time from October through December will leave a gap in years of early influenza outbreak, although the bulk of the Influenza Branch's data supports that seasonal peaks occur in January.
 - The manufacturers responded: Mr. Hosbach/Aventis Pasteur: A managed distribution process to allow more regular vaccine supply will be more the norm at Aventis. Mr.

- Reilly, Wyeth: Vaccine supply will increase with production capacity. But as a general policy, expanding the recommended time period for vaccination is wise.
- ▶ Dr. Helms: *Issue this document as pertinent to this year only* and discuss a change over the next year. There are no hard data to support a change yet.
 - ▶ Dr. Zimmerman: *A decision analysis is needed*. The advantage of delayed vaccination is the delivery of more doses; the disadvantage is the potential of not preventing influenza during the 21% of peak activity that occurs by December. Dr. Cox: There is sporadic and regional activity, and perhaps early outbreaks in nursing homes. There is an optimal time to vaccinate.
- Dr. Pat Noland, State of Rhode Island: *Be wary of advising patients to call physician offices*, a lesson learned from the meningococcal experience. Be very careful in crafting that public message to not imply that the physician has some control over supply. She also reported that Rhode Island distributors were not at all supportive of redistribution of vaccine, although some individual practices did share their shipments.
 - Dr. Nichol also suggested: 1) *add providers under the text on vaccine distribution* to worksites, since many who administer to high-risk groups also do so to worksites; and 2) *strengthen the language about the importance of local initiatives* to join all stakeholders to the health departments to ensure even availability of vaccine; and 3) insert text about the vaccine ordering process and the legal authority under which providers can redistribute vaccine, in this document or on the Website.
 - Dr. Tompkins: To make this a generic document for annual recommendations, drop “projected delay” from the title and change it to, for example, “Influenza Supply Distribution, Vaccine Supplementary Recommendations.”
 - Dr. Overturf: *Add young children to the section on household contacts of those at high risk, particularly since the issue of influenza immunization for children in general is pending*. This was discussed, but encouraging early vaccination for such a large group could hazard the supply to vaccinate those at highest risk.
 - Dr. Orenstein: *Leave “delay” in the title*; dropping it risks missing the desired attention.
 - Dr. Snider: *Consider the impact of the likely pending release of the live-attenuated vaccine*. He urged crafting solutions for the coming year and not thinking too many years in advance.
 - Dr. France: Make the draft recommendation consistent with Dr. Orenstein's letter, particularly his request for the delay of mass vaccination programs in the latter half of October and perhaps in November, to avoid the need to reschedule these clinics.
 - Dr. Modlin: The 1999 benchmark in use was the norm for four manufacturers. The three remaining must build capacity to increase the supply. A sentence should be added to indicate that while that is being addressed, this delay will occur. Dr. Smith also suggested defining “delay” right up front and specifying that it will not be as extensive as last year’s.

The committee agreed to vote on accepting the draft recommendation with the following changes: 1) define what “delay” means and explain and put it into context; 2) address the issue of those patients seeking vaccine early (September, October); and 3) address specific language on the inclusion of children as contacts of high-risk individuals; and 4) indicate ACIP’s consideration of changing the timing paradigm of influenza vaccination that is likely to be included in the statement next year. The vote was taken on the following morning.

HEPATITIS B IMMUNIZATION

Background. Dr. Susan Goldstein outlined the changing epidemiology of hepatitis B in the last 20 years and the new strategies to vaccinate high-risk adults in the United States. The current strategy focuses on prevention of perinatal transmission through routine screening of all pregnant women and vaccination of newborns born to hepatitis B surface-antigen-positive mothers; routine vaccination of adolescents; and selective vaccination of children, adolescents, and adults at increased risk for infection.

High-risk adults are defined as 1) injecting drug users (IDU), 2) sexually active homosexual and bisexual men, and 3) heterosexual men and women with >1 sexual partner in the previous 6 months, previous treatment for another sexually-transmitted disease, and commercial sex workers. Most STD clinic patients should be considered vaccination candidates; as well as 4) inmates of long-term correctional facilities. Other high-risk adults include household and sex contacts of persons with chronic HBV infection, those with occupational exposure, clients/staff of institutions for the developmentally disabled, chronic hemodialysis patients, and international travelers with potential exposure to blood or those traveling for >6 months.

Current Epidemiology. From 1987-1998, reported incidence of acute hepatitis B decreased 76%, from 13.8/100,000 to 3.3/100,000. However, this decline plateaued in the mid-1990's, while incidence remained stable. The overall trend was paralleled by age group for those aged 10-19 (attributed to hepatitis B vaccination), and age 20-29 (attributed to vaccination and behavioral changes such as injection and sex practices). The decline was 53% for those aged 30-39 and 38% for those 40-49. Those at major risk are heterosexuals, men who have sex with men (MSM), and IDUs. Rates have declined in all three of these major risk groups, but the epidemiology has shifted. Transmission through heterosexual activity rose from 21% in the 1980's to 38% in the 1990s, while those associated with MSM dropped 15% to 12%; and those for IDUs, from 20% to 14%. Data on trends in age for acute hepatitis B by risk group reflected a median increase in age of cases from 25 years from 1982-1988 to 30-32 years in 1994-1998.

A total of 56% of acute hepatitis B patients also have had another STD or been incarcerated, clearly presenting an opportunity for prevention of over half of all cases. Data on such missed vaccination opportunities by risk group were charted, and data from hepatitis B virus infection and related vaccination among MSM from the Young Men's Survey (MSM aged 15-22 years). Of those MSM, 11% had serologic evidence of hepatitis B infection, more than double the U.S. prevalence (4.9%). Their prevalence rose from 2% at age 15 to 17% by age 22. Only 9% were immunized against hepatitis B, only 27% knew about the vaccine, and only 9% thought they were at risk of HBV infection. This was despite 90% having a regular health care source; 65% were tested for HIV (most more than once); and 13% had a previous STD diagnosis -- all missed opportunities to administer hepatitis B vaccine. This prompted a rethinking of CDC's immunization strategy, from targeting specific high-risk adults to targeting their frequently-used settings.

Missed Opportunities. Dr. Cindy Weinbaum noted the effective prevention immunizations for hepatitis A and B and their overlap with STD and HIV routes of transmission. The

transmission of viral hepatitis is fostered by lack of service integration with successful hepatitis B vaccine programs in STD clinics, HIV/AIDS testing and counseling sites, family planning centers, drug treatment programs, harm-reduction programs including syringe exchange programs, Job Corps sites, and correctional facilities.

Since even one dose of the vaccine is efficacious in providing immunity for 50% of those vaccinated, it is well worth doing. Hepatitis B vaccination of those incarcerated has been recommended since 1982 to prevent infection both inside and outside of correctional facilities. It has been shown to be feasible and cost-effective. Successful examples were shared of high acceptance in Massachusetts and Texas correctional facilities and of STD clinics in San Diego, California.

But challenges to its implementation include: 1) funding. While rising numbers of juvenile detention facilities are signing up as VFC provider sites, adult vaccination is not covered; 2) the cost savings of pre-vaccination screening depends on local costs and the prevalence of immunity from past vaccination and past infection; and 3) the goal of three-dose completion is generally not feasible and perhaps should be changed to just one dose.

Policy Recommendations. Dr. Margolis cited the proven success of infant vaccination (90% 3-dose coverage) and even for the newer adolescent immunization (~60% in those aged 13-15 according to NHIS data). Demonstration projects have convinced NIP that vaccination of high-risk groups is both feasible and cost-effective when delivered through the good infrastructure of STD and HIV prevention. Vaccination of those at occupational risk and in correctional facilities is also feasible.

However, the lack of a national program is problematic. About 40 highly successful programs are run by states and local jurisdictions, but all are local endeavors with spotty funding. The CSTE and the American Social Health Association are conducting surveys to chronicle the activities underway. In the last 5-6 years, the recommendations have been rewritten to target specific adult risk groups (e.g., disease prevention in the chronic hemodialysis setting produced the current ~70% vaccination coverage). In the fall, new recommendations will address the prevention of viral hepatitis A, B, and C in correctional settings. Hepatitis B immunization has been supported by the IOM, the National Institute of Justice and the National Correctional Health Care Commission.

In the absence of a national program, CDC can provide technical assistance to local efforts, and can use 317 funds for some work. In adult immunization, Medicare funds the care of end-stage renal disease patients, but only funds hepatitis B vaccine at 80% versus 100% for influenza and pneumococcal vaccines. An OSHA rule requires employers to pay for vaccine, and ~5 states routinely vaccinate prison inmates. Medicaid does not cover hepatitis B vaccine. Many health plans do not provide first-dollar coverage, and gaining coverage requires divulging risk factor status.

Dr. Margolis reported additions to this document:

1. The victims of sexual assault are addressed in language taken from the STD guidelines. There are no clinical or case control data, but based on post-exposure vaccine efficacy data and the expected frequency of the perpetrator's surface-antigen positivity, active

- post-exposure immunization is recommended in the text (rather than in background).
2. TwinRix®, the combination hepatitis A and B vaccine, was licensed for adults. That was added to the table of overlapping risk groups pertinent to the recommendations, and text will be written on that. Dr. Modlin noted the need for future ACIP discussion of whether specific recommendations for new combination vaccines are needed.

Discussion included:

- Dr. Stan Gall: *What is the current status of neonatal hepatitis vaccination since its temporary suspension due to thimerosal vaccine content and subsequent reinstatement with thimerosal now deleted?* Prior to July 1999, ~50% of U.S. infants were vaccinated from birth, according to the National Immunization Survey (NIS). That dropped ~70%. Recovery is now at about 30%, as the hospitals that dropped that vaccination from their standing orders slowly reinstate it.
- Dr. Modlin: *About what proportion of adults are considered at risk or high risk; and how many of them are already seropositive?* Of the ~2 million people incarcerated in the U.S. long-term annually, 80% are susceptible. With 20% infected, that is 2 million. The numbers for IDUs and heterosexuals at risk are unknown. But the CDC-funded STD clinics see another ~2 million, with an unknown overlap to those in HIV counseling and testing sites. Including the IDUs, it could be in the 10-million range.
- Dr. Deseda: *A similar strategy of targeting high-risk populations was ineffective in the mid-1980s.* Agreed. Those CDC demonstration projects were in STD settings, not correctional facilities; a few were done with IDUs. The difference is the present ability of the public health infrastructure to access high-risk adults. That should provide pretty high coverage rates. Transmission cannot be eliminated for another 30 years unless the present adult vectors are addressed.
- Dr. Sam Katz: *What has happened with making 317 funds available for adult hepatitis B immunization?* Dr. Orenstein: The FY 2001 budget had an additional \$42.5 million for infrastructure funding. Many states used that to strengthen their childhood programs to compensate for previous budget losses, rather than putting it into hepatitis B prevention. The 317 vaccine budget had no specific appropriation for hepatitis B vaccine for adults, even though that was an IOM recommendation.
- Dr. France: *Did you consider recommending, as done for PneumoVax® use by seniors, to give the vaccine if there is no history or statement of vaccination?* Operationally, this is what STD clinics are doing. To date, ~10% have already been vaccinated; the rest receive the vaccine.

Presentation of the HBV Statement

Review Report.

- Dr. William Schaffner found the statement to be strong and worthy of support. His comments included:
 1. For that one-third without good risk factor information, a separate statement may be advised to emphasize that group, necessary to the goal of interrupting and eliminating transmission.
 2. There is a universal prevention concept up to age 19, after which the recommendations' underlying concept is hepatitis B control through individual and personal protection rather than elimination of transmission. The role remains undefined for the large portion of the 38% transmitted by heterosexuals who present

to individual practitioners as opposed to prisons and STD clinics, the current emphases. Before the funding base needed to build a structure and reach out to partners is in place, a plan and recommendations are needed. A workgroup should be formed to research hepatitis B epidemiology and possible adult interventions. The ultimate goal should be to extend the universal immunization concept beyond age 19 to the periods of young adulthood when so many cases of hepatitis B occur.

- Dr. Jane Siegel added:
 1. Her hope that the document would convey that the recommendations for healthcare workers beyond acute care settings span the continuum of care, to outpatient and surgicenter settings.
 2. The document could better carry through a strong support for the birth dose. Dr. Margolis responded that the first recommendation could “recommend” that the first dose of vaccine be given during the newborn period," rather than "strongly encourage."
 3. The recommendations should be rated based on the evidence. While this recommendation in general is strongly supported by evidence, there are areas of less strong evidence and demonstration. Identifying those could help providers to allocate limited resources based on evidence.

Discussion included:

- Drs. France/Smith: *Adjust the (¶1, last sentence) recommendation to parallel the Harmonized Schedule and the General Recommendations, to read "for infants at low risk of infection with hepatitis B virus, the hepatitis B vaccine series may be completed at any time after six months of age." Dr. Margolis agreed, except that the third dose should be given at six months among the high-risk populations due to early post-natal transmission.*
- Dr. Abramson: *Adjust the wording to read “at six months of age” rather than by six months, to parallel the General Recommendations’ advice of four months between doses 2 and 3.*
- Dr. Deborah Wexler, Immunization Action Coalition: *Consider clearer language specifying “at birth” or “during the newborn period.” This has been adjusted to be consistent with the STD guidelines, but just was not in the current draft at this meeting.*
- Dr. Gall: *What is the policy about vaccination in pregnancy?* He recalled that it is safe to use in pregnancy and joked that a pregnant person “has one STD on board right there.” Dr. Severyn objected to that levity. Dr. Margolis confirmed safety in pregnancy. The recommendation includes vaccinating pregnant women with risk factors, but not to routinely vaccinate pregnant women, based on overall risk to and cost-effectiveness for the 4 million pregnant women annually.
- Dr. Georges Peter: *Please share with the committee, when available, the AAP’s changed recommendation about immunizing premature infants born of hepatitis B surface-antigen mothers; and ensuring that the Harmonized Schedule places hepatitis B directly under zero months.* New data also suggest that the poor response in pre-term infants is better than thought. The schedules will be harmonized.
- Dr. Karen Midthun, FDA: *The package insert reference this vaccine as Pregnancy Category C (no animal or clinical data on reproductive toxicity). While that category does allow pregnant women to be vaccinated if clearly indicated, a blanket statement on safety should be qualified.* Accepted. Several trials have data on pregnant women

inadvertently vaccinated and followed to the birth event (~200 instances). This does not provide strong confidence, but there has been no evidence of adverse events. The text addresses the issue of the risk versus the benefit in terms of HBV.

- Dr. France: *Add text about the strength of new epidemiology to support the success of hepatitis vaccination. And, is it really necessary to restart the series if a child receives dose 3 early; can't a fourth dose be given after 6 months?* Dr. Modlin: There are two issues, number of doses and catch-up. To be consistent with the childhood immunizations paradigm to not add additional doses regardless of the interval from the last dose, additional doses are not needed as long three doses are given. That can be dealt with outside of the statement.
- Dr. Kristine Severyn, Vaccine Policy Institute, Dayton, Ohio: *Much of this discussion is a bit disingenuous; >95% of the population will never be exposed to hepatitis B, nor need they if they maintain "a wholesome, moral lifestyle".*

Dr. Modlin thanked Dr. Margolis and his staff for the clearly immense amount of attention paid to this document in the last few months. He requested its careful review by all present and that comments be sent directly to Dr. Margolis within the next month. The statement will be reviewed again at the October meeting and, hopefully, voted upon. A workgroup is needed to begin addressing the broader and public policy issues raised.

VACCINE SAFETY ISSUES FOR YELLOW FEVER VACCINE

Should the ACIP yellow fever statement be modified?

Dr. Martin Cetron recalled two case reports in 1998 suggesting that the elderly may be at increased risk of adverse events from Yellow fever vaccine, and provided a background of the vaccine's origins. In use since the late 1930s, this vaccine has proven safety and efficacy. It has enabled the control of Yellow fever outbreaks in South America and Africa and is used to immunize persons traveling from developed countries to endemic areas.

Vaccine History. The live-attenuated yellow fever vaccine (LAYFV) was developed in 1927 from the serum of two yellow fever survivors, and the French neurotrophic virus was derived from that. Safety concerns about neurovirulence halted the use of the latter since 1982. The current vaccine produced stems from the Asibi strain, whose virulence was attenuated while preserving immunogenicity and protection. This is not a clonal derivative of a live virus, but a whole population of genetically homologous but distinctive virions. Early on, it produced higher rates of neurotropism and encephalitis, especially among children aged <6 months. However, this was greatly diminished with the development of a seed lot system, and it has been the United Nations standard since 1945. All vaccine now uses this secondary seed lot, termed 17D vaccine type yellow fever virus, in two primary vaccine strains: 17DD, which is used in Brazil; and the 17D-204. A reference strain was derived from the latter, 17D-213, which is manufactured in Senegal and stored at WHO; 17DD is produced in Brazil. The two are very similar (>99.5%) in their sequence and their amino acid homology.

Adverse events (35) due to 17D were reported in the VAERS data 1990-98. They reflect a stepped risk of multi-systemic effects with increasing age (the mid-50s to 60s), with duration from 48-72 hours. These resulted in 14 hospitalizations and three deaths. A comparative

validation of those observations done with collaborators in the U.K. used the hepatitis A control vaccine of the time, and produced no similar stepped increase in age-related reporting risks and no deaths among in >3 million doses. Another U.K. database on Arilvax® covered 1 million doses. It included 36 systemic adverse events and more other quickly-resolving non-serious events, and the same stepwise increase in risk. However, very few vaccine recipients were aged >75 years.

Dr. Cetron then described seven cases of a new yellow fever-like syndrome associated with 17D yellow fever vaccine. These occurred over the last five years among persons who received 17D-204 vaccine. Four were in the U.S. (aged 63-79), one in “Country X” (age 53), and two from Brazil (aged 5 and 22). Yellow fever is resurgent in the Americas and in Africa. It particularly threatens urbanized Brazil, where a massive vaccination campaign over the last 4-5 years has administered >38 million doses of yellow fever vaccine.

The syndrome onset is 2-5 days post-vaccination. All seven cases had multi-organ system failure and six died. Among five cases, four had the 17DD or 17D-204 vaccine-type virus isolated and sequenced. There was no wild-type yellow fever isolated from any of the patients. Dr. Cetron outlined the clinical description of wild-type yellow fever. The clinical syndrome in itself is not specifically pathognomonic. The broad differential diagnosis includes, for example, severe viral hepatitis or malaria, typhoid fever, leptospirosis, dengue, and other viral hemorrhagic fevers. The diagnosis requires histopathology.

VAERS, although a passive system, gives the best indication of incidence. Over nine years and 1.5 million doses among civilians, the incidence rate was ~1/400,000 and the case fatality rate was 3/1.5 million (1/500,000). This is similar to the occurrence of paralytic polio following the first OPV dose. The important element of all these cases is that, despite an aggressive search, no other pathogens were identified nor any other medical etiology to account for the syndrome. Clinically, all the cases shared rapid onset after vaccination; fever; myalgias and arthralgias; elevated liver enzymes and elevated bilirubin; profoundly low platelet counts; lymphocytopenia; low blood pressure requiring vasopressure support; renal failure requiring dialysis; and respiratory failure requiring ventilatory support.

Other possible explanations explored and discounted included previous receipt of yellow fever vaccine and receipt of other vaccines (no one was consistent). Slides of the liver biopsies done were shared, demonstrating a fairly classic but also nonspecific pathology. That highlighted the importance of the monoclonal immunohistochemical staining. The molecular sequencing on virus isolated from four cases (two Brazilian, two in the U.S.) noted no consistent mutation in envelope protein or immunodominant region to explain the 17-DD reversion to wild-type.

The evidence supporting a causal relationship includes striking temporal associations, the isolation of 17D vaccine virus from blood and multiple target organs, compatible histopathology in conjunction with a large amount of antigen, hepatic necrosis and myocarditis/myositis seen in Brazil and “Country X”; an absence of other pathologies/etiologies; that fact that the sepsis-like syndrome is similar in some ways to wild-type yellow fever; and multiple cases (7) involving multiple countries and both vaccine strain subtypes 17D-204 and 17DD. There is also precedent (oral polio, perhaps measles)

and biologic plausibility for LAyFv to cause disease similar to the wild-type disease.

The evidence against a direct causal relationship includes some findings atypical of classic yellow fever, no consistent reversion to wild-type yellow fever genotype (Brazilian follow-up virulence research in primates showed no pathology); and that the syndrome was not reported prior to 1996, with close to a billion doses of yellow fever vaccine distributed.

Unanswered questions include the pathogenesis of this syndrome; whether it is a new or only a newly-recognized event (if rare, it would be difficult to detect; as it would still be if it has been masked in past outbreaks); and whether this is a clinical spectrum or an all-or-none phenomenon. Dr. Cetron suspected the former, since cases have recovered, probably occurring in a continuum. The risk factors are unclear, including how many are host-related. Age may play a role, but not exclusively, and so may underlying host factors such as flavivirus susceptibility or resistance genes. Further research is needed on issues of vaccine strain and production.

There are no good quantitative incidence data yet, nor quantitative risk benefit analyses, but Dr. Cetron's bias placed more risk on entering a yellow fever outbreak area unvaccinated. The additional needed research includes animal virulence studies, full laboratory work-up of cases and perhaps retrospective reviews of suspect cases to define host risk factors.

The conclusions were:

- 17D is a possible cause of this syndrome; it is not clearly due to the emergence of a wild-type clone. It is not exclusively due to any one known clear mutation in vaccine type virus. It may be related to an idiosyncratic host response.
- Most cases occurred after primary immunization
- Incidence is really unknown.
- Yellow fever vaccine probably should be reserved for U.S. travelers to endemic and epidemic areas only; any other reason for administration other than medical risk is not advised.

Proposed Response. The proposed response is:

- Revise the 1990 ACIP statement on yellow fever; write informational letters to vaccination centers and practitioners; possibly change the package insert; and print notices in publications. The Brazilian and U.S. work is fast tracked for *Lancet* publication, as is the VAERS work in the next issue of *Emerging Infectious Disease*.
- Link passive reporting with the IDSA and International Travel Medicine Network of Providers to the VAERS system, and publish a protocol on how to work up such cases.
- Establish an active surveillance system of yellow fever vaccine (e.g., through the ~3600 certified yellow fever vaccination centers and other networks).

Discussion with Dr. Cetron included:

- Dr. Deseda: *What is normally expected from viremia or distribution of vaccine virus in target tissue?* In general, viral replication after vaccination is very contained and minimal and has a serologic response much milder than to wild-type. It is very unusual to see this amount of viral antigen in target tissue with histopathologic damage after vaccination.

- Dr. Offit: *What is the probable risk/benefit for a person aged >65 years traveling to an endemic or epidemic area?* The U.S. deaths are skewed toward the elderly at a reported rate of 1:50,000. There has been a resurgence of yellow fever in South America and in Africa and tourism data of U.S. travelers show a 300% increase of travel to South American yellow fever-endemic areas, and 10% to those in Africa. This rapidly increases the denominator of those exposed, and the manufacturers' rate of vaccine production has not kept pace. Modeling has produced a rough numerator and a denominator of coverage, and indicates a downward trend of 10-20%. And, after 75 years of no yellow fever importation, 4 cases in the U.S. and Europe came from South America (3) and the Cote D'Ivoire (1). Dr. Offit cited as another option, discouraging older persons from traveling to disease-endemic countries.
- Dr. Clover: *Do we know if the doses were given from single- or multi-dose vials, and what is known about the management of multi-dose vials?* All five of the cases in developed countries were from single-dose vials with no common lot number. But the Brazilian mass campaign used vaccine prepared in large amounts.
- Dr. Levin: *Did the older people who died have underlying illness?* Yes, but those were normal for an elderly population and did not require immunosuppressives, nor were there common immunodeficiencies. The young people in Brazil were HIV-negative.
- Dr. Helms: *The medications taken by the elderly may be hepatotoxic (e.g., acetaminophen).* Yes, and toxic exposures can cause some similar histopathology. But there were none such seen, and the variety of medications given to manage and support these patients were not hepatotoxic.
- Dr. Smith: *Please clarify the booster dose recommendations.* Research done among military recruits show durable immunity for 30-35 years and possibly for life. The WHO considered changing the decennial vaccination required by International Health Regulations, but there was some concern that the U.S. experience may not be transferrable globally. In addition, this syndrome appears to stem from primary immunization; the prior immunity of boosted vaccinees may give them much lower or no risk. The epidemiological differences seen may stem from differing proportions of elderly people being primarily exposed both to flavivirus and to yellow fever vaccine.
- Dr. Zimmerman: *Any way to estimate a risk-benefit ratio in perspective for areas to which people travel would be helpful.* Yes, but this is challenged, as with many vector-borne diseases, by focal outbreaks spread non-uniformly. Only regular global surveillance could provide a rational risk assessment. CDC is examining some of these issues in the development of recommendations for travelers at a sub-country-level risk profile, for malaria, yellow fever, and other diseases.
- Dr. Chen: *Are there any DOD data to indicate if this may be a new or newly recognized syndrome?* DOD reports no experience with it, and they would have recognized it in otherwise young, healthy military recruits.
- Dr. Jim Presley, Aventis Pasteur: *This must be publicized, preferably by a CDC/FDA collaboration, but the Brazilian cases should be separated from the U.S. cases due to 1) different strains (DD and 204); different monoclonal antibodies; and difference demonstrated in neurovirulence testing; and 2) the marked difference of the Brazilian cases: youth, no other obvious cause of death; acute illness quite compatible with yellow fever; typical yellow fever histopathology on autopsy and yellow fever virus in high titers isolated from a multitude of tissues.* It should be further investigated whether there really is a syndrome of that nature in the U.S. Aventis Pasteur has already

- submitted a package insert amendment to the FDA to describe these cases.
- Dr. Tony Markham applauded Dr. Cetron and his collaborators' analysis of these cases, particularly with the sparse data available on the American cases. These cases must be taken seriously, particularly in any active surveillance done. The CDC's NCID Division of Vector-Borne Infectious Disease will provide the technical support to evaluate these cases to match the Brazilian level of investigation.

Dr. Clover reported that the Adult Immunization Workgroup had examined this syndrome when it was first presented, and agreed to review it again. A subgroup of volunteers was formed, of Drs. Deseda and Offit., and Dr. Midthun volunteered the services of Dr. Philip Markhoff, FDA's yellow fever expert. Dr. Snider added that CDC has an agreement with FDA to have an FDA representative on every relevant workgroup.

VACCINE SAFETY UPDATES

The Brighton Collaboration. Dr. Katrin Kohl outlined the activities of the Brighton Collaboration, which aims to develop standardized case definitions for adverse events following immunization. This began in fall 2000 under the coordination of Dr. Kohl and Dr. Jean Bonhoeffer, a Swiss academician. The collaboration is currently supported by CDC, WHO, and the European Research Program For Improved Vaccine Safety Surveillance, or EUSAFEVAC. Dr. Kohl outlined the five members of the Collaboration's Steering Committee and its structure.

Since vaccine-preventable diseases (VPD) are less frequent than vaccine adverse events in the developed countries, standardized case definitions are needed to assess immunization safety data in order to ensure ongoing trust in immunization programs. These definitions will allow comparison of safety data from around the world, maximize scientific output from pre- and post-licensure vaccine trial data and from post-marketing surveillance data, and advance scientific progress. Dr. Kohl demonstrated the diversity of safety methods used in recent clinical trials, which tracked fever at different cut-off points.

The case definitions will be developed through expert working groups, each of which will address one adverse events following Immunization (AEFI). These experts will collaborate with participants from the regulatory, public health, and scientific fields, as well as professional organizations and vaccine manufacturers. The target audiences include investigators, health officials, health care providers, and regulators involved in all levels of immunization and vaccine safety.

An inventory of existing case definitions from the literature (both published and not) will be compiled and reviewed by the workgroups, which will develop case definitions by consensus. They will be reviewed/validated by a broader workgroup including vaccine safety organizations and interested individuals; field tested when necessary and possible; and then globally disseminated.

The first AEFIs to be defined are fever, local reactions, intussusception, abnormal crying, convulsion, and hypotonic-hyporesponsive episode. The Local Reaction Workgroup has listed 16 different injection site reactions to be defined. There are currently 5-16 members in

each of five workgroups. Those on fever, intussusception, and injection site reaction with abscess at injection site, have begun drafting their case definitions and their related parameters (e.g., in the fever group, stratification by type of vaccine in order to decide on the duration of follow-up needed post-immunization). A protocol for validation studies is in initial development.

The seven AEFIs tentatively to be defined include allergic reaction, rash, asthenia, paresthesia, SIDS, myalgia, and idiopathic thrombocytopenia. Their selection was based on the frequency and severity of occurrence or by public interest and funding concerns. A chart of the top ten serious and non-serious AEFIs reported to VAERS in the last decade and those being defined by the Collaboration showed a good parallel. The next set of adverse events to be defined will be selected in this month. Dr. Kohl invited review of their Website (brightoncollaboration.org, noting that there is no initial "www"). Draft definitions are hoped to be completed by September 2001; the final draft of the first six AEFI's by March of 2002; and the next seven workgroups to begin this December. She invited collaboration. On Dr. Neuzil's question, she explained that the definitions will include all age groups. Some may be stratified by age, depending on the adverse event.

IOM Immunization Safety Review Committee. Dr. Kathleen Stratton, of the Institute of Medicine's (IOM) Immunization Safety Review Committee, provided its first report. The Committee is sponsored by CDC and NIH to conduct a three-year project to serially address various vaccine safety concerns. For each, the Committee will assess the scientific plausibility of a causal link between the vaccine and the adverse event in question, the significance of the issue in a broader societal context, and then will recommend public health response actions. The Committee meets three times a year and will issue a brief consensus report 60 to 90 days after each meeting. There will be summaries developed for the public and outreach will be done to providers, researchers, policymakers, and the public.

The first meeting (March 2001) addressed MMR and autism; the thimerosal issue will be addressed in July in Boston (Dr. Stratton will return 2-3 months after that to report); and the discussion of multiple antigens and immune dysfunction will occur in November, probably in Seattle. The topics are chosen by the DHHS' Interagency Group (IAG).

The *plausibility assessment* and *causality determinations* are based on review of epidemiologic studies, knowledge of the adverse event's human pathogenesis, and relevant animal models. The *significance assessment* of the issue includes consideration of the burden (seriousness) of the VPD in question, its risk if immunization rates fall; its treatability; the burden of the vaccine adverse event; the level of public concern; and other issues that the Committee feels are relevant (e.g., feasibility of research to resolve unanswered questions).

The Committee's *public health response* comments include recommendations on policy review, targeted recommendations on research and surveillance, and on communications. Aspects of policy review are outside of the Committee's domain, being under the auspices of others such as the ACIP. They will not overlap other committees' domains, but if their work indicates evidence sufficient to recommend to another specific committee for action,

they will do so.

Committee Process.

- An open scientific meeting (that information is posted on the Website) and another one-day Committee meeting are held for each topic.
- The Committee reviews the published literature, and all information and reviews submitted by interested parties. All information is placed in a public access file.
- A background paper was commissioned on the first topic, MMR and autism. Although controversial, it was very effective in drawing many helpful comments when posted on the Website. The Committee reviewed them all. That process will probably continue, but probably with clearer caveats that the posted paper does not represent the Committee's view.
- The Committee reviews VAERS reports as possible, and hears about unpublished data at the public meeting held with the first scientific session. The report briefly discusses how unpublished data might be weighed. The more detail provided, the more that can be done; but because of the lack of peer review, it is doubtful it would sway a causality determination.
- Public access, aside from the public meeting, include a telephone number contact and multiple materials on the Website.
- IOM reports are extensively peer-reviewed (the MMR/Autism report had 17 reviewers), but the responsibility for the report lies with the Committee. The reviewers do not see the final report until it is released.

MMR and Autism Report. The Committee concluded that the evidence favors rejection of a causal relationship at a population level between MMR vaccine and autistic spectrum disorders, based upon a consistent body of epidemiologic evidence showing no such association at a population level.

- The epidemiologic data were taken from the Wakefield case series published in 1998 in the *Lancet* and from the 1998 Peltola et al study of 31 vaccinees recorded in the U.K.'s passive surveillance system. The Patja et al study published in the *Pediatric Infectious Disease Journal* in 2000 followed 169 vaccinees with 173 serious adverse events between 1982 and 1996. Neither of these latter two studies reported cases of autism.
- Three published ecologic studies: Dales et al (2001) studied children born between 1980-1994 in California who were diagnosed with autistic disorder. The General Practitioner's Research Database case study of 2001 followed 350 children in the U.K. aged ≤ 12 years diagnosed with autism between 1988-1999. Again, no trend emerged in the increasing rates of autism with the immunization. The Gilberg et al 1998 study reanalyzed data from a 1991 population study of autism to examine pre- and post-MMR introduction rates. None of these showed an association with increased autism.
- The Taylor 1999 cross-sectional time series study provided the strongest data in three analyses of identified children. It showed no step-up in autism diagnoses after MMR introduction, no change in diagnosis age with vaccination age, and no clustering of diagnosis, parental concern, or autistic regression.
- Three unpublished reports also were reviewed by the Committee, from Dr. Elizabeth Miller (updating the Taylor study, with preliminary analyses supporting it); Dr. Fombonne (reporting a time series analysis reflecting a step-down rather than increase in autism incidence post-MMR introduction), and Dr. Wakefield (reporting rechallenged cases of

regression after MMR vaccine, confirmation of the presence of measles virus, and typing that for wild- or natural-type vaccine strain).

Causality: The IOM approves of using case reports to support causality, but heard none of the depth reported at this meeting that could strengthen a causality argument. The biologic models linking MMR vaccine and autistic spectrum disorders were fragmentary. Too many events would be necessary for the MMR vaccine to cause autistic spectrum disorder.

- No relevant animal model has demonstrated a link between MMR vaccine and autistic spectrum disorder. Those that exist are inapplicable to postnatal insults such as the MMR vaccine.
- Nonetheless, the Committee did not exclude the possibility that the MMR vaccine could contribute to autistic spectrum disorder in a small number of children. The epidemiologic evidence, although consistent and all indicating no association, lacks the precision to assess rare occurrences of MMR vaccine responses that could lead to autistic spectrum disorders. And, although the proposed biologic models linking MMR vaccine were not established, neither were they disproved.

Recommendations. The Committee recommended continued studied because:

- The evidence is limited; no study was particularly exemplary or strong alone and all had flaws.
- The severe burden presented by autism requires a better understanding of the disease, and the burden of diseases prevented by the vaccine is very high. If this issue cannot be resolved to parents' satisfaction about the safety of the vaccine and immunization rates fell, the public health burden of natural measles, mumps, and rubella would be terrible.
- Although the Committee did not specify what sort of attention should be brought to bear, they made several specific targeted research recommendations:
 - Establishment of standardized case definitions or assessment protocols for autistic spectrum disorders.
 - Exploration of whether exposure to MMR vaccine is a risk factor for autistic spectrum disorders in a small number of children. But this is perhaps best delayed until there are biomarkers of either the risk for autistic regression or of one of the steps of the proposed biologic models).
 - Investigation of whether or not the measles vaccine strain virus is present in the intestines of some children with autistic spectrum disorders (to replicate/validate the Wakefield work).
 - Reports to VAERS should provide with as much detail and documentation as possible when any diagnosis of autistic spectrum disorders may be related.
 - Study of the possible effects of different immunization exposures (e.g., children whose families declined their receiving the MMR vaccine). The Committee was very clear that this was not an encouragement of alternatives to the recommended immunizations, but rather an acknowledgment that some children are being immunized in a different way. Targeted clinical studies of these children or these families would be of interest.
 - The Committee endorsed the existing research portfolio of CDC, NIH, and other funders on the risk factors and biologic markers of autistic spectrum disorder, in general.

- ▶ CDC and FDA should review their communications, particularly those on the Internet, to ensure that their information is not inflammatory and is unbiased about the putative link between MMR vaccine and autism.
- ▶ Tangential issues that could be addressed in the Committee's future include discussion between the vaccine and the public health professionals and the public about such questions as: why it is impossible to prove a negative relationship; what is an "acceptable" level of risk for a given vaccine benefit, and how is that best discussed with various stakeholders; how to best convey the meaning of terms such as "association" versus "causality" and what evidence supports them; and ways to research vaccine exposures not directly causing but perhaps triggering conditions of multi-factorial etiologies; the appropriateness of alternative immunization schedules or practices which might be requested in a clinical setting; and the general issues of vaccine and risk benefit communication.

In discussion with Dr. Stratton, Dr. Jackson asked how the report has been received. She replied "about what would be expected" in vaccine safety work. The pediatric and the public health community agree with much of it; the research recommendations and the call for no policy review were considered sensible. Some vaccine safety advocates approved of the report for the most part. Other groups are less happy, mostly with the emphasis of the conclusion rejecting the causal relationship based on the evidence, although the possibility cannot be ruled out.

Update on Thimerosal

Dr. Roger Bernier updated the committee on the progress of transitioning from a thimerosal-containing vaccine supply in the routine pediatric schedule to the present situation of a supply with no, or trace, amounts of thimerosal.

Background. When this first came to widespread public attention in July 1999, three vaccines on the routine schedule contained thimerosal as a preservative: hepatitis B, DTaP, and Hib. The ACIP encouraged clinicians and parents to immunize all infants even if the choice of individual vaccine products is limited for any reason. In October 1999, ACIP stated that those three vaccines can continue to be used beginning at two months, along with monovalent or combination vaccines that do not contain thimerosal as a preservative. Then, after the Vaccine Safety Datalink reports of a possible link to health effects associated with thimerosal, a second Joint Statement by the AAFP, AAP, ACIP, and the Public Health Service (PHS) recommended continuation of the current policy of moving rapidly to vaccines which are free of thimerosal as a preservative. Until an adequate supply of each vaccine is available, use of vaccines which contain thimerosal as a preservative was still acceptable.

Since July 1999, hepatitis B has become thimerosal-free (by Merck in September 1999 and then by GSK in March 2000). All of the Hib supply is now thimerosal-free, as is the DTaP supply (Aventis Pasteur in March 2001 and GSK since 1997). Two other companies dropped out of the market. In fact, all the routine vaccines on the pediatric immunization schedule are now thimerosal-free. Others still containing it (e.g., influenza, Td, and DT) are not part of the routine immunization schedule. The remaining supply of thimerosal-containing DTaP vaccine is probably small and should be quickly finished. The Hib and hepatitis B vaccines last released into the public sector have not yet expired, but the

remaining supply should be quite limited.

The ACIP has chosen not to express a vaccine preference relative to thimerosal. While that is now moot with the thimerosal-free product, expressing a preference would influence the use of any existing vaccine stocks containing thimerosal. The Committee was asked if it wished to continue the current policy, or to make a recommendation that could decrease the use of the small estimated number of hep B, Hib, and DTaP doses with thimerosal remaining in doctors' offices and public clinics.

Dr. Modlin thanked Dr. Bernier for the immense amount of time and intellectual energy he devoted to this issue and the balanced approach he provided. He also noted that, in addition to the policy implications, there could be implications for thimerosal-containing vaccines used throughout the world. Dr. Bernier agreed. The staff was not ready to identify options for the Committee on this day, but only requested an indication of its wishes.

Discussion with Dr. Bernier included:

- Dr. Chen: The Europeans are moving in the same direction as the U.S., as reported at the recent WHO Immunization Safety Meeting. There is some concern for the **EPI**, but the schedule used there does not contain the amount of thimerosal exposure that led to the concern in the U.S.; the issues would just need to be framed properly.
- Dr. Zink of GSK stated that their hepatitis B vaccine is free of preservative.
- Dr. Snider: *Could there be any implication to other vaccines not now included in the schedule, such as LAIV if it is considered?* One of the potential consequences of making a change could be to change people's perceptions of other vaccines. Care would be needed about attaching the concept of hazard to thimerosal. The hepatitis B vaccine poses issues because it is both for infants and adults.
- Dr. Zimmerman: *Stating a preference can pose implications* for influenza, TD, and perhaps other things. Going beyond the present policy raises potential problems.

Dr. Tompkins moved to support the current policy. With no objection, **that was accepted** as the Committee's response.

Proposed Research on Thimerosal-Containing Vaccines and Developmental Deficits. Dr. Thompson summarized the background of guidelines of the Food and Drug Administration Modernization Act of 1997. This required a review of biologics containing, and the guidelines for, methylmercury and thimerosal's ethylmercury. Only studies on methylmercury were available. EPA's guidelines are the most stringent; the routine vaccine schedule would exceed the EPA's standards for methylmercury exposure to children aged <6 months.

A June 2000 meeting reviewed analyses using the data of two VSD HMOs, Northern California Kaiser (NCK) and the Group Health Cooperative (GHC). That report associated cumulative ethylmercury exposure in the first year of life with language and speech delay, ADHD, tics, stammering, and unspecified developmental delays. However, the analysis had weaknesses, including in its statistical associations and inconsistent subsequent analyses.

A follow-up, two-phased, retrospective cohort study was proposed, with Phase I focusing on

sensitivity versus specificity (through a broad range of neuropsychological tests, outcomes from the VSD screening analysis, and domains affected by methylmercury exposure reported in previous studies). Phase II would follow-up on Phase I with specificity to the deficits and patterns seen from Phase I. A larger sample size would be required, perhaps one with different children than in Phase I. An external multi-disciplinary panel review of the proposal in March commented:

- The study design's separation of Phase I and Phase II (3-5 years) was not efficient or timely. A hybrid study to increase the timeliness of the results and reduce the cost of the study was advised.
- Opinions differed as to whether low birth weight infants should be included or excluded.
- The potential bias of including the NCK as a study site, the source of the strongest results in the VSD screening analysis, was raised
- There are few ethylmercury studies available to guide definitions of the exposure groups and possible threshold effects.
- The consultants recommended conducting pharmacokinetic studies and extensive data collection on alternative exposures and potential confounders.
- Suggestions of outcome measures included: reducing the number of domains in the study; focusing the domains based on methylmercury studies and results, selecting highly sensitive but brief tests, and adding measures on speech and visual-spatial ability.
- The retrospective cohort design study was felt to be well worth doing, but opinion differed if the two-part study was a sound approach. There was also general opinion voiced that the Phase I results would not necessarily ensure finding any results in Phase II.
- There were no strong opinions to exclude NCK as a site, but there was general agreement that it should not be analyzed alone.
- Overwhelmingly, the panel believed that the association between thimerosal and autism could not be studied within this design. They recommended instead a case control study, which NIP will do. They also did not feel that a prospective cohort design study was imperative. Some disagreements about the correct interpretation of the results from a retrospective study related to ethical considerations.

A follow-up, similarly multidisciplinary meeting in May reviewed the revised test battery. The panel members added measures based on group input, and revised the protocol:

Design: Retrospective cohort study.

Cohort: Subjects will be selected based on cumulative thimerosal exposure from vaccines at age 3 months, since the highest exposure per kilogram occurs at age 2 months if ACIP recommendations are followed.

Testing: Standard neuropsychological testing battery of all participants at age 7 and 9 years; confirmatory evaluations of children testing positive on certain screening tests. (In essence, Phase II will be done the same day as Phase I).

Exposure groups: Three: low (<25 µgm ethylmercury; medium: 25-62.5 µgm; and high: ≥62.5 µgm. This may be changed to two exposure groups, of those who received hepatitis B vaccine at birth versus not. Alternative exposure will also be researched: cumulative exposure at age 6 months, 1 year, and 2 years, with weight-adjusted analyses. So, although the sample will be selected based on cumulative exposure at 3 months, all exposures will be explored.

Exclusion criteria: Severe perinatal and selected congenital disorders, receipt of hepatitis B immunoglobulins, low birth weight babies (<2,500 gm) and gestational age <38 weeks.

Outcome measures: Phase I: verbal ability, visual-spatial ability, executive functioning and attention, short-term memory, fine manual motor tasks and achievement, language delay, speech delay, and ADHD; Phase II: a) characterization of prevalence estimates for language and speech deficits, and ADHD, testing those measured at 1.5 SD below national norms on selected Phase I measures; b) other exposures and potential confounders, including proxy measures for other forms of organic mercury, lead, PCB's, alcohol, and other drugs, and from abstracted medical records, questionnaire responses, and IQ tests to parents/caregivers.

Sample size Phase I: small; Phase II, ~3400 (assuming background prevalence of 2.5 in the low exposure group, with a power of 80% and a two-fold difference in neurodevelopmental delay rates) with ~1100 per exposure group (800-850 from each of four VSD HMOs).

Next steps: NIP review of the protocol; discussion of funding/budgeting; presentation to the IOM Immunization Safety Committee July meeting; identification of an independent contractor for the study planning phase (procedures, sampling frame, standardized testing, pilot and actual study).

Discussion with Dr. Thompson included:

- Dr. Modlin: *Why exclude low birth weight babies, the group most likely to be at risk and to signal?* The screening analysis indicated no effect from thimerosal exposure within low birth weight children; and great likelihood of poor neurodevelopmental outcomes in such children, who are also less likely to get immunized. Such confounding by contraindication requires a randomized trial. Dr. Modlin: *But this group is sizable, and is truly vulnerable to adverse effects of toxin exposure early in life; and the true confounding effects of low birth weight on adverse outcomes begin for those with gestational age of ≤ 30 -32 weeks.* Dr. Chen: Most of the birth weights are ~2500 gm; only a very few are much lower, so this seems an artificial cut-off if a very low birth weight group was really desired. Discussion will continue with the IOM.
- Dr. Orenstein: *A decision has not been made to go forward with this study at this point,* pending review of budget considerations and priorities since thimerosal was removed from the supply. The major issues relate to vaccine injury compensation therapy and implications to the developing world.
- Drs. Jackson/Modlin: *Many African-American babies who are very well developed fall below the 2500 gm weight cut-off and would be excluded. Use something much lower than 38 weeks and 2,500 grams.*
- Dr. Plotkin: *Phase I is generally a hypothesis-finding phase; but Phase II will only try to confirm the reality of that statistical difference among all the variables, among the same population?* Phase I is a more traditional toxicology study which uses continuous measures and ends when it is determined that the exposure caused "x" point difference in a particular outcome. This Phase II focuses on following up on the VSD results. It adds those screening measures' specific outcomes to the traditional toxicology study to follow up on the same individuals and accurately classify them as either speech-delayed, language-delayed, or ADHD. The multiple-measure issue is a known problem that will have to be addressed.
- Dr. Plotkin: *Will this be blinded for the parents, who probably are or will be aware of*

related lawsuits? Yes. There has been discussion of how the design can reduce that potential confounder.

- Dr. Halsey: *Will the investigators and reviewers be masked to the exposures?* Yes. *Explore whether you can increase study power to be able to detect differences even if they are small (likely) and do not reach an odds ratio of two. The study should be done because of the added strength of a retrospective cohort analysis as compared to case control studies.*
- Ms. Lynn Redwood, of SafeMinds, *took exception to cohort selection based on age only to 3 months, and using 12.5 µg to separate the medium- and low-exposure groups. Mercury's long half-life will not reach peak blood concentrations until age 6 months.* Dr. Thompson responded that there is a very high positive correlation between 3- and 6-month cumulative exposure (~ 0.7-0.8), and the highest exposure per kilogram occurs at two months of age for most individuals. Ms Redwood: *Right. But then it says six months because of the stair-stepping of excretion concerns that need to be addressed.*

PUBLIC COMMENT was solicited, but the requesters, Dr. Zink and Ms. Redwood, had already spoken, so the meeting adjourned at 5:35 p.m.

JUNE 22, 2001

UNFINISHED BUSINESS

Review of the Edited Influenza Supplementary Statement

The meeting reconvened at 8:00 a.m. the following morning with a discussion of the edited influenza supplementary statement that Dr. Schwartz had provided for the members' overnight review. Dr. Schwartz summarized the changes made:

- Format changes placed the goals up front, with the description of production estimates and the recommendations, followed by the supporting data. The text under recommendations was simplified.
- A recommendation for mass immunizers was added, which includes local and state health departments.
- The recommendation about communication to high-risk patients was modified to avoid them all calling their physician's office about vaccine availability.
- Text was added to indicate that this year's situation may become the norm, and that ACIP will consider later what recommendations should be routine as opposed to unique for this season.

Dr. Schwartz outlined several other issues for discussion:

- Use of the terminology of "delay" or "decreased early season availability." The advantages of the latter are: 1) to deflect concern about the causes of the delay; 2) to decrease public alarm; and 3) to potentially more accurately reflect the long-term situation. However, he felt the advantages of using "delay" still seem to be greater: 1) it accurately reflects the perceptions of physicians and of others in the system of what is the "norm;" 2) it better captures the stakeholders' attention; 3) it preserves CDC's credibility in the face of investigations and conspiracy theories; and 4) it accurately reflects this year's situation without assumptions about future production/distribution decisions.

- To provide perspective on the magnitude of the problem, he added text (“Distribution through October will be substantially greater than during 2000 when production delays occurred”). And, to avoid the confusion of addressing current and future objectives in a single document, he added as a goal a prioritized or phased system for this year while still emphasizing the Healthy People 2010 goals.
- To address close contacts of pediatric patients, the parenthetical comment can be revised to a footnote. Staff will work with the AAP to better clarify that issue.

Discussion with Dr. Schwartz included:

- Dr. Siegel (and general consensus): *Replace “those who care for them” with a more specific statement referencing health care workers to make it very clear that they need to be immunized early.*
- Dr. Neuzil: *Strengthen the text stating the importance that manufacturers, distributors, and vendors inform providers of the amount of vaccine available under “Recommendations for Manufacturers”*
- Ms. Linda McKibbin, CDC Office of Health Care Partnerships: *There are several places in the recommendations where the priority of distribution to nursing homes could be placed, including under providers for manufacturers and for health departments. That can be done if the Committee desires, but there are some special concerns about the elderly population (waning immunity and October vaccination rather than earlier) that make it tricky. Text can be developed recognizing that groups such as the frail elderly (>65 years old) should be given priority for earlier vaccine, and that standing orders are one approach to improve immunization rates within this population.*
- Dr. Nichol: *Perhaps include text to explain that references to “providers” includes health care organizations and long-term care, etc., as well as individual providers. That could be added as a recommendation to manufacturers and distributors.*

Dr. Word questioned the discussion, noting that nursing homes and chronic care facilities were already listed as priority groups. Dr. Modlin summarized the committee’s consensus to allow Dr. Schwartz to work out the final wording with staff to reflect the Committee thoughts.

VOTE: *Conflicts:* Aventis, or Wyeth, or Medeva.

Dr. Johnson moved that the Committee support the supplementary statement as presented by Dr. Schwartz. Dr. Levin seconded the motion.

In favor: Levin, Brooks, Word, Tompkins, Helms, Offit, Johnson, Smith, Deseda, Modlin.

Opposed: None.

Abstentions: Rennels, Clover.

The motion passed.

Dr. Snider noted the two-stage process of the Committee’s advice to CDC and then its decision of whether to accept those recommendations. He thanked the Committee and staff for their consistent excellent crafting of recommendations, such that they are generally accepted as advanced. He expected that any changes would be editorial rather than substantive issues, but if any of the latter are made, the Committee will be informed.

AGENCY UPDATES

National Immunization Program (NIP)

Dr. Orenstein reported the success of 35th National Immunization Conference from May 29-June 1. Over 1500 people participated in the agenda, which included a Cyber Café, a Webcast, and will produce a CD ("Everything You Want to Know About Immunization").

NIP Budget. The President's FY2002 budget submission included a 3% (\$109 million) decrease for CDC overall, but a 4% increase for NIP. That includes \$14 million for the 317 Grant Program (mostly for pneumococcal conjugate vaccine purchase); \$4 million for vaccine safety activities; \$1 million for global immunization activity (polio); \$1 million for extramural research; and a mandated \$2 million cost of living increase.

Pneumococcal conjugate vaccine. Early concern about uptake has lessened. As of May of 2001, >8 million doses were purchased, comparable to those of Hib-containing vaccines. However, since much of this is probably filling the pipeline, the implementation of pneumococcal conjugate vaccination is not at routine immunization levels; and the resource needs and necessary degree of catch-up remain unknown, especially for the state programs.

Eradication Programs. *Measles* in this hemisphere is still at record lows. PAHO data were shared showing ~90% immunization coverage. The U.S. had 86 cases in 2000 (a record low, 30% of which were importations and 18 of the 60 indigenous cases import-associated), and 60 cases as of June 9, 2001. Although this was higher than the prior year, 36% of the 60 were imported, and in perspective, there were 36,000 cases in 1990. There is no evidence for re-establishment of indigenous transmission. Canada, Mexico, and El Salvador also reported cases, and only Hispaniola appears to have indigenous transmission.

Polio eradication is making tremendous progress. Global polio funding increased in the FY 2001 budget by \$1 million (to total ~\$107). At the end of 2000, ~20 countries were considered endemic (mostly the Indian subcontinent and sub-Saharan Africa), a 99% reduction since the program's beginning in 1988. The target is to terminate transmission by the end of 2002 and to certify eradication of polio (3 years without cases) by the end of 2005. Dr. Orenstein also presented the latest data on the Hispaniola outbreak. The Dominican Republic's last known case was identified on January 25. Haiti is doing less well, with the last known case's onset on April 29. Both countries are trying to terminate transmission with oral polio vaccine immunization.

Food and Drug Administration (FDA)

Dr. Midthun reported two meetings of the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). During the March meeting, they discussed the license application for GlaxoSmithKline's (GSK) combination vaccine containing DTaP, hepatitis B, and inactivated poliovirus vaccine. Efficacy for the new combination product was based on a comparison of the immunologic responses induced by the combination vaccine vs. licensed vaccines (GSK's DTaP vaccine and hepatitis B vaccine, and Wyeth Lederle's OPV vaccine). The combination vaccine was non-inferior to the comparator

vaccines with regard to all the antigens with the exception of the FHA component of the pertussis vaccine. The VRBPAC was split on whether efficacy had been demonstrated. The VRBPAC discussed the safety data but did not vote on the question of safety because of outstanding manufacturing issues. The VRBPAC agreed that additional safety data should be collected, especially in the context of concurrent immunization with Prevnar, as there were no data on such concomitant administration available. The majority of the committee indicated that these data should be obtained pre-licensure, although some members thought that this could be done post-licensure. The development of new conjugate pneumococcal vaccines was also discussed. Prevnar's® recommendation for routine use prevents a placebo-controlled efficacy study in the U.S. with any new such vaccine. The majority of the committee indicated that a demonstration of immunologic non-inferiority in comparison with Prevnar could be used to support efficacy, in lieu of clinical endpoint data. The question of how new serotypes would be evaluated was complex. Although it was agreed that this should be done based on immune response as well, it was not clear what the comparator should be.

In May, the VRBPAC discussed the use of adenovirus-transformed cells as a new substrate for producing vaccines (e.g., for HIV) that cannot be produced in more conventional cell substrates. The VRBPAC generally concurred with the FDA approach to date in evaluating the adenovirus-transformed cell substrates for tumorigenicity, oncogenicity, and adventitious agents, and provided additional helpful input on evaluation. The July meeting agenda includes discussion of Aviron's license application for live attenuated influenza virus vaccine.

New product approvals include the GSK TwinRix® combination hepatitis-A/-B vaccine for active immunization against hepatitis A and hepatitis B in individuals aged 18 or more years, and Aventis Pasteur's new preservative-free formulation of Tripedia®, which contains only a trace of mercury (less than 0.5 mcg per dose versus 25 mcg per dose in previous formulation).

In response to Dr. Katz's question, Dr. Midthun confirmed that immunogenicity, efficacy and safety data obtained for vaccines tested in other countries can be used to support license applications for these products in the U.S.

National Vaccine Injury Compensation Program (NVICP)

Dr. Geoffrey Evans reported the monthly statistics for FY2001. An increase in claims from ~15 to ~18/month is probably due to more publicity about the Program and to a lag time for the claims filed. Claims for new vaccines include 343 for hepatitis-B (gathering medical records will require 3-5 years until adjudication) a few for Hib and varicella, and ten claims to date for rotavirus vaccine. The latter has no specific injury listed, but a Notice of

Rulemaking is in development to add intussusception. When published as a final rule (in several years), an 8-year retroactive coverage period is likely. There have been 32 claims on DTaP. There are still about 20 pre-88 claims remaining. Awards totaling \$1.25 billion have been paid to date. The Trust Fund balance is \$1.67 billion; ~\$200 million is collected annually.

DTP was the predominant vaccine cited in claims 1990-97 (73%), followed by MMR (11%) and OPV/IPV (5% each); rubella (3%), DT/Td/T, 2%; and others, 2%. Coverage for *pneumococcal conjugate vaccine* has caused some confusion. To be added to the Vaccine Injury Table (VIT), a vaccine must be recommended by CDC for routine administration to children, and Congress must impose an excise tax. Once done, coverage is retroactive for 8 years. The excise tax for conjugate pneumococcal vaccine predated licensure somewhat. The VIT included it Category XIII, which is reserved for new vaccines, and the coverage dates back to the effective date of the excise tax. Pneumococcal vaccine, except for the 23-valent pneumococcal vaccine given to adults and older children (since it is not a general-use recommendation), was included in May with no specific injury listed. The rule should be final in two years. The NVICP Website offers further explanation.

The "Vaccinate America's Children Now Act", which would reduce the vaccine excise tax, has some bipartisan congressional support, but its future is uncertain. On March 29, Reps. Dave Weldon and Jerry Nadler will discuss their bill in a press conference. Similar to the Vaccine-Injured Children's Compensation Act, it requires the burden of proof standard used in veterans' claims processes. This loose, non-science approach, does not require a positive association, but accepts effects "deemed to be vaccine-related by a fair and impartial person." It also extends the statute of limitations from 3 to 6 years for both death and injury claims, based on the petitioner's first knowledge of injury. Other provisions include family counseling reimbursement and the establishment of trusts.

A September 1999 hearing on the program and a recent bipartisan report recommended the establishment of a reasonable alternative standard, and consideration of how to increase the number of claims compensated. There is interest in this since the newer 12 vaccines/conditions do not have the clear outcomes of the vaccines of the original VIT, which still must show a causation-in-fact. The difficulty and cost of doing so for the new vaccines has caused a significantly increased number to be dismissed. To avoid the claimants' return to the tort system, standards that embrace both science and provide a more consistent approach are being pursued.

Discussion with Dr. Evans included:

- Dr. Abramson: *Were the hepatitis-B claims most from older people?* Of the first big bolus, ~50 claims were for persons aged ≤ 18 ; about half of those were neonatal doses. *What would be the claims process for adverse reactions to influenza vaccine for high-risk children?* They would go straight to the tort courts until there is a general-use recommendation for influenza vaccine issued.
- Dr. Chen: *One reason for these modifications is a major difference in the law's ultimate implementation versus its original intent.* He explained that changes to the VIT were to be based on science, but without funding provisions for doing the required scientific research. So annually, there is budget competition with NIP for vaccine purchase, etc.,

even though there is a \$1.5 billion trust fund. The current Washington solution seems to be to simply remove the scientific aspect to allow faster and easier payments. He felt that the stakeholders involved (e.g., the AAP, industry) should protest the subversion of the law's original intent and make an alternative case for the law's modification.

- Dr. Levin: *Why is hepatitis-B so predominant in active claims, and what happens to the percentage dismissed; do they go to the tort system?* DTP lawsuits tracked through 1997 drop significantly. They seem to be not going through the tort system because they are included on the table; negligence need not be proven. Other reasons for its dominance include that the hepatitis B claims deadline was approaching, along with the attorneys' motivation to file claims after the related and very publicized French government action.

National Vaccine Program Office (NVPO). Dr. Martin Myers accepted the committee's good wishes on his announced intent to resign as NVPO Director. The Assistant Secretary for Health is beginning the process of identifying his successor, who will be based in Washington, since the NVPO is now a component of the DHHS Office of Public Health and Science. He will remain to ensure an orderly transition.

Dr. Myers described the relationship of the DHHS Interagency Group (IAG), whose membership is from federal agencies conducting vaccine-related activities (DHHS, DOD, USAID). It serves as a policy facilitator and coordinator. The related advisory committees include FDA's VRBPAC, the NVICP's Advisory Commission on Childhood Vaccines, and the National Vaccine Advisory Committee (NVAC) which advises the Assistant Secretary on vaccine policy issues.

Current NVPO activities include coordination of the Pandemic Influenza Plan, which includes a series of annexes (e.g., infection control, triage and care for children, etc.). NVPO sponsored a technical workshop in March on the use of anti-viral drugs in the pandemic setting; reviewed the NIP's revision of the pediatric/adolescent and adult immunization standards; and it coordinates the Polio Laboratory Containment Activity. Related to that, the CDC pilot study is complete; NIH's will be so in the next month; and pilot surveys will begin soon to complete a national inventory by year-end. The process will then begin of increasing the biocontainment level for work with wild-type poliovirus. NVAC briefed the Secretary on the vaccine supply issues, and a workgroup is examining the issues related to introduction of new vaccines. Another workgroup is developing guidelines for the states' use in implementing the recommendations for new vaccines. The vaccine supply delays and shortages have been subjects of much discussion. Topics include the shortages of influenza and tetanus-toxoid containing vaccines (except for the pediatric DTaP), and the shrinking list of producers of meningococcal, varicella, and DTaP vaccines. There are now no licensed producers of OPV for use in outbreak control in the U.S.

The NVAC and its Subcommittee on Vaccine Safety and Communication has been briefed by the IOM Vaccine Safety Committee and held a public forum about the process of identifying future topics. The Subcommittee was asked to consider the process of identifying and recommending future topics to the IAG for the IOM Committee to pursue.

A workshop on intussusception and rotavirus vaccines will be sponsored by NVPO to

explore that attributable risk, since this is a critical vaccine for development both in the U.S. and worldwide. Documents of the Workshop on Aluminum in Vaccines are in press, and the Combination Vaccines Workshop will be in the July issue of *Clinical Infectious Diseases*.

Dr. Georges Peter, the NVAC Chair, commented on the NVAC's recommendations regarding the Polio Virus Laboratory Containment. Dr. Walter Dowdle presented the plan in detail. The participation and cooperation of laboratories nationally, private as well as governmental, was encouraged, to be sure of identifying all the stock. He also elaborated on the Workgroup on Public Health Options for Implementing Vaccine Recommendations. This was requested by ASTHO to help them establish priorities in developing school, day care (and perhaps college) immunization requirements. This does not involve identifying vaccines, but rather, suggesting ways with which the states can implement vaccine recommendations (from mandates to incentives). NVAC will sponsor three workshops across the country to hear the state health departments' perspectives, along with private groups, industry and other partners. A draft report by year-end is planned. Finally, he noted the nascent status of the Workgroup on Strengthening Vaccine Supply. There is now a need to address supply-related problems, which are broader than the current status of specific vaccines.

National Center for Infectious Diseases (NCID)

Dr. Allison Mawle reported the May 30, \$70 million gift of the Bill and Melinda Gates Foundation to fund the development and production of a meningococcal A conjugate vaccine. This ten-year project is in partnership with the private sector, developed by a working group spearheaded by WHO and the Seattle-based Program for Appropriate Technology in Health (PATH). CDC is the leading technical partner. Sub-Saharan Africa has ~200 million people at risk for meningitis. So far in 2001, at least 40,000 people have been infected, and >4000 died (a probably under-reported total). The problem in developing a vaccine has been the lack of a guaranteed market.

Once the conjugate vaccine is developed, the foundation will oversee its evaluation in Africa, licensure process, effectiveness and safety monitoring, and financing the vaccine for distribution. The latter will probably be linked to the Global AIDS Vaccine Initiative (GAVI) process. Finally, the vaccine will be introduced through mass and routine immunizations – including a vaccine useful among infants – to completely eliminate meningitis in Africa.

NCID was the CDC pilot project for polio laboratory containment, which went well. A Web-based interactive interface is now in development to survey all labs for those potentially holding wild polio cultures. Education about this initiative and process has begun with contact with professional organizations, most recently, the APHL meeting and with ASM.

GENERAL RECOMMENDATIONS ON IMMUNIZATION

Dr. William Atkinson reviewed the highlights of changes to the ACIP document of General Recommendations, which has been in revision for several years:

- Re-insertion of the definition pages.
- Related to the new four-day grace period, a footnote (Draft #5, page 12) recommending that physicians and other health care providers comply with local or state vaccination

- requirements when scheduling and administering vaccines.
- Addition of another footnote on page 12 exempting rabies and anthrax vaccines from the 4-day grace period, due to their unique schedules and spacing.
- Page 13, bottom text, revised to say that the IPV series “may be rather than “should be” completed before the first birthday.
- Page 15, additional text was inserted to exempt parenteral LAV not given simultaneously from repeated vaccination of those given <4 weeks apart, when the combination of yellow fever and measles vaccine is administered. Recent data indicate that yellow fever and measles vaccines probably do not interfere with each other. The yellow fever statement also will be amended, and the congruency of the General Recommendations and the new hepatitis statement will be ensured.
 - ▶ Dr. Peter: *Data are weak that indicate interference between two live virus vaccines given within 28 days parenterally.* That new recommendation will be changed. *Similarly, a viral infection within four weeks is not a contraindication for vaccination.* Dr. Jane Seward reported a Vaccine Safety Datalink (VSD) study indicating that MMR provided within 30 days before varicella vaccine led to an increased risk of varicella vaccine failure and breakthrough disease. When given on the same day, MMR vaccination shows no difference, but within 30 days, the risk of varicella vaccine failure rises, although that for OPV given within a month did not.
 - ▶ Dr. Gall: *Insert a paragraph on pages 45-46 to address pneumococcal vaccination during pregnancy.* That will be done.
 - ▶ Dr. Abramson: *Since a recent JAMA article indicates a potentially lower response to immunizations after a viral illness, a workgroup to study this seems advisable to suggest a recommendation.* There was general agreement to retain the amended text presented at this meeting (Page 15, lines 26-30) in order to err on the side of safety and to provide some guidance to frequent provider inquiries on this issue. The issue will be researched issue through a workgroup. Text will be added on the lack of clarity about this and that it will be studied further.
- A paragraph on Palivizumab® and its exception to interferences in the IG live vaccine section was added.
- On pages 19-22, the text on contraindications and precautions was combined and moved for more prominent placement toward the front. The Table (5) of Contraindications and Precautions was updated and retained. Text will be added to note that contraindications and precautions change, and to refer the reader to the Website for the latest updated table.
 - ▶ Dr. Levin suggested the same be done for the section on unknown or uncertain vaccination status. He also noted that the (page 20) National Standards for Pediatric Immunization Practices are now the Standards for Child and Adolescent Immunization.
 - ▶ Wording on aspiration (page 24), previously recommended, was altered to parallel the Red Book statements, which are not a direct indication to aspirate.
 - ▶ A large new section on jet injection was added, a very comprehensive piece developed by Dr. Bruce Weniger. The committee agreed to reduce this to ~2 paragraphs and to retain the ~30 references. A footnote was suggested to note that the entire document is available by request on the Website.
 - ▶ Text (pages 31-32) on non-standard vaccination routes and sites was changed to only recommend repeat injections of those vaccines whose immunogenicity is known to be

compromised if given in a route or site not recommended (i.e., currently, rabies and hepatitis-B vaccines given in the buttocks and hepatitis-B vaccine not given intramuscularly).

- ▶ Two paragraphs on syncope (pages 33-34) were added, including a policy change to parallel Red Book text, advising a 15-20 minute observation period after vaccination. This was supported by VAERS data on injuries from falls sustained after syncopal episodes, mostly among adolescents and within 15 minutes of vaccination. There was agreement that, although many childhood vaccines are given to children not yet walking, the term syncope is general enough to include unconsciousness or a lapse of consciousness, and can apply to other reactions. This change would not apply to massive immunization campaigns or administration of OPV. And, since this document cites expert opinion that persons be observed, it does not carry the weight of a recommendation as a new standard of care or any legal liability. Text will be added to indicate that most of the syncopal episodes have occurred among adolescents and adults.
- ▶ A brief section was added on acute vaccine reactions (page 34), to advise stocking epinephrine in case of anaphylaxis, and addressing the issue of safety needles and reduction of injection injuries. NIOSH reviewed and approved it.
- ▶ The thimerosal allergy section (page 42) was altered for clarification.
 - ▶ Dr. Word suggested *editing the text that "thimerosal as a preservative has been removed from pediatric vaccines," since it is in influenza vaccine.* That will be added.
 - ▶ Dr. Abramson: *Is the trace amount of thimerosal still present in some routine vaccines a problem for those allergic?* Dr. Midthun thought that must be assumed. A phrase will be added stating the potential presence of trace amounts of thimerosal. Dr. Zink, of GSK, supported that, noting the manufacturers' clarity that trace amounts of thimerosal may remain after the vaccine production process, but at levels undetectable by current scientific analyses.
- The international adoption section (page 47) was changed to the Immigrant/international adoption section, to clarify this as pertaining not just to adoptees, but to anyone vaccinated outside the U.S.
 - ▶ Dr. Smith: *The adoptee data are from a limited number of studies; we would not want to recommend serologic testing or revaccination of thousands of adoptees if a documented immunization is on hand.* The wording will be tweaked to specify this only if the validity of vaccine administration to an international adoptee or immigrant is in question.
 - ▶ Dr. Overturf agreed to review this in relation to the 2003 Red Book, noting the absence of any table to suggested serological testing and specific approaches.
 - ▶ Dr. Schwartz reported staff review of the studies' laboratory methods and their satisfaction that the data support the general adequacy of vaccination records. That reassurance could be better reflected in this draft. He offered to help to draft that and to involve the AAP as well. He also suggested the reinsertion of a table rather than the currently dense text.
- A resource directory will be added with a succinct listing of relevant Web and telephone resources, and the reference list will be refined.

Further discussion with Dr. Atkinson included:

- Dr. Levin: *Insert text on the conjugate pneumococcal vaccine.*
- Dr. Vernon, Merck Vaccine Division: *Include, in the Resource Directory, Web sites with good vaccine safety information (e.g., the AAP).*
- Dr. Chen: offered to help to incorporate other definitions (e.g., to distinguish between “reaction” and “adverse event”) and suggested that the new text on management of acute vaccine reactions cross-reference to the VAERS reporting described later.
- Dr. France: *Can a statement be inserted about the impact of adequate reimbursement on vaccine coverage to encourage managed care organizations to cover them?* Dr. Peter: That recommendation was made two years ago in the NVAC statement, “Strategies for Sustaining Success,” published in *JAMA*.
- Dr. Nichol: *Insert an explicit suggestion that not only primary care practitioners but some specialty practitioners administer immunizations to their patients.*
- Dr. Evans: *Insert text on vaccine risk communication; he offered such wording done by NVICP and the Red Book.* Two or three sentences will be inserted under patient information (page 61). Dr. Chen volunteered to help draft the language, noting also that the issue of VPD risk among people who are exempt might be addressed.
- Dr. Word: *Check whether the text about blood transfusions with packed red blood cells should reference 5 months, not 6 months.* All numbers will be checked for their consistency with previous ACIP publications.

Dr. Modlin asked for other small edits to be provided to Dr. Atkinson, who outlined a time line for next steps. Pending approval on this day, edits will be done in the next month and the document put through formal NIP clearance. *MMWR* cannot run this until September, meaning it will not be published until November. He will try to give it to them by August, in case a prior opening occurs. But if not, he hoped it could be published on or near November 12, the 25th publication anniversary of the very first General Recommendations document, which was three pages long and had no references.

Vote. Dr. Tompkins moved to accept the General Recommendations as proposed.

The motion was seconded. There were no conflicts. With all in favor, **the motion passed**, to applause.

Dr. Atkinson offered to e-mail the final document to interested Committee members when it is cleared by NIP and prior to *MMWR*’s editorial work and clearance. Finally, he reported requests to share the document with Program Managers, even in draft form, before it is formally published, and asked the committee’s opinion. There was no objection voiced.

UPDATE: DISCONTINUATION OF HUMAN RABIES VACCINE FOR INTRADERMAL PRE-EXPOSURE USE

Dr. Charles Rupprecht reported the unexpected news that Aventis, the only manufacturer producing the human rabies vaccine used for intradermal (ID) pre-exposure administration, had decided to cease production. They cited this as a business decision. ID rabies vaccine is only licensed in the U.S.

Causes for Concern. Rabies is the most significant global viral zoonosis. However, human rabies cases in the U.S. remain uncommon due to:

- Prevented exposure to rabid animals. But cases may be under-reported (e.g., an investigation by the CDC/California Health Department determined a February rabies death that was retrospectively diagnosed in June).
- Proper post-exposure prophylaxis after any exposure,
- Pre-exposure vaccination (PEV) of those considered at risk (e.g., veterinarians, animal control officers, and laboratory diagnosticians who may contact the rabies virus directly or indirectly). The priming provided by this vaccination simplifies the post-exposure management by eliminating the need for rabies immune globulin and requiring only two intramuscular booster immunizations on days 0 and 3. The PEV is delivered in three doses on days 0, 7, and 21, either intramuscularly or, with the now discontinued product, intradermally.
- However, this is a specialized niche. Since rabies is a zoonosis, not a contagious virus like polio or hepatitis, the vaccine is an orphan drug. As such, its discontinuation even further threatens rabies prevention and control. The licensure of the human diploid cell vaccine (HDCV) in 1980 released the first cell culture vaccine to the market, and was the first immunogenic and efficacious product. But the first HDCV was expensive (~\$100/dose and requiring 3 doses). The ID vaccine licensed in 1986 for a single-use application allows a smaller dose. But in general, this vaccine's use was not extended to intradermal pre-exposure vaccinations except among Peace Corps workers in developing areas. To the present day, the literature support the economic benefit of continuous serological monitoring of those at risk and intradermally boosting only when the serology becomes undetectable.
- Those populations at risk make this supply termination of ID vaccine a concern; >80% of U.S. veterinary schools use ID rabies vaccination pre-exposure. Such students are a financially disadvantaged group on whom a greater cost will have an impact. There also are concerns about returning to the practice of dispensing multiple doses from a single-use vial for ID.
- There are similarly doubts about the efficacy of routine intramuscular vaccination when serological titers are undetectable.
- This lessens public health flexibility in an already orphan product.
- The global crisis of the availability of rabies immune globulin (Rlg) causes grave concern. If ID vaccine can be quickly dropped due to a business decision because of the problems of the production and availability of the Rlg used in the developing world, Rlg could suffer a similar business decision at any time.

Ironically, rather than focusing on reservoir and vector controls (i.e., dogs in the developing world), the WHO is considering the use of ID vaccination of children. The recent CSTE meeting passed a unanimous statement of their concern over the possible discontinuation of RIG, and called for alternative techniques, methods or strategies to alleviate the related concerns.

Possible solutions include:

- Reconsideration of the business decision; CDC has requested that.
- Offering the intramuscular product at the intradermal price. New vaccines in general are considering this due to ID's cost-saving delivery mechanism.
- RFPs and Small Business (SBIR) grants seeking alternative, more economical biologicals for rabies prevention and control as a whole, should be issued by the NIH

and FDA, CDC, NIP, etc. Or, FSS schedules could be used, under which the federal government becomes a broker and potentially a supplier to end-users.

- The problems with orphan biologicals suggest a serious need for federal government involvement.
- Renewed communication is needed for rabies prevention and control, here and abroad. A supplemental *MMWR* statement will be issued to advise those end-users.

Discussion with Dr. Rupprecht included:

- Dr. Offit: *Is the IM product used, but diluted, in the developing world?* Yes, WHO sanctioned this, especially with the shortage of RIg and because of the issues related to nerve tissue vaccine in the developing world. *Could discontinuing ID vaccine use in this country infer that ID is not as acceptable, perhaps driving those developing countries to the less-safe nerve cell vaccine?* CDC has worked with WHO and the PAHO for the last 10 years to replace the nerve tissue vaccines with ID vaccine, which we strongly promoted as safe and effective. A meeting next month will address that issue to avoid any such inadvertent message about the vaccine's utility or safety. *What is the price differential?* The price differential has been creeping closer within the last few years, but it was \$65-70 for ID and \$100-120 per IM dose.
- Mr. Hosbach, of Aventis, stated that Aventis did not make this decision lightly. But they knew that the IM product could fill the gap, as it is essentially the same vaccine. GMP requirements demand continuous facility maintenance and upgrade. This product serves a very small customer segment, but requires a very manual process. Aventis considered the potential investment to upgrade the facility to a more mechanized process (posing less risk to the human workers), but doing so would make the ID cost to far exceed that of the current IM product. So, Aventis allows all their ID customers to buy the IM vaccine initially at the ID price. That particularly targets the veterinary students, although many schools buy the vaccine for them, and many have their rabies vaccine reimbursed by insurance. However, Dr. Rupprecht disagreed; a CDC check of 27 schools found that the students bear most of those costs.
- Dr. Modlin: *Is the vaccine truly an orphan drug, or is it just in a small market?* CDC believes it is both, affected by its small market and by the little time/attention paid it. Dr. Midthun: Orphan drug status mainly refers to products considered for licensure, but the standards for safety and efficacy are the same.
- Mr. Reilly, of PHARMA, clarified further. No biologicals fit the orphan drug definition. The Orphan Drug legislation encouraged pharmaceutical drug manufacturer with the criteria of exclusivity and a sole presence on the market for a certain period of time.
- Dr. Offit: *Can we be assured that dropping ID vaccine here will not drive the use of nerve cell vaccine elsewhere?* Dr. Plotkin: ID development was driven by cost issues in the developing world. A tailored message is needed; that is, that the discontinuance of ID stemmed from its cost of production with manufacturing facility upgrade. But he felt that ID vaccination will remain; ACIP just needs to decide whether to recommend its off-label use. The IM vaccine is licensed for ID use in Asia and perhaps elsewhere.

Dr. Modlin noted that the Rabies Statement would have to be updated, and asked for volunteers for a Rabies Vaccine Workgroup. Drs. Offit, Brooks, Marchessault, and Plotkin did so. Dr. Jane Gilbert, of Chiron Vaccines, volunteered to serve as a consultant. Dr. Abramson added that the AAP will participate, since this will involve pre-exposure

prophylaxis for traveling children. Dr. Midthun doubted that FDA would support sanctioning off-label use and use of a multi-use vial for single uses. She promised to supply an FDA representative to the workgroup. Dr. Snider also suggested in put from the WHO, and Dr. Wharton suggested the state public health veterinarians.

UPDATE ON DEVELOPMENT OF HIV VACCINE

Dr. Tim Mastro, of the NCHSTP Division of HIV/AIDS Prevention, reported on ongoing HIV vaccine trials and the issues related to preparing for activity after the trials' results are released, particularly regarding communication.

Globally, the 20-year old HIV epidemic has caused ~60 million HIV infections and ~25 million deaths. Of the ~36 million currently infected, ~25 million are in sub-Saharan Africa alone, and the prevalence rates of some southern African countries are ~30%. North America has ~900,000 prevalent HIV infections; the U.S. has had 750,000 AIDS cases and ~450,000 deaths. Global HIV incidence last year was ~5 million new infections (~15,000 daily), ~40,000 in the U.S. annually (>100/day).

The epidemic has accelerated in the last ten years, and a safe and effective HIV vaccine is needed to slow it down. Vaccine development has proven difficult for many reasons, including that natural HIV infection does not confer protective immunity; the lack of an ideal animal model with which to evaluate products; no known correlates of human protection; and great variability of HIV strains within a wide variety of genetic subtypes, whose importance is unknown as regards protective immunity.

To date, >70 Phase I and II HIV vaccine human clinical trials have been done, 12 in developing countries. Only one product advanced to Phase III clinical evaluation. Two efficacy trials of VaxGen's recombinant envelope protein gp120 preventive (not therapeutic) vaccines are underway in the U.S. and Thailand. The gp120 is expressed in mammalian cells. VaxGen, under Dr. Don Francis, is funding its own trials. Both trials are of a bivalent product, each with 300 micrograms of each antigen in an alum adjuvant, using T-cell and macrophage trophic virus strains. The VAX004 trial of AIDS VAX® B/B, mostly conducted in the U.S., is using two viral B strains, and VAX003 in Thailand is using one of the same B strains and a product with subtype E, the predominant HIV strain in Thailand. Both trials are randomized, double blind, and placebo-controlled. The AIDS VAX® gp120 vaccines primarily induce antibody. The AIDS VAX® B/B trial should be completed in the fourth quarter of 2002; the Thai trial of AIDS VAX® B/E should be completed by the third quarter of 2003.

Only two other Phase III trials are planned, both using the Aventis ALVAC® canarypox vector to deliver HIV antigen and induce cytotoxic T lymphocytes. The AIDS VAX® B/E and B/B also will be used as boosters in these. The U.S. Army's Phase II current ALVAC® plus SP120 trial in Thailand should produce a go/no go decision later this year, based both on the epidemiology and immunology determined. The Thai trial may include 16-20,000 people in a community-based Phase III trial that may begin next year. The immunogenicity data of the NIH's HIV Vaccine Trial Network's large Phase II trial of an ALVAC product and the AIDS VAX® B/B will determine if a Phase III trial in North and perhaps Latin America, will

begin potentially in 2003.

The VaxGen study model was shared, tracing the rationale for using gp120, the envelope of HIV. It is cloned into synthetic gp120 by genetic engineering in mammalian cells. Once purified, it is placed in a vaccine and injected to induce antibodies to gp120 and, hopefully, to block HIV infection. Its safety was demonstrated in >5,000 HIV-negative volunteers and >500 HIV-infected persons. When evaluated as a therapeutic vaccine, no serious adverse effects were found, only minimal reactogenicity.

An overview of the both AIDSVAX efficacy trials was provided. Ongoing evaluation is done of product safety and any trial-related social harms (e.g., discrimination). Community advisory boards are in place. The primary trial endpoint is HIV infection; secondary endpoints are: transient HIV infection, reduction in viral load and slowing of disease progression; product safety; sieve analysis (that the vaccine will protect against strains very similar to the vaccine strain, but not others); and behavioral effects of being in the vaccine trial.

The trials were each outlined.

- *VAX004, North America and the Netherlands*; sponsored by VaxGen; 61 local sites. CDC participation. Cohort: 5190 men who have sex with men (MSM) and 300 high-risk women. Vaccine: bivalent MN/B strain and a GNE/8, a macrophage trophic B strain. Schedule: 2:1 vaccine/placebo ratio. Trial duration: 3 years; expected completion: October 2002. First report on efficacy: November, 2001. 61 trial sites, centralized data management system and specimen handling.
 - ▶ Statistical power/sample size calculations: Primary endpoint/infection, 90% power, to reject the null hypothesis of vaccine efficacy of 30%, if the true VE was 67% using a two-sided test. Assumption: no vaccine effect until after immunization #3, HIV incidence of 1.5%; annual loss of 10% in year 1 and 5% each in years 2 and 3.
 - ▶ CDC role: Funds 6 trial sites in the VISION Vaccine Sub-studies Network. Cohort: (n-800) 800 participants (18% of the full trial) and a comparison group. Focus: 1) *behavioral aspects*/motivation of participation, determinates of risk behavior and any change related to a trial; whether participants un-blind themselves (self-test to determine which test arm they are in); what contributes to good trial retention; whether people use post-exposure prophylaxis for sexual exposures, including antiretrovirals; 2) *Qualitative issues* through in-depth interviews and focus groups: perceptions of being in a trial, decision-making, motivations and trying to understand the trial experience; 3) *Virologic aspects*: antiretroviral resistance and genetic characterization of breakthrough strains; cellular and humoral mucosal immunity in both men and women; assessment of care after infection; individual site and community-level factors contributing to high enrollment levels, retention and protocol compliance.
 - ▶ NIH role: Funding lymphocyte collection from the HIV-negative participants to research correlates of protection.
 - ▶ Overall progress: 5400 enrollees, 94% male, median age of 37. Good follow-up (91% retention). Two serious adverse events (SAE) of cellulitis that resolved. Reduction of reported risky behaviors since baseline enrollment; minimal social harms reported.

- *Thailand* collaborators: Bangkok Metropolitan Administration (BMA), Mahidol University, VaxGen, CDC HIV/AIDS Collaboration in Bangkok. Cohort: 2,545 injecting drug users (IDU) in treatment programs; Vaccine: bivalent B/E virus vaccine; 7 doses, 1:1 ratio. Duration: 3 years; expected completion in 2003; first efficacy report November 2002.
 - Site characteristics/Bangkok: ~8 million people, explosive epidemic among IDUs for the last 12 years; ~30 - ~50% HIV prevalence among IDUs; an estimated ~40,000 active injecting heroin users; 17-clinic drug treatment program operating since the 1960s. Extensive review/approval of multiple IRBs.
 - Overall progress: Of 5,000 screened, 34% were HIV-seropositive; 93% male, median age of 26. Good follow-up (97% retention); no vaccine-related SAEs. Decrease in reported risk behaviors since enrollment; minimal social harms.
 - Problems: Incarceration is common, but continued voluntary follow-up has been possible.
- The two trials share a Data/Safety Monitoring Board. Chaired by Dr. Walter Dowdle, it has 10 multi-disciplinary committee members, both Americans and Thais, who meet twice a year. The 5 reviews to date have found no serious problems with trial conduct.
- Stopping rules: SAE safety concerns, increased susceptibility, rapid disease progression associated with vaccination. The procedure has not been set, if one trial reaches a stopping point, about what to do with the other trial, since they involve different challenges and products.

Future Considerations include a partially effective HIV vaccine. Efficacy could be characterized by protection from infection (efficacy for susceptibility); or by lowered transmissibility or infectiousness (to affect the epidemic and perhaps slow disease progression in the individual).

The set point of plasma HIV viral RNA levels, the viral load, is established ~6 months after primary infection. Viral load is directly related to the rate of disease progression and the rate of infectiousness (high loads = rapid disease progression and high infectiousness). Without treatment, the period from infection to AIDS onset can vary from 2-20 years.

The assumption is that pre-existing antibodies from vaccination could blunt viremia and establish a systematic viral set point that could profoundly affect the disease progression and infectiousness. Partial vaccine effects could include a reduced chance of getting HIV-infected if exposed, protection from some modes of transmission (e.g., mucosal, not parenteral); protection from some strains of HIV and not others (e.g., strains within or across HIV subtypes); and lower the viral set point to slow disease progression and decrease infectiousness.

The Committee's advice on how to prepare for the results of these trials was invited, particularly with the U.S. trial's interim analysis due in 6 months. All the involved parties, including VaxGen, CDC, FDA, and NIH, should jointly interpret these results. Then, the planning for how to communicate these results must be done, before the trial's end as well as afterwards, to ensure a coordinated message of the results' meaning to the general public, affected communities, and the medical and public health communities.

A CDC multi-disciplinary consultation will be held in September in Atlanta to discuss the use of a partially effective HIV vaccine, identify important issues, and outline future research, including future HIV vaccine trials. If this product is licensed, placebo-controlled trials are unlikely. If not, the need to continue trials with realistic expectations must be conveyed. Among these realities are the complexity of issues involved in HIV vaccine implementation (e.g., vaccine demand, production capacity; HIV prevention and international implications; ethical and legal considerations; duration and breadth of protection; co-administration with other vaccines, etc.).

Discussion with Dr. Mastro included:

- Dr. Johnson: *What public communication is expected if the trial is not stopped this fall?* That is in discussion in CDC Office of Communication Office and VaxGen's communication staff. The message may be geared to adjusting expectations.
- Dr. Katz: *What effect is expected on the implementation and the initiation of trials with more promising antigens (e.g., cytotoxic lymphocytes, CD8, CDL stimulation) if this trial fails?* A trial is a failure if it does not produce interpretable results. If the trial definitively resolves gp120 as of low efficacy, that is a success. Without animal models and correlates of protection, that cannot be known yet. Nonetheless, a tremendous amount will be learned operationally from these trials about enrolling people, conducting an HIV vaccine trial, etc., all of which will benefit future trials. But the point was well taken. It must be clearly communicated that expecting a total success of a definitive vaccine from the *first* HIV vaccine trial is unrealistic. But the pace of vaccine evaluation must be accelerated, with 5 million HIV infections last year. Aside from the ALVAC® canarypox products, DNA vaccines are in development, and there will be questions of whether to proceed with the first or wait for the others with a good chance of high level efficacy.
- Dr. Nichol: *What is your study power to exclude a vaccine efficacy of zero (it seems it must be 100% to do so), and how will the results be interpreted if the confidence intervals are wider than they were for the power calculation?* There is more power to exclude zero with a vaccine efficacy that might be down in the 30% range. The VE of 67% shared at this meeting was just the stopping rule. There will be discussions with the FDA of what outcome might lead to licensure of this kind of a product.
- Dr. Abramson: *How strong is the educational effect (i.e., are you slowing down the rate of HIV infection in the placebo groups, and will this likely have an impact on the speed by which outcome can be determined?)* That is the issue of study effect: if the prevention education and interventions are so well done that there is virtually no incidence in your trial population, there is no power to evaluate the vaccine. The incidence rates of the trials are not shared with investigators, but they are substantial and are consistent with the trial design. Despite communication, enough high-risk sex still occurs in the U.S. and injection drug use in Thailand, to ensure study power.
- Dr. Tompkins: *Will the therapy of patients who convert be individualized or standardized (and if so, what?)* The North American trial did not assume responsibility for care of those infected in the trial, since it was due to risk behaviors, so the trial sites linked people to care in their own setting. The follow-up is standardized under the study protocol for assessment of viral load and CD4 counts. Treatment more standardized in Thailand since the BMA manages those people's care; their treatment standards are evolving. At the trial's commencement, it a 2-antiretroviral regimen for a CD4 count < 500, which is being re-evaluated now. The reality in Thailand, with their high HIV

prevalence, is that they cannot afford to provide antiretrovirals for everyone in their system. Those in the trial actually have a higher standard of care than others in the BMA.

- Dr. Chen: *Is there a member of the Data Safety Monitoring Board who has expertise in rare disease epidemiology as well as infectious disease epidemiology?* That is uncertain; Dr. Dowdle is the Chair, and the Board is multi-disciplinary (ethicists, statisticians, Thai clinicians, community representatives, etc.).
- Dr. Christine Severyn, Vaccine Policy Institute: *Would you comment on the opposition of the late Dr. Albert Sabin to the development of an AIDS vaccine, which was recently supported at the April Vaccine Research Conference in Arlington, Virginia?* Dr. Mastro wished to be optimistic, but believed that the world needs a safe and effective HIV vaccine that can protect people from HIV.

HARMONIZED SCHEDULE

Format. Dr. Natalie Smith thanked the Harmonized Childhood Schedule Workgroup for their work. They decided to continue to publish an annual schedule in journals, CDC's hard copies, and on the Web, and to consider any major or urgent issues on a case-by-case basis. The format of the schedule was altered to approximate that of the Minnesota State Health Department, which previously was presented to the ACIP. The schedule and footnotes are now on the same page. The recommended ages extend through 18 years. A column indicating the 11-12 year-old assessment may be changed to indicate an adolescent assessment, to promote assessment at every visit. Below a dotted line the vaccines for selected populations are listed (Hepatitis A, influenza, pneumococcal polysaccharide vaccines). Both color and black and white versions are available. The CDC Website and Hotline information are listed.

Content. Dr. Wharton reviewed the previous format developed by Dr. Jacqui Gindler and others several years ago. It served well, but has been streamlined using some improvements developed by NIP partners:

- The footnotes are now columnar, and the schedule is on an 8½"x11" sheet (the format *MMWR* is moving to by 2002), enabling most of the previous text to be included but in a less cluttered fashion.
- The colors used allow even black and white printers to distinguish the differentiations. Another version can use white and striped bars for catch-up.
- Differences from the previous format are: 1) explicit indication of catch-up vaccination (the green-striped bars) for hepatitis-B, MMR-2, varicella, and pneumococcal conjugate vaccine; 2) the adolescent assessment visit is highlighted, although the column title could change; 3) additional vaccines for selected populations are included rather than the single hepatitis-A for selected populations before.

Remaining issues for consideration include:

- The bar width for hepatitis-B catch-up is wider than the others
- The title of the pneumococcal conjugate vaccine column is not matched by the pneumococcal vaccine line.
- Inclusion of pneumococcal polysaccharide vaccine with conjugate PPV/PCV.
- Placement of the "selected populations" line.

- Numerical indication of multiple doses involve some copyright issues (e.g., MMR-1, -2, etc.).
- Which vaccines to indicate for use in selected populations.

The Committee approved the change in format. Dr. Modlin reported his and Dr. Smith's discussion of solutions: 1) changing the bar widths to be uniform and 2) changing the pneumococcal conjugate title to pneumococcal vaccine, to include both vaccines and to allow pneumococcal polysaccharide to be included and appropriately labeled. The numerical indication of multiple doses could be resolved by 3) including a “#” number sign, and changing the label for range of “acceptable” dose to range of “recommended” dose. But the Committee's guidance was requested on the placement of the birth dose convention (e.g., the preferred first dose of hepatitis-B vaccine is at birth, so the label would be placed there), and on additional vaccines for selected populations.

Discussion of the elements included:

- Dr. Abramson: *I am concerned that citing vaccines for selected conditions could cause others to be forgotten (e.g., meningococcal vaccine).* Dr. Modlin: Vaccines could be added on an annual basis, based on whether they should be used in a general population.
- Dr. Overturf: *Why are the DTaP dose 5 and IPV dose 4 not in a gold bar?, and pneumococcal conjugate vaccine is marked for catch-up to ~5 years of age, but is licensed for safety to a higher age group and is given to certain high risk groups at higher ages.* The ACIP recommendation does not include the use of conjugate vaccine beyond five years of age in any group, even if so licensed. Such use of vaccine in older children is an issue for this schedule. The issue is addressed in the footnote, but additional wording for the footnote could be crafted when the schedule is adopted in October.
- Dr. Johnson: *Perhaps we should mark the recommended age with a lightly colored bar around DTaP, Hib, IPV and PPV in the 2, 5, 6-month columns.* That is consistent with what was said before and could be changed.
- Dr. Zimmerman: *The MMR dose 2 differs from the old schedule.* That is to distinguish the routine dose 2 from the catch-up dose, a distinction now made with ovals. *Pneumococcal polysaccharide is not indicated in children with pure or simple asthma; confusion may result.* Dr. Clover: *List both.* The delineation can help practices stocking both to decide when to use each, a common question since the licensure of the conjugate vaccine
- Dr. Plotkin: *This is a good opportunity to support the recommendation of a birth dose of hepatitis-B, which unlike other vaccines, poses both programmatic and immunologic implications.* Dr. Zimmerman: It was moved to the birth dose in 1999, but some advocated putting it back in the middle to be consistent with the existing policy that prefers combination vaccines. Preferring both a birth dose and a combination vaccine is inconsistent. Dr. Modlin: Hopefully, this inconsistency will be resolved with the decision on the hepatitis-B vaccine statement in October.
- Dr. Wexler, Immunization Action Coalition: *1) Ensure that the table's bars go across to reflect every age, including the 7-10 year-olds to remind about that catch-up opportunity; and make the 14-18 year-old range, 13-18, to include all ages from 5-18. 2) Extend Td on the catch-up vaccination to age 18 years and IPV to age 17 to allow for*

immigrants, etc.; and 3) Hib catch-up should extend to age 5. Dr. Wharton: The definition of “catch-up” was discussed in the Workgroup. The catch-up bars are confined to vaccines that either have relatively new recommendations or relatively new emphasis on policy implementation. Since there has been a longstanding recommendation about Td boosters, the bar is yellow, not green, for the first Td dose, which is a routine recommended booster, not a catch-up. The danger is that many catch-ups could be included, which could decrease the impact of those vaccines highlighted.

- Dr. Wexler: *Rather than overlaying the PPV with the PCV, insert an extra line.* Dr. Diane Peterson, Minnesota Department of Health, appreciated Dr. Wexler’s comments, knowing from experience that “if there’s anything that can be misinterpreted, it will be.” The problem with adding columns (e.g., the recently-added 24-month column) is the necessarily decreasing font size. Minnesota has not had misunderstandings yet that assessments at other ages or catch-up should not be done, although it could happen.
- Dr. Peter: *I am very concerned that our attempt to be all-inclusive and to perhaps take the place of the detailed recommendations could lead to confusion and lose some of the initial purpose of having a universal schedule.* Dr. Orenstein agreed. The schedule was not designed to handle every situation and should be kept as simple as possible.
- Dr. Evans: *Can we insert something about safety (i.e., the legal requirements for reporting and the NVICP), which applies to all the vaccines listed?* He suggested 2-4 lines about VAERS and the NVICP to alert providers to their existence, and Websites or telephone numbers. Dr. Peterson: The back of the Minnesota schedule has catch-up schedules, vaccine reaction and disease reports, the VAERS number and the Website.
- Dr. Abramson: *Move everything under the dotted line to a second page.* Dr. Wharton: That would take hepatitis-A off, which was inserted last year, and could cause confusion if deleted again. Dr. Smith: It is important to emphasize influenza. Dr. Brooks liked the one-page format, which is easy for practice settings to post. He found the dotted line acceptable, and commented that influenza vaccination is a key component of preventive health.
- Dr. Richard Jacobs, a member of the Academy’s Education Program: 1) agreed that again changing the hepatitis-B text or bar will confuse practicing pediatricians; and 2) the Prevnar® conjugate pneumococcal vaccine in the green bar could be accompanied by the Hib catch-up. At least that component could be moved to a catch-up table of those preferred for select populations, but that could also include 23-valent unconjugated vaccine. That will be confusing. Perhaps the second page is disliked, but it has all the necessary explanatory footnotes. Without that, the table must be clear and free-standing.
- Dr. Zimmerman: *Please provide the next iteration for a July conference call.* Dr. Wharton said that will be done and summarized the changes for the next version: try to keep the pneumococcal polysaccharide vaccine; influenza and hepatitis-A with the dotted line; wait until the hepatitis-B statement is finalized to decide on the wording and bar format. She also asked if the Committee agreed that a catch-up schedule, if developed and approved in time, could be published concordantly with the harmonized schedule. There was general agreement.

Adult Harmonized Schedule

Dr. Vishnu-Priya Sneller named the partners in the long-discussed schedule of adult

immunization: Drs. Neuzil and Schaffner for the ACP; Dr. Clover for the AAFP, and Dr. Gall for the ACOG. The advantages of standard immunization schedules for adults are the provision of standard guidelines for and increased visibility of harmonized immunizations by providers.; increased focus of provider organizations on the adult immunization issues; an opportunity to highlight the most important messages/changes in adult immunizations for media report annually; and increased adult immunization. The public health targets for the next decade include a 90% vaccination rate for those aged ≥ 65 years and 60% for those aged 18-64 for whom these vaccinations are recommended.

The *Process of Harmonizing the Adult Immunization Schedule* includes: communication with the representatives of those provider organizations which had issued immunization schedules to their members; current comparison of those to determine what needs to be harmonized; subsequently, future development of a schedule format for approval by the ACIP and provider organizations, and development of an annual review/revision process similar to that of the childhood schedule.

The recommendations of the ACIP (1991), ACP Green Book (1994), and the ACOG technical bulletins (1992 and 1992) on immunizations during pregnancy and rubella in pregnancy were reviewed and summarized by Dr. Sneller. Since they are fairly well harmonized, any real or perceived differences are now the focus:

- Decennial Td booster recommendations of ACIP and ACP.
- Revaccination of older adults with a 23-valent PPV recommended by ACIP and ACP. These differ both the strength of the recommendation (ACIP's being stronger) but also in the indications for revaccination (ACIP specifies; ACP's is unclear if the revaccination is single or multiple). ACP and ACIP also differ in wording on revaccination of persons with the 23-valent PPV for those vaccinated with the 14-valent PPV. However, this may be moot since most of those vaccinated with the 14-valent are probably already revaccinated with the 23-valent.
- ACIP/ACP recommendations differ in strength about MMR measles vaccination of persons born prior to 1957.
- ACIP issued recommendations for hepatitis-A, meningococcal vaccine, varicella and Lyme disease since 1991. ACP has not published additional recommendations for adult immunizations.

Formats considered include 1) the graphic representation of the Minnesota State Health Department, which may be altered to collapse the first two columns to ages 19-49, to avoid changing annually when people "age out" of the measles vaccination age; 2) a tabular format on high risk patients with chronic disease or conditions for the easy review of sub-specialty practitioners; 3) another tabular format summarizing vaccinations for special populations. The one-page schedule is very similar to that of the childhood schedule, designed for ease of use and comfort of reference for those providing these immunizations.

Channels being considered to communicate this to the general public are the mailing list of the Immunization Action Coalition; the state health departments' communication channels and newsletter mailing lists; and medical specialty groups' Web or mailed newsletters. Once available, the adult immunization schedule could also be published by the media and other community-based organizations serving older adults, or those organizations addressing the

prevention/management of chronic diseases.

At their meeting on this morning, the Adult Immunization Workgroup Subcommittee decided not to wait until the entire harmonization with the provider organizations is complete if that involves a substantial delay. They will, rather, work with the provider organizations to publish an article or report with a table indicating the areas of harmonization and describing the areas of disharmony being negotiated, and then provide updates later on.

Discussion included:

- Dr. Schaffner thanked those involved in this work, which could be a milestone in adult immunization activities. It could gain the attention of many of the scholarly and professional societies relating to adult patients and their practitioners.
- Dr. Zimmerman: 1) The AAFP immunization schedule (on their Website) will also have to be harmonized; 2) agreement should be sought on an age-based Minnesota-style schedule format, since details (revaccination, high risk groups, etc.) could take a long time to resolve.
- Dr. Ray Strikas, NIP: commended the work group for a nice and very encouraging beginning. He suggested publishing it around August or September to avoid overburdening the influenza season recommendations, and not publishing it during development/publication period of the childhood schedule, to avoid compounding the AAP's and CDC's work. He was unsure that a simple schedule could be quickly accomplished for the Td booster. With the Td shortage, this is significant issue has to be resolved before recommending on Td boosters.

LABORATORY-ACQUIRED MENINGOCOCCAL DISEASE

Dr. Nancy Rosenstein reported several recent accounts of laboratory-acquired meningococcal disease that has caused great concern in the health care community. A high rate of meningococcal disease was found among laboratory workers, suggesting enhancement of the current guidelines for laboratory safety and a reinforcement of current ACIP vaccination guidelines.

Data Presentation. Dr. James Sejvar reported ~3,000 cases of meningococcal disease reported in the U.S. annually, with a case fatality rate of ~12%. *Neisseria meningitidis* is transmitted by close direct contact with respiratory secretions, and serogroups B, C and Y cause most disease in the U.S. The only U.S.-licensed vaccine is a quadrivalent polysaccharide that protects against serogroups A, C, Y and W135, but not B. It is safe and effective, but does not have 100% efficacy and requires repeat doses.

The CDC/NIH publication, *Biosafety in Biological and Biomedical Laboratories (BMBL)* classifies *Neisseria meningitidis* as a Biosafety Level (BSL) 2 organism. Guidelines advise the personal protection of laboratory coats and gloves and facial protection as appropriate, and the use of primary barriers such as biological safety cabinets (BSC) for procedures that might cause splashing, spraying or splattering of droplets. However, no such procedures of increased risk are listed.

MMWR reported two fatal cases of probable laboratory-acquired meningococcal disease in

1991, the first in the U.S. CDC then recommended that work with high concentrations or large quantities of organisms be conducted in a BSL-3 laboratory, and immunization of lab workers. In 1997, ACIP recommended consideration of vaccination for research, industrial and clinical lab personnel routinely exposed to *Neisseria meningitidis* in potentially aerosolized solutions. The general assumption was of risk primarily to research and industry personnel frequently exposed to these quantities, many of whom are thought to have been vaccinated. But the risk to clinical laboratory personnel was less clear.

Upon the cases of probable laboratory-acquired meningococcal disease last year, reported in close time proximity, CDC assessed the frequency of these infections to reconsider the laboratory safety/vaccination guidelines.

Members of various infectious disease, microbiology, and infection control professional organizations were contacted through electronic mail discussion groups. A case was defined as a laboratorian with a history of meningococcal disease consistent with acquisition in the laboratory setting, and with a serogroup matching a recently-handled specimen. Basic descriptive epidemiologic information was collected on behaviors and laboratory practices that might have predisposed exposure to aerosols or droplets, based on the known mechanism of meningococcus transmission.

This uncovered 16 previously unreported cases from six countries of probable laboratory-acquired meningococcal disease in the past 15 years, all among microbiologists and most cases among females. The cases split fairly evenly between serogroup B and C; 8 cases (50%) were fatal. Ten cases with information available indicated a median interval of 4 days between handling the probable source specimen and symptom onset. None of the reported cases occurred among workers in hematology, chemistry, or pathology.

A slide charting all cases reported in the past 15 years was shared. Of the 16 previously unreported cases, 6 were from the U.S. in the past five years. No one knows the number of microbiologists in the U.S. The denominator of laboratorians at risk was estimated by multiplying the ~3000 isolates of pathogenic meningococcus cultured in hospital laboratories annually by an average of three microbiologists handling it during the laboratory investigation. Over 5 years, this produced an average attack rate of 13/100,000 population at risk per year, compared to a rate of 0.2/100,000 for adults aged 30-59, the age group of most laboratory workers. Many of the case microbiologists were reported to have performed common microbiological laboratory procedures, but 15 of 16 cases did so outside of a BSC or aerosol screen.

The conclusions were: 1) that U.S. rates of laboratory-acquired meningococcal disease are much higher than initially suspected, and represent a substantial occupational hazard to microbiologists; 2) the high case fatality rate may be due to reporting bias, but could also reflect highly virulent strains and high density organisms encountered in the laboratory setting, compared to natural transmission; 3) that all of the cases were among microbiologists, and not workers in other sections of the laboratory, suggests that exposure to meningococcal isolates and not patient specimens represent the increased risk; 4) although not a breach in laboratory safety technique, almost every case manipulated the isolate on the benchtop and not in a BSC. A similar finding of high resulting disease risk

came from a recent U.K. study. Importantly, all of the cases detected were in *clinical* laboratories, perhaps because safety guidelines may be stricter in research and industrial laboratories; and more of the latter personnel may have been vaccinated.

Based on these findings, laboratory safety should be emphasized for prevention of laboratory-acquired meningococcal disease, as should implementation of additional safety precautions when manipulating those isolates; specifically, doing so in a BSC. If a BSC is not available, other methods of aerosol protection may be appropriate. But, if adequate safety equipment is unavailable, the risk should be minimized and the isolate should be transferred to another laboratory.

The staff recommended:

- The use of the quadrivalent polysaccharide vaccine as an adjunctive measure in the protection of microbiologists as an additional safety precaution to minimize laboratorians' risk of infection and due to the limitations of the vaccine.
- Research and industrial laboratory scientists routinely exposed to *Neisseria meningitidis* in potentially aerosolized solutions should consider vaccination, and microbiologists should be educated about the increased risk of infection and the seriousness of illness so that laboratory leaders and individuals can make informed decisions regarding vaccination.
- In instances where *Neisseria meningitidis* is inadvertently handled outside of a biosafety cabinet, antimicrobial chemoprophylaxis should be considered for the exposed microbiologist.

These recommendations do not conflict with the current ACIP guidelines, and were suggested for incorporation into the next ACIP guidelines. The staff will next publish their findings and recommendations for laboratory safety and vaccination in the *MMWR*. The endorsement of the American Society for Microbiology is expected, as well as other stakeholders. CDC plans to initiate prospective surveillance for cases of laboratory-acquired meningococcal disease, to continue to assess the rates among laboratorians and the effectiveness of the recommendations. Finally, the reassessment of current laboratory safety practices was encouraged.

Discussion with Dr. Sejvar and Dr. Rosenstein included:

- Dr. Tompkins: *1) What type of exposure is really relevant here? Most meningococcus isolated in the clinical lab is not in spinal fluid, but in sputum cultures, which cannot all be read in BSCs. Was any case caused by just opening the plate and doing the analysis, or were they all from concentrations of organism done in serological testing with its aerosolization?; and 2) It is unrealistic to expect a transfer of suspected meningococcus to another laboratory in the absence of a BSC. The 6 U.S. cases used to calculate the rates had cultured isolates from either blood or cerebral spinal fluid; none from respiratory secretions. Data for all of the cases collected are not available, but CDC is trying to ascertain that. The common theme of the cases was the manipulation of isolates of culture outside of BSCs. No cases were reported among individuals in a lab who handle only specimens.*
- Dr. Tompkins: *I understand that. But many labs use automated devices to read the blood culture, and the result is unknown until the sample is taken out, plated, and the*

gram stain is done. That is not an inherently dangerous step. Dr. Rosenstein: We have struggled with this issue over the past 6 months, as Dr. Johnson can testify, having reported one of the initial cases. We have broadly vetted these recommendations with laboratory colleagues, both at CDC, those who write the safety guidelines, the state health departments reporting these cases, and ASM. They agreed with the specimen transfer – although perhaps it cannot always be accomplished – and that a suspicious CSF or blood culture should not be handled on open bench.

- Dr. Tompkins: *In thinking about patient care, laboratory capacity for specimen identification is critically important. There must be an alternative, such as a close-fitting TB mask, without a BSC. Transfer is just not acceptable.* Dr. Rosenstein: We support transfer if there is not appropriate aerosol protection. We hope that it will be determined if an aerosol guard or TB mask is sufficient, but that has not yet been done. We are trying to ensure understanding of the increased risk associated with common practices, such as reading these on the bench top. The role of laboratorians and other organizations is to determine whether a BSC is really needed or if simple aerosol shield is sufficient.
- Mr. Hosbach, Aventis Pasteur: *Vaccination is safe, and could be “recommended” rather than “considered”.* The polysaccharide is limited in its lack of meningococcus B. But all of Aventis’ workers in manufacturing are vaccinated routinely every five years, as the package insert recommends (3-5 years). Blood tests are also done to ensure adequate antibody responses and protection during exposure.
- Dr. Johnson: *Agreed.* ACIP’s previous recommendations have been equivocal for laboratorians. Calculated risk to microbiologists handling meningococcal specimens shows a considerably higher risk than that for which ACIP recommends vaccine use in outbreak control. The recommendations already advise vaccination for those working in laboratories expected to encounter meningococcal isolates likely to be aerosolized. Without opening up the entire statement, that point could be strengthened,
- Dr. Rosenstein: *We were struck that many microbiologists could be vaccinated for a very uncommon exposure, and still not prevent the serogroup B that constitutes half of these cases.*
- Dr. Clover: *Perhaps we could define what “routine” is in a clinical laboratory in the ACIP recommendation. And, the recommendation wording is stronger for college students’ exposure risk (3/100,000) than here (13/100,000).* But Dr. Modlin advised caution about using the 13/100,000 number, which is only a rough calculation.
- Dr. Tompkins: expected that the ASM would prefer “should be considered” for such voluntary vaccines. Some lab Directors would probably highly recommend it, but another may have a lower risk assessment. But she agreed that college students should have a much lower risk than that for microbiologists. She was unaware of this lab safety problem, and she expected the educational effort behind this study to be its most important aspect. She advised “strongly considered” as a recommendation and leaving the decision up to the laboratory.
- Dr. Overturf: *Mandated or not, the issue of the immunization cost can be large for big laboratories with many microbiologists.* This is an issue on the laboratories’ network. Many seem to want this, although who will pay is at question.
- Dr. Schaffner: *Agreed,* laboratorians are very interested in this. But apropos of which laboratories, he noted that one cannot recommend seat belts only for those driving fast. He expressed some worry that the prophylaxis aspect could require ciprofloxacin, which

- requires careful thought – not the least about the institution's legal liability.
- Dr. Helms: *Research into the basis of how these aerosols are generated is needed to see if something more systematic is occurring in the laboratory.* For example, the response to finding Legionella in a water system would not be prophylaxis for the patients or immunization, but finding the cause in the water system.
- Dr. Clover: *Can the denominator be better refined?* Dr. Rosenstein: We are open to suggestions, but 6 months of communication with laboratory organizations indicate that this is just not an existing number. If the 3 cases in 2000 that prompted this research is dropped, the number is significantly lower, but is still 7/100,000. In light of that, CDC felt compelled to issue a quick notification. And with the licensure of the meningococcal conjugate likely soon, the revision to incorporate that into the ACIP statement will also be an opportunity to revisit the language for laboratory workers and college students.

USE OF ECONOMIC EVALUATION FOR SETTING HEALTH POLICY

In response to the ACIP's request, Dr. Phaedra Corso, of the the Division of Prevention, Research and Analytic Methods, of CDC's Epidemiology Program Office, discussed economic evaluation: its basic methods, the issues related to interpreting the evaluations' results, and the related economic evaluation tools and training opportunities at CDC.

Policy Application. Components of feasibility addressed in crafting national health policy include biologic (i.e., a vaccine available to address the health outcome of interest); technical (vaccine administration); political and social (no unacceptable risks to parents or society in general); and economic (cost compared to the associated outcomes). Economic evaluation is the application of analytic methods to identify, measure, value and compare the costs and consequences of interventions. *Identification* is the delineation of the possible interventions or strategies of interest. Quantitative *measurement* includes epidemiology, decision sciences, meta-analysis, and economic evaluation.

Economic evaluation includes several methods:

Cost benefit analysis converts the common denominator or the common outcome measure into dollars, to allow comparison across health and non-health outcomes. Its advantage is that it provides a list of all costs and benefits over time. Its theoretical basis is that all costs and benefits can be quantified in dollar terms for analysis. Costs that occur at different times (i.e., costs of intervention, delayed benefits) or different amounts of costs and benefits occurring over time can also be addressed by a cost benefit analysis. This analysis also provides the summary measure in one single value, the net present value (also referred to as net benefits or the benefit/cost ratio).

Cost utility analysis uses a health metric as the common denominator to compare different health interventions (e.g., quality-adjusted life years -- QALY -- or disability-adjusted life years -- DALY). This analysis incorporates length and quality of life, and allows their comparison through the concept of utility. Utility is the consumer preferences for being in a particular health state. Cost utility analysis allows the capture of the timing and duration of disease disability. It provides a ratio of the costs (the numerator) divided by the common health metric (the denominator).

Cost Effectiveness Analysis: uses a common natural unit (e.g., cases prevented or lives saved). This analysis is used to compare the results of interventions that affect the same health outcome. It provides a summary measure as a ratio, with dollars in the numerator and the natural units as the denominator.

Components of an economic evaluation:

1. *Framing the study*: involves five components: the study problem (health outcome of interest, and why), audience (the users of the economic evaluation, what are their information needs and their uses of the data), perspective (e.g., the entity bearing the costs and benefits of the intervention; or of society, regardless of who bears the costs), time frame (period in time during which the intervention occurs), and analytic horizon (the period during which all the intervention's costs and benefits occur – e.g., for vaccination, the entire influenza season). All five components should be explicitly defined at the outset of any economic evaluation.
2. *Quantifying costs* involves four types of costs: direct medical costs (diagnostic tests and procedures, drugs, medical supplies); direct non-medical costs (program administration, physical space, utilities, etc.); indirect costs (those associated with productivity losses); and intangible costs (fear, anxiety, pain of vaccination). Hard to quantify, the latter are typically not included in an economic evaluation, but are mentioned in the discussion section.
3. *Quantifying outcomes* in the *Cost Benefit Analysis* can be done from at least two approaches: a) The human capital or cost of illness approach uses lifetime earnings as a proxy for productivity losses due to either morbidity or premature mortality. This is a conservative estimate; b) The willingness to pay approach is increasingly used in public health; and c) contingent valuation surveys (respondents are asked questions to gauge their marginal willingness to pay to rid themselves of a particular health condition, such as parents' willingness to pay to reduce the intussusception risk associated with rotavirus vaccine). This enables calculation of the value of a statistical life for use in a cost benefit analysis.

Quantification in a *Cost Utility Analysis* is achieved through utilities, which describe consumer preferences for being in a particular health state, or for reducing morbidity or mortality associated with an intervention. Utilities are rated from zero (worst case; death) to one (perfect health). In direct measurement of individual utilities, all the components of the health state are described (physical, mental, functional). They are then measured through rating scales (between 0-1); time-tradeoffs (willingness to trade a certain life duration in a bad health state for a shorter life duration in perfect health); standard gambles (how low the probability of death must be for a person to be indifferent between zero and one); and person-tradeoffs, in which a population-level utility is used for DALYs (how many poor health outcomes are tolerable to merit a certain number of good outcomes such as number of lives saved).

With these crude measures, one can calculate the quality-adjusted life years gained from an intervention, and compare the outcomes between doing an intervention and not doing one. On the other hand, if survival duration or life years saved is the measure,

the quality of life associated with the intervention is not important.

Cost Effectiveness Analysis involves the difference between intermediate (persons immunized, cases prevented or disease averted) and final outcomes (life years or lives saved). The latter data are often not available, so many evaluations use intermediate outcomes. This is appropriate as long as it is explicitly stated.

4. *Sensitivity analysis* is an entire field to itself. It should always be done with an economic evaluation. Providing one point estimate for cost effectiveness or cost benefit analyses is inappropriate, because the point estimates vary depending upon population, incidence, and model parameters in general.
5. *Interpreting results* involves three myths, that: a) only programs with a positive net present value or a positive net benefit should be implemented; b) that programs with <\$50,000 per QALY saved should be implemented; and c) cost savings equals cost effectiveness.
 - A. The two summary measures of cost benefit analysis are net present value or net benefits (benefits minus cost) and benefit cost ratio (benefits divided by costs). The first is clearly a strong argument for investing in a program, since benefits outweigh costs. But there are 3 other factors involved in setting health policy: biological, technical, and political economic feasibility. In the fact of a negative net present value or benefit, other justifications are needed to recommend the policy. The previously-used benefit cost ratio (benefits divided by costs) is currently less used, because it results in a single number. For example, Program A costs are \$1, benefits are \$10, producing a net present value of +\$9. On the other hand, a multifaceted Program B's single ratio of 5 could be misleadingly less than Program A's, when in fact the its return on investment could be greater. As an example, the recent publication by Kristin Nichol in *Archives of Internal Medicine* about vaccination's direct and indirect costs (including those averted), benefits, and sensitivity analysis of the worst- and best-case scenarios.
 - B. Investing in programs that are <\$50,000 per QALY saved is a hypothetical number with no empirical or theoretical basis. The dollar values have never been inflated to current-day dollars, so the number is fictitious. Dr. Corso used a comparison of vaccination to screening tests, demonstrating the superiority of the former.
 - C. "Cost effective" does not equate to "cost savings," a truth of particular interest to the ACIP and the vaccination field. Vaccinations were not considered cost saving 10-20 years ago, but now are known to be cost effective, if not cost saving. That means that relative to other clinical preventive services being done, vaccination programs are still extremely cost effective. But in calculating that, the population level is significant, since what may not be cost saving at a sub-level could be so at another level.

The conclusions are that 1) economic evaluation is valuable to the decision-making process and should always be included in setting health policy; and 2) interpreting these results is

often complex and requires much more than a 45-minute presentation.

CDC has an intensive training course on the mechanics of cost benefit, cost utility, and cost effectiveness analysis. It also provides technical assistance, including a two-year post-doctoral Fellowship program involving economists throughout CDC. An economics contract with the Research Triangle Institute allows CDC program offices to commission economic evaluation to fill gaps in the literature. CDC is also developing a standardized methodology to allow universal comparison on cost utility analyses.

Discussion included:

- Dr. France: *It seems as though an HMO would always be interested in both the cost utility analysis (for general policy issues to compare it to other standardized accepted prevention programs) and cost effectiveness analysis (to decide on age levels of children to be immunized and the differing impacts) when reviewing some new policy.* Agreed. The cost effectiveness side is limited and suitable for the micro level, but for setting broader health policy at a national level, cost utility analysis is appropriate.
- Dr. France: *Is there an easy place to access comparisons when considering the cost utility of something?* Other clinical preventive services are probably the closest comparison to that. Those are called lead tables, which are increasingly published in peer review journals, so that may be a place to start. CDC's DPRAM office will help in that search, as well.

PUBLIC COMMENT was solicited. With no response, the meeting adjourned at 5:50 p.m. with Dr. Modlin's thanks to all the participants.

I hereby certify that, to the best of my knowledge, the foregoing Minutes are accurate and complete.

John F. Modlin, M.D., Chair

Date

