

CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICE

Records of the Meeting Held on

October 17-18, 2001

Atlanta Marriott North Central Hotel
Atlanta, Georgia

CENTERS FOR DISEASE CONTROL AND PREVENTION
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

Marriott Century Center
Atlanta, Georgia
October 17-18, 2001

<u>Agenda Item</u>	<u>Purpose/Action</u>	<u>Presider/Presenter(s)</u>
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 Hlth) 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 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 (NCID,DVRD)	Discussion Decision/Vote	Dr. H. Margolis 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)
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>		

Agenda Item**Purpose/Action****Presider/Presenter(s)**

8:00 Unfinished Business from Previous Day

Dr. J. Modlin (Chair, ACIP)

8:30 Updates

Information

National Immunization Program
Food and Drug Administration
Vaccine Injury Compensation Program
National Institutes of Health

Dr. W. Orenstein (NIP, OD)
Dr. K. Midthun (FDA, CBER)
Dr. G. Evans (HRSA)
Dr. C. Heilman (NIH, NIAID)

National Vaccine Program
National Center for Infectious Diseases

Dr. M. Myers (NVPO)
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
DBMD)
Vaccine on invasive disease during 2000 and
plan for tracking vaccine failures
Update on vaccine supply

Information

Dr. C. Van Beneden (NCID,

Discussion

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

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ATTENDEES:

Committee Members

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

Ex Officio Members

Dr. Benedict Diniega (DOD)
Dr. Geoffrey Evans (NVICP)
Dr. Amy Groom, IHS
Mr. Randolph Graydon (HCFA)
Dr. Carole Heilman (NIH)
Dr. Karen Midthun, FDA
Dr. Martin Myers, NVPO
Dr. Kristin Nichols, (VA)

Liaison Representatives

Dr. Jon Abramson (AAP)
Dr. Eric France (AAHP)
Dr. Stanley Gall (ACOG)
Dr. Randolph Jackson (NMA)
Dr. Samuel Katz (IDSA)
Dr. Martin Mahoney (AAFP)
Dr. Jose Ignacio Santos (NICCH, Mexico)
Dr. Victor Marchessault (CNACI)
Dr. Kathy Neuzil (ACP)
Dr. Georges Peter (NVAC)
Dr. Gary Overturf(AAP)
Dr. Kevin Reilly (PhARMA)
Dr. David Salisbury (DPH, London)
Dr. William Schaffner (AHA)
Dr. Jane Siegel, (HICPAC)
H. David Wilson (AMA)
Dr. Richard Zimmerman (AAFP)

Executive Secretary

Dr. Dixie E. Snider, Jr.

Office of General Counsel

Kevin Malone

Epidemiology Program Office

Linda McKibben

National Center for Infectious Diseases

Miriam Alter
Elizabeth Bolyard
Lynn Brammer
Joseph Breese
Carolyn Bridges
Linda Chiarollo
Scott Demon
Roz Dewart
Keiji Fukuda
Roger Glass
Allison Mawle
Ann Moen
Martin Meltzer
Dick Moyer
Joe Perz
Alicia Postema
David Shay
Kanta Subbarao
Eric Weintraub
Cynthia Whitney
Rachel Woodruff

National Immunization Program

Lorraine Alexander
Robin Annison
William Atkinson
Roger Bernier
Kris Bisgard
Carolyn Bochina
MaryAnn Bryant
Tameka Byrd
Scott Campbell
Christie Casey
Bob Chen
Susan Chu
Gary Coil
Nancy Fenlon
Patrick Flaherty
Katie Fullerton
Edith Gary
John Glasser
Beth Hibbs
Penina Haber
Jim Harrison
Sonja Hutchins
Laurie Johnson
Dewa Joseph
Sharon Katz
Duane Kilgus
Charles LeBaron
Peng-jun Lu
Dean Mason
Mehran Massoudi
Mary McCauley
Gina Mootrey
Trudy V. Murphy
Tippavan Nagachita
Serigne NDiaye
Glen Nowak
Dianne Ochoa
Dennis O'Mara
Walter Orenstein
Ismael Oretaga-Sanchez
Paba Palihaardana

Elizabeth Parson
Kelly Plott
Larry Pickering
Jeri Pickett
Bette Pollard
Lance Rodewald
Jeanne Santolli
Kari Sapsis
Judy Schmidt
Susan Scheinman
Ben Schwartz
Jane Seward
Kristine Sheedy
Jim Singleton
Vishnu-Priya Sneller
Ray Strikas
Pamel Srivastava
Kathy Towers-Solis
Anjella Vargas
Donna L. Weaver
Bruce Weniger
Melinda Wharton
Skip Wolfe
John Zhany

Other CDC

Maria Cano
Jon Getse
Baoming Jiang
Suzanne Johnson-DeLeon
Vanda Kelly
James Lai
Tasneen Malik
Linda Moyer
Julie Orta
Rolinda Watkins
Ian Williams

National Vaccine Program Office

Steven Sepe

Food and Drug Administration

**Norman Baylor
Phil Krause**

National Institutes of Health

**Albert Kapikian
Lone Simonsen**

Others Present

**Daniel A. Allwine, Athens, Ohio
Bascom F. Anthony, Biologics Consulting Group
Mark Bagorrazzi, Haddonfield, New Jersey
Michele Bailey, Pittsboro, North Carolina
Joseph Beaver, TN Department of Public Health
Bryan Bechtel, Infectious Disease News
Sallie Bernard, Safe Minds
Richard M. Cacth, Chamble, Georgia
Pat Cannon, Wyeth
Dan Casto, Merck
Jill Chamberlain, Vaccine Bulletin
Kathleen Collingh, San Francisco, California
Kevin Connolly, Merck
Lenone Cooney
Paul Coplan, Merck
Christine Curtis
Dack Dalrymple, Bailey and Dalrymple
Michael Decker, Aventis Pasteur
Carmen Deseda, San Juan, PR
Elizabeth DeSouza, Glaxo, Smith-Kline
Natalie deVane, St. Davids, Pennsylvania
Richard Dinovitz, Wyeth Lederle
Dan Douglas, Sabin Vaccine
Craig Engesser, Wyeth
Stephen Feher
James Froesh, Aventis Pasteur
Oren Fuerst, Becton Dickinson
Diane Gaskins, GA Immunization Program
Bruce Gellin, Vanderbilt University
Jayne Gilbert, Chiron Corp.
Ruth Gilmore, Georgia Immunization Program
Jennifer Gottlieb, Cohn & Wolfe
Eric Greenbaum
Jesse Greene, SC Department of Health
Kenneth Guito, Aventis Pasteur
Jeff Hackman, Gaithersburg, Maryland**

Page 4 - Others Present (continued)

Tamar Halpern, Buffalo, New York
Neal Halsey, Johns Hopkins Univ.
Claire Hannan, ASTHO
Celine Hanson, Austin, Texas
Garner Harris, USA Today
J. Scott Harward, Glaxo, SmithKline
Rick Haupt, Aventis Pasteur
Penny Hector, Merck
Kathy Heidish, Lawrenceville, Georgia
Emma Hitt, Roswell, Georgia
Shannon Housel, New York, New York
Philip Hosbach, Aventis Pasteur
Bruce Innis, Glaxo, Smith-Kline
Martha Iwamoto, Atlanta, Georgia
Melanie Jackson, Georgia Department of Health
Sheldon Jacobson, Urbana, Illinois
Charlotte Kroft, Philadelphia, Pennsylvania
Barb Kueter, Merck and Company
Edgar Ledbetter, San Antonio, Texas
Pam Lennard, Atlanta, Georgia
Rick Linder, Doyleston, Pennsylvania
Scott Litherland, Parallax Communications
Joy Mara, Mara Communications
Erique Medina, Beavercreek, Ohio
Michelle Mattilin, Aventis Pasteur
Slaoui Monce, Glaxo, Smith-Kline
Stan Music, Merck
Marie Murray, Atlanta, GA
Thomas Netzer, Aventis Pasteur
Patricia Nolan, Rhode Island Health
Barbara Ochester, Glaxo-Smith-Kline
Peter Paradiso, Wyeth Lederle
Diane Peterson, Minnesota Department of Health
Stanley Plotkin, Aventis Pasteur
Terry Polins, Athens, Georgia
Linda Quairk
Jane Quinn, Glaxo, Smith Kline
Lynn Redwood, Tyrone, Georgia
Barbara Reilley, Houston, Texas
Anne Rogers, Penn State
Zeil Rosenberg, Becton Dickinson
Florian Schodel, Merck

Page 5 - Others Present (continued)

Charles Seabrook, Decatur, Georgia
Matt Strasburger, Merck
Kathleen Stratton, Institute of Medicine (IOM)
Stacy Stuerke, Merck
Anne Schwind, Glaxo, Smith-Kline
Frederic Shaw, Austin, Texas
Ben Sloat, Atlanta, Georgia
Salley Somerfeldth, Nashville, Tennessee
mark Sorrentino, CNMC
Anna Marie Spain, Martinex, Georgia
Maureen Stewart, Research Triangle Park, North Carolina
Dirk Teuwen, Aventis Pasteur
John Trizzino, Bastian, Virginia
Ruport Vessey, Merck Research Labs
Ted Tsai, Wyeth Pharmaceuticals
Miriam Tucker, Pediatric News
Theresa Turski, DHR, GPH
Thomas M. Vernon, Merck
Peter Vigliarolo, Cooney Waters
Deborah Wexler, Immunization Action Coalition
Matt Williers, Georgia Department of Public He
Marcellette Wise, Glaxo, Smith-Kline
Greg Yoder, Peachtree City, GA
Laura J. York, WLW
John Zahradnik, Aventis Pasteur
Thomas Zink, Glaxo, Smith Kline

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

October 17-18, 2001

OCTOBER 17, 2001

OPENING COMMENTS/DISCLOSURES

Dr. John Modlin, Chair of the Advisory Committee for Immunization Practices (ACIP), convened the meeting at 8:30 a.m. He asked the members, in introducing themselves, to provide any statements of financial conflict of interest. With such a statement, they may still participate in all discussions, but may not vote on any issue related to that conflict, nor may they introduce or second resolutions pertaining to the Vaccines for Children (VFC) program.

ATTENDANCE

The members, liaisons, ex-officio representatives, agency and support staff, and interested members of the public in attendance are listed in the preceding pages. Those reporting potential conflicts were:

Dr. Rennels: conducted vaccine trials with Wyeth, Lederle, Merck, Glaxo Smith-Kline and Aventis Pasteur.

Dr. Paul Offit: is co-holder of a patent on a bovine-human rotavirus vaccine and consults on its development with Merck & Company.

Dr. Myron Levin: conducts research with Merck and with Glaxo Smith-Kline.

Dr. Richard Clover: Potential conflicts of interest with Wyeth Lederle, Glaxo Smith-Kline, Merck, Pfizer and Bayer.

COMMITTEE BUSINESS

Dr. Snider made several announcements:

- He welcomed Dr. Stephan Foster, new liaison from the American Pharmaceutical Association.
- The ACIP home page is www.cdc.gov/nip/acip; the ACIP e-mail address is acip@cdc.gov.
- The 2002 ACIP meeting dates are: February 20-21; June 19-20; October 16-17.
- Although not yet appointed, the amended ACIP charter's three new members increase the membership to 15, which requires a meeting quorum of eight members.
- The charter authorizes the Executive Secretary or designee to temporarily designate ex-officio representatives to vote, when less than eight appointed members are qualified to vote due to the lack of a quorum of members without financial conflict of interest. The ex-officio representatives are requested to vote and to disclose any potential conflicts of interest.
- New ACIP policies/procedures are:
 - A consumer representative member will be appointed.

- ▶ New member nominees will be solicited from present members and liaisons, and in future also will be solicited through a Federal Register announcement. Nominees will be asked their willingness to serve, and be provided an orientation session.
- ▶ Members may provide technical advice to manufacturers, but not participate on a manufacturer's advisory board to provide advice larger in scope than technical advice.
- ▶ Company stock ownership >\$5,000 must be divulged..
- ▶ A formal vote to recommend a vaccine cannot be taken prior to FDA licensure.
- ▶ Emergency ACIP meetings may be arranged to address issues between scheduled meetings, and, if justified, be held without a prior Federal Register notification.
- ▶ ACIP working groups must include two or more ACIP members, and may include other CDC staff, FDA staff members when appropriate, and ex-officio and liaison representatives. Workgroup members are designated as special government employees to allow proprietary information to be shared. Manufacturers' representatives can serve as workgroup consultants, but not as official members.
- ▶ ACIP's discussions are open. Specific meeting times are reserved for official public comment, but comments can be provided at the Chair's discretion during open discussions.

NVPO/NVAC WORKSHOP: ROTAVIRUS VACCINE AND INTUSSUSCEPTION

Dr. Myron Levin, Chair of the ACIP's Rotavirus Workgroup, reported on the NVPO/NVAC Workshop on Rotavirus Vaccine And Intussusception, held September 5-7, 2001. The ACIP workgroup decided to base its activity on that workshop's information and outcomes.

Dr. Georges Peter summarized the meeting's observations and conclusions about the association of intussusception and rotavirus. Although the discussion focused on RotaShield™, there were important implications for vaccine policy in general, such as setting acceptable vaccine risk and its management. Dr. Peter described the discussions of the RotaShield™ experience, attributable risk of intussusception, and assessment/management of risk.

Background: Previous findings discussed included the January 2000 WHO/GAVI meeting, which determined: 1) an international priority for rotavirus; 2) the problems associated with RotaShield™ should not inhibit further prevention research; 3) knowledge remains limited about the epidemiology, causes, pathophysiology, and pathogenesis of intussusception. The weakness of the epidemiology of intussusception, based on hospital discharge data, involves

miscoding and variations in hospital practice (e.g., hospitalization of 2-3 days, to a very short stay, to no hospitalization at all).

Rotavirus/Intussusception. The burden of *Rotavirus* disease involves hospitalization rates (1:16 in Venezuela; 1:77 in the U.S.), and a decreased but still appreciable mortality over the past 15 years. The incidence of intussusception varies between countries: low and apparently declining in the U.S. , higher in the developing world. Few studies have shown an association between natural rotavirus disease, gastroenteritis, and intussusception. Japanese work in the late 1970s found an association between rotavirus and increased intussusception. If this is attributable to certain rotavirus strains, the vaccine strain could be one. One animal model links rotavirus as a cofactor to intussusception, at least in mirroring disease. A CDC pathology study of rotavirus-associated intussusception cases was too limited to determine the pathogenesis of this complication of RotaShield™ vaccination.

RotaShield™ The RotaShield™ experience of pre-licensure trials, vaccine distribution, and intussusception studies was reviewed, along with several studies' further investigation. Also reviewed was an assessment of the attributable risk of intussusception from RotaShield.™

1. *CDC, Murphy et al (New Eng J of Med).*
 - A. Case-control (validated cases) study of hospitalized patients in 19 states who received rotavirus vaccine. Cases matched to 4 controls. Case definition: hospitalization with radiographic, surgical, or autopsy-confirmed diagnosis.
 - B. Case-series study. Same case finding and case definition; subjects were their own controls. Evaluated any uniform distribution of intussusception post-vaccination or occurrence shortly after vaccination.
 - C. Results: Both studies showed elevated ratios of incidence risk and odds ratio, significant for the post-vaccine intervals of 3-7 days and 8-14 days, but no difference after >15-21 days. The low odds rate after the 21-day interval could be because higher-SES infants were more likely to have received rotavirus vaccine and have a lower baseline intussusception risk than infants who did not receive RotaShield.™
 - D. Conclusions: These findings did not support the concept of a compensatory decrease or a temporal shift. There is evidence of a strong, temporal and specific causal association between RotaShield™ and intussusception, higher in the 3-7 day windows after both doses 1 and 2. The overall attributable risk was one excess case for every

4,679-9,470 vaccinated infants. That is lower than the original estimated range of 1:2500 to 1:5000.

2. *CDC, Vaccine Safety Datalink study, Kramarz et al.* Cases (hospitalized and non-hospitalized) in 10 large managed-care organizations were validated; Cohort: 61,000 RRVTV vaccinees and 463 infants with intussusception.
 - A. Case definition: radiographic, surgical or autopsy-confirmed diagnosis. Relative risks were consistent with those in the Murphy *et al* study (elevated 3-7 days).
 - B. Conclusions: i) intussusception risk was increased 3-7 days post-dose 1; ii) overall vaccine attributable risk was 1:11,703 vaccinated infants; iii) plausibility of association was supported by the correlation between the 3-7 day highest risk period to the period of vaccine virus replication in the intestines.
3. *Retrospective Longitudinal Cohort Study (Ped Infectious Dis Jnl)*
4. *Chang, et al, ecological study:*
5. *NIH/NIAD, Simonsen et al: ecological study (Lancet).* A 10-state analysis being extended to 21 states. The latter data provided similar conclusions.
 - A. Ten-state analysis; case finding study of hospital discharge diagnoses; no controls. Case definition: hospitalization with discharge diagnosis of intussusception.
 - B. Findings: Based upon vaccine coverage of 28 percent, hospitalization for intussusception decreased from an incidence of 4.7 to 3.1 cases among infants aged 45-210 days. Incidence of the 9 months during vaccine administration, compared to the same period the previous year, showed a 1% increase that was offset by a decrease among older infants. That suggested a temporal shift and possible triggering mechanism. The overall vaccine attributable risk was lower than the CDC estimate and considerably lower than that in the 21-state study's larger population. The latter's coverage rate paralleled the National Immunization Survey's at 12.8%. Attributable risk was 1:18,000-33,000.
6. *Verstraeten et al: VAERS analysis: Assessment of VAERS efficacy in detecting cases (47% case detection rate).*
7. *Rhodes et al, CDC Follow-up to Kramarz et al VSO study (in progress).* Relative risk among a small number of cases demonstrated a marked increase 3-7 days post-vaccination, equal between vaccinated and unvaccinated infants 3 weeks post-vaccination. No compensatory drop was shown.

Workshop assessment of attributable risk of intussusception from receipt of rotavirus vaccine:

- No question, the causal association of RotaShield™ and intussusception is strong, temporal and specific. However, no epidemic of intussusception followed RotaShield™ introduction. Both the coverage rate (12.8%) and the population-attributable risk (~1:10,000 children) were lower than initial estimates.
- A rotavirus trigger of intussusception, compensating a post-vaccination increase by a subsequent decrease, is an intriguing but unproven hypothesis.
- An association of OPV with intussusception was demonstrated in initial studies, but not subsequently. A causal association between OPV and intussusception could not be excluded by a majority of CDC's June 2000 expert panel, due to insufficient data.

Risk perception. A session with six presenters found an important influence in the public's perception of risk. Media influence in risk perception was noted, raising the importance of risk communication. Such as program in the United Kingdom was shared.

Tolerable risk for RotaShield.™ There was no consensus on acceptable risk. Policy options for vaccine utilization include elective usage, selective recommendations for high risk groups, universal recommendation, and a universal recommendation with a mandate. An opinion survey of pediatricians about rotavirus vaccine indicated the importance to them of community benefits and costs, such as adverse events and disease; vaccine costs; parental anxiety; and (particularly in rural, under-served communities) the availability of specialized medical services for adverse reactions. Febrile convulsions, being more common in children, were a lesser concern. National and international perspectives, and professional and public acceptance of a recommended vaccine is important to its uptake, as is the industry perspective and risk communication.

Future considerations. Dr. Sam Katz then reviewed discussions (in the workshop and several conference calls) of the use of the still-licensed RotaShield™ vaccine, which may be a trigger to intussusception. China apparently has a viable rotavirus vaccine in use, which is prepared from a lamb strain of rotavirus. The questions discussed were:

1. Does the ACIP wish to reconsider its decision to withdraw the recommendation for universal use of RotaShield™ in the U.S., either at this meeting or in February 2002, or at another time?
2. What information does the ACIP require from the Workgroup in order to prepare for a vote in February? Pending information includes Dr. Peter's written report on the workshop, a final analysis of the Rhodes extended follow-up study; background materials on the

strengths and limitations of intussusception risk studies; and an update of studies of vaccine safety predictors (e.g., in animal models and by imaging done during rotavirus infection). Two other manufacturer product studies are under investigation (Merck and Glaxo Smith-Kline). The importance of public confidence and the conception of how vaccine decisions are made has risen with public interest in vaccines due to the bioterror potential of anthrax and smallpox.

3. Does the ACIP want to provide guidance to manufacturers regarding all vaccines' acceptability for universal use in the United States? If so, what is the appropriate forum for such a discussion? A unified, voiced expert opinion on rotavirus and intussusception is necessary to retain public confidence.

Discussion included the following:

- Dr. Smith: *When might ACIP have pending study information?* The expansion beyond VSD sites is delayed by abstraction of practitioners' chart, etc. Results should be out by February.
- Dr. Brooks: *Are there any data on intussusception related to the Chinese vaccine?* There are no data known as to whether that strain induces intussusception. But intussusception in China differs greatly than that in the U. S. There is a 7-9 times greater incidence there, and a seasonal (winter) association.
- Drs. Abramson/Overturf: The AAP and its Committee on Infectious Disease (COID) would not recommend RotaShield™ universally.
- *What would Wyeth require to re-market the vaccine?* Dr. Reilly: RotaShield™ is still licensed and production facilities remain. It would be produced again upon a universal recommendation and a need for it in the U.S., but there would be some start-up time.
- Voiced perspectives:
 - ▶ Dr. Offit: Rotavirus mortality is not high in the U.S., but it is worldwide, and it rarely causes intussusception. ACIP must determine the acceptable level of serious side effects for generally non-fatal but high-morbidity diseases in the U.S. A discussion about changing the RotaShield™ recommendation is important because American children do still die from rotavirus disease. That discussion should not damage public trust.
 - ▶ Dr. Snider: 1) The VRBPAC advice about rotavirus vaccine studies provides a *de facto* decision on acceptable risk, in approving protocols of a sample size to detect that risk. Regardless of RotaShield,™ rotavirus vaccines will be required. 2) A series of types of vaccine recommendations could be made. While discussion of appropriate level of risk

will be useful, decisions on the type of recommendation to make, based on risk levels, are complex and require more time than is possible in one meeting.

- Dr. Katz: This is not a totally novel situation. OPV was used despite a 1:750,000 risk of vaccine-associated paralytic polio (VAPP); measles vaccine is still used although it may cause thrombocytopenia in 1:75,000 children, which has not destroyed public confidence; and whole-cell pertussis vaccine was used for many years until the acellular product was made.
- Dr. Orenstein: The ACIP recommendation for universal vaccination was very controversial even before the intussusception factor was known, based on discussions of vaccine cost and the balance of risk and benefits. Intussusception tipped the balance for what was a very close vote. But there is no new information to prompt changing that decision.
- Dr. Chen: Most classical pre-licensure trials are able to detect events between 1:1,000-5,000. They are designed for efficacy outcomes, more than for safety, but they also support vaccine safety for licensure. Post-marketing studies reveal the rare events (e.g., 1:100,000), and at times have forced a policy change. The challenge is how to bridge the smaller efficacy study confidence ranges to those of the post-marketing studies. Improved surveillance technology could aid this.
- Dr. Abramsom: All of medicine is based on risk and benefit, making this a disease-by-disease discussion and preventing any generalization acceptable risk assertions. The AAP decided that an intussusception risk of 1:10,000 is unacceptable. However, rotavirus vaccine could be a good vaccine if it was safe enough.
- Dr. Snider stated for the record that one unintended consequence of the ACIP recommendation was to impact rotavirus vaccine availability in different settings and populations abroad. Specific risk populations were not identified in the U.S., other than some association with socioeconomic status and severe outcomes. That identification would have allowed a risk-benefit analysis and vaccine targeting. There is also little risk information for developing countries, except that rotavirus seems more prevalent and causes more severe infection outcomes. Many believe that RotaShield™ could provide tremendous benefit and little harm in those settings. Such considerations are important for future discussions about how to recommend for the U.S. within the context of the effect of ACIP recommendations elsewhere in the world.
- Dr. Roger Glass, NCID: Initially, RotaShield's™ cost was the worry, but private sector uptake was good. Estimates of benefit are that ~150 rotavirus hospitalizations would be prevented, and up to 1000 office visits, for the one intussusception event that

occurred. The disease burden is clearly important compared to the intussusception risk, and the benefits still outweigh the risk.

- Dr. Orenstein: The biggest issue was the vaccine cost, not the question of significant risk factors for serious disease. But for any rotavirus vaccine, a ~\$100 cost should be calculated for some oral rehydration for every baby born in the country, to justify RotaShield's™ primary prevention.
- Dr. Offit: The actual risk of 1:100,000 or 1:500,000 can only be determined with the large post-licensure studies. But that should not defeat a universal recommendation for vaccines which are of universal benefit. Otherwise, any universal recommendation would have to wait until 2-4 million children could be immunized, hopefully over a reasonable period of time.
- Dr. Katz: Dr. Snider's comments are germane and important. About 452,000 deaths due to rotavirus gastroenteritis occur annually. Even in the U.S., although oral rehydration may have reduced the numbers somewhat, the disease burden is still very large. He was less worried about the ACIP recommendation's effect on the rest of the world, citing three historical examples: U.S. smallpox vaccination ended in 1971, but smallpox elimination continued for another 6-9 years elsewhere; the introduction of IPV did not destroy the global OPV program; and while the U.S. switched to acellular pertussis vaccine, most of the world still uses whole-cell DTP.
- Dr. Reilly: The difference with the original RotaShield™ recommendations was that only the U.S. had reviewed it for approval, and only the ACIP had recommended it at that time. Wyeth Lederle would have continued production if they reasonably could have expected vaccine acceptance in underdeveloped countries. But Wyeth's polling of those countries' health departments and ministers of health indicated that, even with a recommendations by the WHO for the vaccine's use, they would not use one turned down by the recommendation board of a major country. Regarding the vaccine price, Wyeth would have adjusted that to allow underdeveloped countries' use, as done in the past.
- Dr. Salisbury: A better understanding of how numbers and feelings are interpreted, and how the public interprets those, is necessary, because every live virus vaccine in future will involve those issues. For example, 1:10,000 is not felt to be acceptable, but what about 1:20,000? Feelings also are subjective; there should be an informed public debate on risk and benefit. Other feelings also bearing more examination are the acceptability to the user for this number of children to be dying and hospitalized against this particular event, and why this adverse event is prioritized above others. The risk of intussusception does not

differ greatly from that of ITP after MMR (1:23,000). The parents' feelings must also be determined, and the media carriage of such U.S. recommendations outcomes affects public perception elsewhere.

- Dr. Abramson: The AAP's concern over the 1:10,000 number and opposition to a universal recommendation was based on several factors: 1) Wyeth indicated that only a universal recommendation would prompt vaccine production; 2) a higher than expected number of children required surgery for intussusception, and it is harder to detect in those aged <3 months; 3) there is a tremendous shortage of pediatric radiologists in the U.S. Despite empathy for the need abroad, the AAP's primary responsibility is to recommend for U.S. children.
- Dr. Modlin: Dr. Murphy's paper indicates a similar surgery rate between the vaccine-associated cases and those not so.
- Dr. Orenstein: 1) ACIP's policies are made in public; 2) values are integral to all immunization recommendations; and 3) the already-present concern about the cost-benefit was intensified with the detection of the intussusception risk.

The committee members agreed to await the needed information cited in this discussion, particularly related to other strains and different vaccines, and that on other outcomes than intussusception. After considering that, the answers to Dr. Katz' three questions could be discussed in February. Dr. Brooks and Dr. Offit expressed their discomfort with reconsidering the existing recommendation. Dr. Levin summarized that the workgroup would accumulate the relevant information as indicated by the committee to allow a response in February.

ISSUES RELATED TO INFLUENZA VACCINE

Dr. Bonnie Word reported on the September 10-11 Influenza Workgroup meeting's discussions of potentially expanding influenza vaccination to children. Four topics were examined: additional data on inactivated influenza vaccine safety and effectiveness data, economic issues of expanded use, and implementation and feasibility issues. Options were discussed.

Influenza disease burden among children. Dr. Tim Uyeki summarized the available data on influenza morbidity in terms of attack rates during influenza epidemics, hospitalization data, the little data on out-patient visits, and complications.

Influenza Morbidity. Longitudinal family studies of influenza have been done in Tecumseh,

Michigan; Cleveland, Ohio; Houston, Texas; and Seattle, Washington.

1. Seattle, Hall CE *et al*; 1966-69 study primarily of serologically-detected influenza infection. Attack rates: children aged 0-1 (24.4%); 2-5 (26.5%); 6-19(18%); adults (14.1%). Complications in children hospitalized for influenza A and B: pneumonia, bronchitis, croup, bronchiolitis, fever without a source (no respiratory symptoms), and febrile convulsions. Topical papers:
 - ▶ *Pediatrics*, September 2001, 30-40% of children in Hong Kong hospitalized for febrile seizures during winter and influenza (influenza A) season.
 - ▶ *New England Journal*, 2000: 1) Izurieta *et al* and 2) Neuzil *et al* used indirect methods to develop an excess hospitalization rate.
 1. Izurieta *et al*: Studied two large west coast HMO populations, 1992-97, hospitalization rates (per 10⁶ person-months) for defined acute respiratory conditions, using local virologic surveillance data to define influenza periods, with adjustments for RSV season. In the healthy children, excess rates for acute respiratory conditions (less the summer baseline rates) were 151 (0-1 years) and 26 (2-4 years) (Northern California Kaiser); and in the Group Health Cooperative cohort, 127 (-01); 5(2-4); and 5 (5-17). The rates among high-risk children with chronic underlying conditions were also much higher than those of healthy children, with much higher hospitalization rates in both HMO cohorts.
 2. Neuzil *et al*: This was a similar analysis of hospitalization rates for acute cardiopulmonary conditions, using 19 years of Tennessee Medicaid populations data of healthy children aged <15 years old. The study defined influenza/RSV circulation periods and examined excess rates. The highest excess rates were in the youngest children (103.8 excess cases, 0-6 months; 49.6 cases, for those 6-<12 months; 18.6 cases for those 1-<3 years. The rate declined further with age. As with Izurieta's results, high-risk, chronically ill children had very high excess hospitalization rates (19.2 for those aged <1 years; 7.6 for those 1-<3; 2.3, 3-<15 years). These are 2-4 times higher than for healthy children. For out-patient, healthy children, Tennessee Medicaid data from 1973-93 cited influenza for up to 35% of excess visits in winter among those aged <3 years. Total out-patient visit rates were highest for infants aged <6 months, followed by infants aged 6-12 months, then by those 1-3 years. And, still-unpublished data from a 25-year prospective study those Medicaid children followed for culture-confirmed influenza, 9.5% had a symptomatic health care visit that was associated with culture-positive influenza each year.

Otitis Media Morbidity. Acute otitis media (AOM) was studied in a 6-year Finnish study (Ruuskanen *et al*) of both hospitalized and out-patients. AOM was diagnosed in 35% of patients with influenza A, and in 42% of children with influenza aged 2 months-7 years (Heikkinen *et al*). A clinical trial with Finnish day care children aged <3 years, also by Heikkinen *et al*, showed AOM in 67% of those aged <3 years who were unvaccinated and influenza-positive. An LAIV clinical trail among children aged 15-71 months, unvaccinated and influenza culture-positive, showed 21% with AOM in year 1 and 12% with it in year 2.

Rare neurological complications include acute encephalitis and acute necrotizing encephalopathy, which are normally associated with influenza pandemics and sporadically reported in epidemics. However, Japan has had a substantial increase in cases of both since 1994 that are associated with influenza A, all in young children. Within 1½ days of onset of a sudden high fever is rapid onset of neurological symptoms, and seizures are very common. Rapid progression to coma occurs in a large percentage of the cases. This is not associated with aspirin use and there is no Reyes Syndrome-like presentation. Neuro-imaging often shows bilateral thalamic necrosis, brain stem, and cerebellar involvement. Neurological sequella (paralysis, decreased functioning) are frequent, and the case fatality ratio is high. Death often occurs shortly after onset. Japan has an estimated 100-200 fatal cases of acute encephalitis or encephalopathy annually. Data from a related paper (*Lancet* 2000) was presented. These data indicate an under-estimation of influenza's impact, particularly under-reporting in patients presenting with atypical symptoms (e.g., young children with non-respiratory symptoms, particularly only gastrointestinal symptoms), or fever without a source, sepsis-like syndrome. Influenza also is rarely confirmed by testing; it is usually clinically diagnosed. There are few good published mortality data pertaining to young children.

Use of TIV Vaccine in Children. Dr. Kathy Neuzil summarized the working group's discussion about the use of trivalent inactivated influenza vaccine (TIV) in children, focusing on safety and effectiveness/efficacy. Their methods were: 1) a Medline search for and review of TIV studies in children; 2) review of additional studies referenced in Medline articles. Studies excluded were those of whole virus vaccine or foreign TIV not comparable to the U.S. products, and any pre-1981 study (when the vaccine antigen content was lower than the current vaccine's).

The key studies presented to the ACIP were randomized, controlled trials (RCTs), although

smaller immunogenicity and safety studies were also reviewed and discussed. The RCTs fell into three categories: children in day care; studies comparing the TIV to the LAIV; and two unpublished studies.

Day Care Studies focused on children aged <5 years in day care, with an end point of AOM. *Heikkinen et al*: 187 children aged 1-3 years who received TIV were compared to 187 unvaccinated (no placebo) children (no safety data taken). Overall efficacy for culture-proven influenza and reduction in influenza-related AOM was 83%.

1. *Clements et al*: 185 day care attendees aged 6-30 months. The care facilities were randomized to receive TIV or placebo (no safety data taken). Influenza vaccine protected against AOM during the influenza season, but not before or after.
2. *Hurwitz et al*. Day care attendees aged 24-60 months received inactivated or hepatitis A vaccine. Parents assessed and reported adverse reactions; both vaccines were well tolerated. Vaccine efficacy measured by seroconversion was 45% (CI 5-66%). No significant differences were seen for respiratory illness, otitis, physician visits, or antibiotic use, but a companion paper reported a reduction in respiratory illnesses among family member and contacts.

RCTs reviewed were efficacy trials of TIV and the cold-adapted influenza vaccine (CAIV) in children (2 studies at Baylor and Vanderbilt Universities, four publications: vaccine compared to the current vaccine, the same antigen component, and split virus vaccines. The CAIV was bivalent at that time; the concentration in some studies differed slightly.

1. *Baylor family study*. This 3-year study was published in three separate papers:
 - a. *Gruber et al*, 1985 study (year one). Families were randomized to receive placebo, TIV and CAIV; cohort was 189 healthy children aged 3-18 years; weekly phone contacts were done, and home visits when clinical illness occurred. Blood specimens, nasal wash or throat culture were obtained from these patients. The circulating strain was B, a drift strain from the inactivated vaccine. No serious adverse effects were reported, only local tenderness at the site in ~20% of children receiving the TIV and 19% of those receiving placebo. Results: The placebo group demonstrated that influenza is common among children: laboratory-confirmed in 30-55% and clinically confirmed in 30-40%. Demonstrated TIV efficacy increased with the children's age, 62% for infection and ~76% for clinical illness.
 - b. *Clover et al*, 1991 (year two): The same study design was used. An H1N1 drift strain

circulated. No safety data were collected. Influenza was lab-confirmed in 20-25% of children. Efficacy was not statistically significant in those younger than 10-19 years, but was highly efficacious in the 10-19 group. No illness was reported.

c. *Piedra et al* (year three). Mild reported local and systemic reactions were reported following vaccination. No difference emerged between the groups, with a 76% protection rate against symptomatic H3N2 infection. There was insufficient power to compare within the age group, but a similar pattern of improvement with age was reported. These children were followed to a fourth year with no additional vaccine dose. Prior years' vaccination protection did not extend into year four.

2. *Vanderbilt study, Edwards et al.* This was a large 5-year study of >5000 healthy subjects randomized to receive TIV, LAIV, or placebo. Cumulative data were reported in 1994; the pediatric portion was reanalyzed/reported in 2001. Pediatric analysis was of 791 healthy children aged 1-16 years who participated in years 2-5 with an H3N2 strain circulation, one a drift strain from the vaccine's; and H1N1 circulation in two of the years.

a. Safety assessment: Fever, local reaction, systemic reactions (sore throat, coryza, lethargy, lethargy, chills, nausea, headache, muscle ache, cough). Local reaction was assessed through diary cards kept for 5 days post-vaccination. Significant results were similar to those among adults, in age groups 1-5, 6-10, and 11-15:

- ▶ TIV, common side effects were sore arm, redness, and induration, the rates of which increased with age. Efficacy was demonstrated for both vaccines based on seroconversion and on illness, for both H1 and H3N2 years. The vaccine was more efficacious with increasing age.
- ▶ Culture-positive illness: Overall rates were 4-7% lower than the Baylor studies of patients self-presenting to hospital. Power was insufficient to delineate culture-positive influenza illness by age group, but vaccine efficacy was estimated to be ~92% for H1N1 disease and ~77% for H3N2 disease.
- ▶ *High-risk populations.* Studies since 1981 among a limited number of children with a limited number of conditions indicate comparable safety profiles and immunogenicity studies. Data were insufficient to assess efficacy.

Unpublished Data presented were:

1. *Greenberg et al, University of Pittsburgh:* This study evaluated TIV in children aged 6-24 months (half to those aged 6-12 months, an age group of sparse data), with an endpoint of AOM. Limited safety data; no serious adverse events (SAEs) were related to vaccine or placebo. There was a 66% reduction in culture-positive flu in year one, no reduction in year two (a year of low illness rates), and no difference in AOM episodes.
2. *France et al, VSD Data Analysis.* This was an analysis of population-based studies of less common vaccine side effects in children in the GHC and Kaiser Permanente HMOs. Data cover the period 1997-99 and 148,000 influenza vaccinations. Initial analysis: post-vaccination status versus other control periods in the same children; and >1000 outcomes for in- and out-patient and emergency department visits. Preliminary data indicate no obvious associations with influenza vaccine.

Summary: These inactivated vaccines are well tolerated in all age groups, but there was insufficient power in the published studies to assess uncommon adverse effects. The studies support the protective efficacy of TIV against all three strains of influenza virus, including among young children and during drift years. Future work should include continued safety monitoring, including studies of rare events and of co-administration of influenza vaccine with other early childhood vaccines.

Economic Studies of Influenza Vaccination. Dr. Kristin Nichol reported to the ACIP by telephone link from Minneapolis. She reviewed some of the terms used in economic analyses and reported on the Workgroup's review of studies and discussions about the cost effectiveness of vaccination, particularly childhood immunizations, and other preventive services.

Definitions:

- Cost effectiveness analysis (CEA): presents the results in cost per health care outcome (e.g., dollars per life saved).
- Cost utility analysis (CUA): analysis presenting results in cost per unit of quality-adjusted health outcome (e.g., dollars per quality-adjusted life year or QALY). The QALY incorporates the impact of the intervention both on the quantity and quality of life.
- Cost benefit analysis (CBA): assigns all outcomes a dollar value and presents the results as net costs or savings.
- Monetary costs typically included in these analyses are costs averted or prevented with an

intervention; and indirect costs, which refer to productivity losses prevented or productivity gained due to the intervention. CBA typically includes these costs; CEA sometimes includes them; and CUA generally does not include those as a monetary cost, but implicitly incorporates them into the denominator or the QALY.

- *Caveats:* CE need not be cost saving to be worthwhile, although cost savings are generally considered dominant and worthy of adoption. Although most present health care system interventions are not cost saving, they are considered CE and potentially adoptable. This depends on: 1) the CE threshold or value that society or the payer is willing to pay for that outcome; 2) the importance of the disease in severity of morbidity or mortality; and 3) other factors such as feasibility or logistics, availability of the intervention in the case of vaccines, etc.

Dr. Nichol referenced a recently published review (1976-97) of economic studies, particularly of clinical preventive services, to catalog economic analyses of U.S. health care services. It showed:

- A median cost \$14,000/QALY for all clinical preventive services studies; >50% cost <\$50,000/QALY.
- The economics of immunization across the age spectrum had a median cost of ~\$1500/QALY.
- Previously published economic analyses of other childhood immunizations (MMR, DTaP, hepatitis B, varicella, pneumococcal conjugate vaccine, and IPV versus OPV) demonstrated cost savings for MMR, DTaP and hepatitis B and varicella, from both the societal and healthcare-payer perspective. Pneumococcal conjugate vaccine was not cost saving, but its ~\$80,000 cost per year of life saved was thought reasonable for the outcome achieved. Analysis of the move from OPV to IPV produced incremental costs of \$3 million per VAPP case prevented.

Methods to review studies for pediatric influenza vaccination: literature search and structured review of five published studies using CDC's evaluation checklist for economic studies; extensive group discussions; and additional review of unpublished works in progress.

Published studies reviewed were as follows:

1. *Meltzer et al* assessed the economic impact of pandemic influenza in the U.S. Their assumptions were also compatible with epidemic and interpandemic influenza periods.

Results: Influenza vaccine to age 18-19 is unlikely to be cost saving unless the total vaccination cost, direct and indirect, is <\$20 per child vaccinated. Rather than vaccinating the general pediatric population, a greater economic return would come from immunizing high-risk children.

2. *1981 Office of Technology Assessment (OTA) report* assessed the CU of influenza vaccination across all age ranges. For younger age groups, the cost per QALY ranged from \$724 for those aged 15-24 years to \$1,032 for those aged <3 (in 1998 values). Again, maximum CE would come from vaccinating those at high risk. But also noted was that even the highest cost for those less <3 years is “a very low price to pay for a year of healthy life.”
3. *CE analysis of clinical trial data of intranasal influenza vaccine* presented the break-even cost per person vaccinated with a licensed vaccine sold on the open market. If the LAIV costs more for the vaccine and administration than the break-even cost, then vaccination generates net cost to society. But if the vaccine/administration costs are lower, vaccination would be cost saving. The break-even cost varied depending on the setting described: group-based vaccination (e.g., a school or other public walk-in clinic) was efficient, versus individual-based program where the parent would take time off from work to bring the child into the health care provider for immunization.
4. *CE of influenza vaccination in children aged 6 months to 4 years, and 5-17 years* demonstrated net costs or savings of \$1.28 (for the younger children in a restricted [doctor’s office] setting) to \$21.28 (in a more flexible or highly efficient setting). Findings were similar for older children.

Summary: The studies differed substantially in quality and the analytic method used, and the outcomes/costs included. However, conclusions were that:

1. The studies generally suggest a cost saving from influenza vaccination of healthy young children if vaccine and its administration cost <\$20-25. CE at higher costs depends on the agreed-upon threshold for defining what is cost effective and worthwhile. These studies’ CE ratios are comparable to some of ACIP’s recent childhood vaccination vaccine recommendations, but the older childhood vaccinations are more clearly cost saving.
2. A substantial portion of the studies’ benefits from vaccination traced to the indirect costs prevented, mostly of avoided parental work loss; healthier children inferred less work lost. This also applies to other immunizations (e.g., varicella, pneumococcal conjugate and rotavirus vaccines).

3. The illness burden of influenza is notably less for healthy children than high-risk children, suggesting targeted immunization.

Works in process. Additional useful information is expected from: 1) the CDC/Harvard collaboration to assess the economic implications of various strategies to reduce influenza morbidity in children; 2) the CDC (Meltzer *et al*) economic analyses of a) the economics of routinely vaccinating healthy children aged <5, based on the Neuzil and Izurieta studies; and b) the household-based costs/benefits of vaccinating children in day care against influenza (Hurwitz *et al* study); and 3) a stochastic model of community influenza and prevention that incorporates herd immunity into the model (Policy Analysis Inc. and Wyeth Lederle). The latter will examine the clinical/economic benefits of vaccinating healthy children.

Identified research needs include: 1) the ACIP's determination of an appropriate threshold for defining CE; 2) further exploration of influenza epidemiology (e.g., complication rates, health care use, impact on productivity for children and families, time and regional variations, etc.); 3) analysis of the incremental costs/benefits of universal versus high-risk immunization, age-based versus risk-based, higher immunization rates in all groups versus the economic benefits of high-risk groups; 4) the implication of vaccination versus testing and treatment strategies; 5) the costs/benefits of vaccination by setting and compliance level; 6) the implications of herd immunity; and 7) to consider all this in the context of feasibility and vaccine supply.

Implementation Challenges. Dr. Natalie Smith reported discussions of some vaccine implementation challenges:

- Whether TIV and/or LAIV are chosen, 1-2 doses will be added to the routine childhood immunization schedule.
- This is a seasonal vaccine, and there is little experience of vaccinating children in a ~2-month time frame.
- Currently, no co-administration with other vaccines is licensed.
- Continued activity is needed to ensure that high-risk children are immunized, something still not well done.
- Delivery issues have been experienced for the adult influenza vaccine.
- There are ongoing discussions between private providers and traditional mass public or private influenza clinics (e.g., grocery store chains, pharmacies, etc.).
- The LAIV licensure application states its use for healthy children only. Issues remain as to

how to screen the youngest children, with or without reactive airway disease (RAD), and how to distinguish whether TIV or LAIV should be given. The application also is requested for ages ≥ 12 months, requiring TIV administration to those aged 6-12 months and the stocking of both vaccines.

- *Manufacturing* issues include the realistic ability to increase production and distribute on time.
- *Reimbursement* is an issue since many providers are on capitated plans. Lead time will be needed to establish reimbursement rates in both the public and private sectors.
- *Impact on the VFC and 317 Programs* bears analysis; both's funds are already limited. Some states had no line item to implement the last couple of new vaccines, and funding will be needed for the public education, outreach and delivery involved with administering these vaccines to children.
- *Risk communication and education* will have to make the case that routine influenza vaccination of children is necessary. It is often perceived as a mild disease by both providers and the public.
- *Effectiveness* is an education issue because the vaccination will not prevent all influenza, just as the rotavirus vaccine does not prevent all diarrhea.
- *Safety perceptions* pertain to both the trivalent and live attenuated virus, and require different messages. For example, there is no reassurance for LAIV, as for TIV, that one cannot get influenza from the vaccine, because LAIV is not a killed virus vaccine.
- *Epidemiology* bears improvement. Aside from efficacy and safety monitoring, this involves immunization coverage levels and vaccine implementation in sub-populations (including those at highest risk of severe complications with influenza). Surveillance needs to be improved, hopefully in parallel with the focus on increased public health surveillance for bioterrorism.
- Upon a universal recommendation for children, the NVICP will have to cover adverse events in both children and adults.

The University of Rochester study by PAI was presented to the workgroup. They conducted focus groups with primary care providers and two surveys that included pediatricians and family physicians; a time and motion study of the injection process of patient communication; and a database study including insurance data. Preliminary conclusions indicate physicians' agreement that universal flu vaccination is feasible, despite identified barriers of cost, vaccine safety, doing reminder recall, and the impact on other vaccinations. Challenges would arise from

availability of only an injectable flu vaccine, inclusion of 6-12 month-olds, and if the vaccine is not licensed for co-administration with other vaccines. There are also significant additional practice time costs for additional visits. However, alteration of currently inefficient practices for flu vaccination (e.g., adding vaccination-only office hours) would help, as would using all current visits as vaccination opportunities.

The perspectives of managed care, the AAP, and the AAFP on universal immunization were provided to the workgroup and discussed. All agreed to the importance of focusing on the disease burden and evidence-based medicine, and of having a solid education campaign for the providers and the public.

Economic Analysis of NIP Impact. Dr. Ben Schwartz noted the additional emphasis needed on vaccination cost benefit and/or effectiveness, and the economic implications to the vaccination program. For example, some states implemented a two-tiered system for pneumococcal conjugate vaccination, which provided the vaccine to VFC-eligible children but not necessarily to those covered under the 317 Grant Program.

An NIP economic analysis assumed a universal recommendation for children aged 6-35 months, receiving two doses in year 1 and one subsequent dose, and a vaccine cost averaging \$4.25/dose. The pediatric program data indicates VFC as covering ~45% of vaccine purchase, 11% by the 317 Grant Program and 6% by states. Several different vaccine coverage scenarios were developed for vaccine costs only (not administration or state health department infrastructure costs):

1. Year one: 20% vaccination coverage with TIV.
2. Year two: 20% vaccination coverage, but more children requiring only one dose.
3. Consistent state scenario: 80% coverage with TIV.
4. Alternative state scenario: 80% coverage divided evenly between LAIV (at \$15/dose) and TIV.

Analysis:

- A. Low current influenza vaccine coverage among young children; ~10% of the U.S. population at high-risk and only ~10% of those receiving vaccine (a 1% overall coverage). Total costs: \$390,000 for ~90,000 vaccine doses.
- B. Scenario 1 above: Overall ~\$10 million, most borne by VFC (the 317 cost was ~\$1.7

million for ~2.5 million vaccine doses).

- C. Scenario 2: Costs and vaccine utilization decrease, but are perhaps offset by increasing coverage. Using only TIV, ~\$25 million cost to VFC; \$4.9 million to 317; \$2.4 million to states; for ~7 million vaccine doses. If a mix of LAIV and TIV is used, cost would double for the same total doses.

Conclusion: Under any scenario, the costs are more reasonable than those of other recently-recommended vaccines. With the likely sufficient time over several years to ramp-up the program, funding and infrastructure increases are possible to support the program.

VRBPAC Perspective. Dr. Karen Midthun outlined Aviron's biologic license application presented to VRBPAC in July 2001. FDA presented safety and efficacy data for Aviron's LAIV to prevent influenza in persons aged 1-64 years and in travelers to areas where influenza is circulating. VRBPAC's opinion was requested about:

1. Adequacy of the data to support vaccine efficacy in persons aged 1-17 years. The committee was almost evenly split on this, but the majority would have voted yes for an indication raised either to 15, 18, or 24 months of age.
2. Adequacy of the data to support efficacy in adults aged 18-64 years. Thirteen members of the advisory committee voted yes, two voted no.
3. Adequacy of the data to support safety in *healthy* (not high-risk) persons aged 1-64 years. A committee majority voted no; but outstanding additional safety data analyses are anticipated.

Time lines: FDA completed its review of the biologics license application and issued a complete response letter at the end of August. Generally, the sponsor replies to FDA's complete response letter, and FDA reviews that new material within six months. An approval letter or another complete response letter is then sent.

Issues related to universal influenza immunization. Dr. Keiji Fukuda summarized the issues at question about universal influenza vaccination of children: influenza's status as a serious health risk; the vaccine's effectiveness; influenza vaccine safety concerns; and feasibility of recommendation implementation among parents and physicians, economic considerations, and programmatic concerns. The VRBPAC meeting indicated that the fall and winter of 2002 is the earliest possible time that a licensed LAIV would be available.

Questions for the ACIP:

1. Does ACIP want to vote at the next meeting (February 2002) on whether to recommend routine influenza vaccination of children, or at a later time; and when should those recommendations take effect?
2. Upon the formal vote, what should be the upper age range for routine influenza vaccination of healthy children (6 months to 2 years; 6 months to 3 years; or 6 months to an older age limit)?

Timing considerations:

1. ACIP vote in February of 2002, with the recommendations implemented for the fall of 2002.
 - ▶ Advantages: a) protection is provided as early as possible to children; b) since an LAIV would not be licensed by then, those related issues for children can be debated separately from those of TIV (i.e., recommend vaccination of healthy children); c) the recommendations could be published in the annual ACIP influenza prevention and control document; d) a moderate lead time is provided to implement educational efforts. Vaccine production ramp-up time would be limited.
 - ▶ Disadvantages: a) ACIP may not feel adequately prepared to vote; b) the pediatric community may not be sufficiently prepared to accept a new vaccine recommendation; c) vaccine availability is never certain; d) and adding this agenda item to the normally long and complicated February session would be a challenge.
2. ACIP vote in June or October, 2002.
 - ▶ Advantages: a) ACIP has more time to deliberate the issues; b) a dedicated session could be held to focus simply on pediatric influenza vaccine issues; c) an LAIV may be available by then, providing another option for vaccinating children; and d) the publicity of that licensure would help to focus attention on children.
 - ▶ Disadvantages: a) voting later reduces the time available for educating the public and developing educational materials or to ramp-up vaccine production; b) separate recommendations would be published in a supplemental document, which is generally less-read than the primary document; c) if an LAIV is licensed, ACIP will have to address the pediatric issues for both vaccines, which could be confusing for both ACIP and the public.
3. Vote later, implementing in 2003 or later.
 - ▶ Advantages: a) more relevant information might be available, particularly economic and

feasibility studies; b) this provides more time to deliberate issues and c) to educate the pediatric community about the recommendation's rationale; d) there may be more lead time for vaccine production.

- ▶ Disadvantages: a) the longer the delay, more children at high risk of complications will be unvaccinated; b) again, there is the potential confusion of dealing with both pediatric and live attenuated vaccine issues at the same time.

Potential options are:

1. Recommend influenza vaccination of children aged 6 months to 2 years.
 - ▶ Advantages: a) This is a conservative recommendation, supported by the recent pediatric hospitalization data; b) the small age range provides an option of expanding upward; c) greater feasibility since this has the least impact on pediatric practices.
 - ▶ Disadvantages: As a conservative recommendation, many high-risk children may not be vaccinated.
2. Recommend influenza vaccination of children aged 6 months to 3 years.
 - ▶ Advantages: a) This would provide protection for more healthy children who would be at risk for influenza-related hospitalizations.
 - ▶ Disadvantages: a) healthy children have a smaller and less-clear risk of flu-related hospitalizations; b) data are unclear about the clear high-risk category ends; c) increasing the age limit increases the logistical and feasibility issues, particularly for pediatricians.
3. Recommending flu vaccine for children aged 6 months to some older age group (4, 5 or older).
 - ▶ Advantages: a) this could increase vaccination of children with chronic medical conditions; b) it is in keeping with recommended vaccine for people aged 50-64 years; c) if herd immunity can be attained, this could dampen community epidemics, again depending on how many children are vaccinated and how high the coverage rates are.
 - ▶ Disadvantages: a) a higher risk of flu-related hospitalizations has not been shown in older ages; in fact, the available studies suggest the reverse for serious complications such as hospitalization; and b) higher age limits increase feasibility issues, particularly for pediatricians.

Discussion included:

- The February 2002 agenda will probably not allow the kind of discussion needed to properly consider these issues. The Rochester feasibility study analysis should be available

in the next month or so.

- Dr. Abramson: The result of the upcoming AAP's discussion will be shared with the ACIP.
- Dr. Zimmerman: The AAFP will consider and probably be satisfied with the data on disease burden and the vaccines' efficacy. Further safety data and implementation issues will be of concern. He felt that vaccination of pre-school age children, as was done for polio, could be addressed in February, but data to support the broader recommendation may not be ready even by fall 2002. He suggested a step-wise approach of moving to routine vaccination over three years, based on safety data, vaccine availability and feasibility. There was some agreement that ACIP should consider a lenient zone between a non- and universal recommendation.
- Dr. Offit: *Are there any data on the relative capacity of LAIV or TIV to protect the young (<2 year-old) child?* The Wyeth and Aventis Pasteur TIV vaccines are licensed to 6 months to prevent influenza; Evans' is licensed for four years of age. Additional data are needed for routine use and concurrent vaccine administration.
- Dr. Offit: *Are there any data to compare TIV and LAIV to prime the young child's mucosal immune system?* No, although the literature has some studies of concurrent use of the inactivated or trivalent vaccines. The Safety and Efficacy Workgroup reviewed those data; there are no studies of the current LAIV compared to inactivated vaccine. The prior studies, which are small and of not necessarily comparable vaccine, showed better immunogenicity in the younger groups with the live attenuated and in the older groups with the inactivated.
- Dr. Katz: Adding another injectable vaccine could be inappropriate until a live attenuated vaccine is available. But since the indication is only to one year of age, some children will need to be injected. The working group focused on separating the vaccine need from the availability of the live attenuated vaccine.
- Dr. Levin: *Do we know that 6-12 months-olds respond adequately, or those a little older?* No; the Clover and Gruber data started at age 3; the Edwards data started at age one. The unpublished Greenberg data will include 250 doses to 6-12 month-olds.
- Dr. Peter: The Japanese and Tecumseh data suggest a possible beneficial community impact from universal immunization of young children. The Texas (Glezen *et al*) studies may be presented at the next meeting; if they also so indicate, that will strongly support a universal recommendation.
- Dr. Abramson emphasized that the ACIP's vaccination recommendation for 50-64 year-olds, a risk group at less high risk for hospitalization than young children, strongly supports extending the recommendation to them.

- Dr. Overturf: The staged recommendation introduction could help defer problems from vaccine shortages.
- The data do not indicate that mortality is a major issue, but the Neuzil study had insufficient power to detect an excess. The Luce, Cohen, and White studies examined parental illness, secondary illness, and work loss.

An informal poll of the committee revealed the following opinions:

- Dr. Levin: More data on which to base the lower bound are unlikely by February.
- Dr. Deseda was concerned about adding another injection to an already busy schedule. It is too early to make a decision.
- Dr. Tompkins: Discussion should be staged; no recommendation is possible in February.
- Dr. Smith agreed, and was concerned about the manufacturers' required lead time to ramp up production.
- Dr. Brooks supported the staging discussion required and favored live-attenuated over inactivated vaccine.
- Dr. Clover supported a staged discussion. February will be too early to consider a universal recommendation.
- Dr. Word: A deadline for discussion must be set; if not in February, then in June.
- Dr. Offit: Do not wait for LAIV licensure to decide; discuss in February the use of the TIV to determine sufficiency of data to support a recommendation. If adequate, vote.
- Dr. Rennels agreed with Dr. Offit. Implementation issues are very important. A February vote depends on the feasibility studies' results.

There was general agreement to discuss this in February, and if there are enough data, to vote then. But to vote on what, exactly, remained unclear: a recommendation to encourage usage in certain populations, or to make a more universal recommendation. Dr. Fukuda offered one more point for consideration. Vaccinating older children (i.e., those in school) raises the discussion of the status of 18 year-olds, a different matter offering much less data.

Influenza Vaccine Production Update. Mr. Dennis O'Mara, of the NIP, updated the committee on this year's influenza vaccine production and distribution in the United States. Data were provided by Aventis Pasteur, Wyeth Lederle, and Evans Vaccine. Current data indicated a decline of 4 million doses from that expected to be available on October 1. By October 31, ~44.6 million doses should be distributed, ~56% of this year's total projected vaccine supply.

While distribution was slightly ahead of the most recent projections, still, only ~28% of the projected 2001 influenza vaccine supply had been distributed by September 30.

Dr. Midthun added a few notes to this report.

1. FDA approved a supplement to Evans' license application for their influenza virus vaccine at the end of September. That licensed the new thimerosal-reduced formulation (0.1 µg of thimerosal/dose versus the previous 25µg). This vaccine is licensed for use down to age 4 years. Evans anticipates making roughly half a million doses of this formulation for the U.S. market this year.
2. FDA approved Wyeth's supplement to their influenza vaccine on October 16 and released TIV stock from Wyeth. Dr. Reilly reported their expectation of shipping vaccine in late October, and large shipments in November and the early December.

HEPATITIS B RECOMMENDATION

Dr. Hal Margolis presented a final review of the Hepatitis B statement. Alterations from the previous iteration were as follows:

1. ***Birth dose of Hepatitis B vaccine:*** The wording was changed to reflect a stronger recommendation: administer dose 1 to the infant soon after birth and before hospital discharge, but before 2 months of age; and to explain that combination vaccine can be used with a monovalent birth vaccine dose.

ACIP response:

- Dr. Levin: Make the case a little stronger than in the previous text.
- Dr. Zimmerman: The present and impending combination vaccines make this a routine four-dose system. A fair number of providers want to wait to use the combination rather than the birth dose.
- Dr. Abramson: The arguments for adding the birth dose (disease prevention, potential lives saved) out weigh those against (convenience). A better case must be made for the data suggesting better vaccination rates. The AAP's COID will recommend the birth dose to the Board.
- Dr. Modlin: This is the first use of the term "recommended" for this dose, versus the 1991 recommendation's equal status for the birth or 1-2 month dose – a significant incremental change.

- Dr. Mahoney: AAFP concerns include that frequent delays or even a disconnect between hospital activity and report to the OB/Gyn's office, potentially results in an extra dose. However, an ACIP recommendation may help eliminate those communication issues. And, pragmatically, some hospitals will not reimburse the newborn dose.
- Dr. Deborah Wexler, of the Immunization Action Coalition, reported a) their survey of all 50 states' hepatitis coordinators about the birth dose. All responded and 48 supported an ACIP recommendation for the birth dose. The 2 dissenting states support the birth dose, but did not think the recommendation would help change some doctors' minds, but the AAP recommendation might. And b) she agreed to the problem of communicating vaccine dose information, which recently resulted in an infant's death due to hepatitis in Michigan. She provided documentation from the states of known errors, including mis-transcription, not testing the mother, ordering the wrong test (i.e., antibody, not surface antigen). Giving the vaccine within 12 hours of birth could prevent these medical errors.

Options, therefore, were to: 1) delete the “no later than 2 months of age” to immunize all babies, regardless of mother's status; or 2) simply separate them into two sentences. The physician's choice is not withdrawn, and the ACIP historically has provided a range even when stating a preference. Hospital cost is a real factor in physician decision. ***Agreement to option #2.***

2. ***Pre-term infants.*** New studies and extant data show that vaccination of pre-term infants of any gestational age and weight born to a surface antigen negative mother should be delayed until one month of age. Post-exposure issues are addressed here and in the post-exposure section.

ACIP response:

- Concern was expressed about the definition of “premature,” which could include a 36 week-old infant. Most study data have used weight rather than age. There are data indicating some poor immunogenicity in the in 2000-2500 gm category. The definitions can be addressed in the background material. Use weight-based data if they are robust. The document will reflect the data as accurately as possible to provide maximum guidance. Dr. Margolis agreed to work with the workgroup on this language.

3. ***Children from other countries with hepatitis B immunization.*** A documented three-dose schedule is acceptable in older children and adolescents; children who received their last dose at <6 months should receive an additional dose at six months of age; children without

documentation of a complete hepatitis B vaccine series should receive the complete series.
ACIP response: Accepted.

Other comments:

- Dr. Levin: *Insert text about immunization during pregnancy.* That was strengthened in the background, but can also be inserted in the section on vaccination of persons in groups at increased risk of infection. Similar text in the General Recommendations can be referenced.
- Dr. France: Correct the inconsistency of pages 37 and 62. Page 62 says to give dose 3 under age 6 months and then dose 4 after age six months, and page 37 (line 11) says to repeat the three-dose series when the child is off the series.
- Dr. Schaffner: *Expand the page 65 background paragraph recommendation to immunize inmates* to reference not only intra-institutional hepatitis B prevention, but also the broader public health objective of immunizing inmates before their release back into the community. State that corrections officials can make a substantial contribution to the elimination of Hepatitis B by vaccinating inmates who will be returning to their communities and may reassume high-risk behaviors.
- Dr. Schaffner: *Wordsmith page 63* (initiate vaccination in high-risk adults and adolescents) and page 62 #4 (choose a vaccination schedule that can deliver a complete immunization series).
- Dr. Schaffner: *Amend page 63* (STD clinic clients should be considered candidates for vaccination) to “All clients attending STD clinics should be should be screened and vaccinated, if indicated..”
- Insert text to support the implementation of a hepatitis B school-entry requirement by the remaining states without it.

Use a strength of evidence table or designate that separately in parentheses after each recommendation? The ACIP policies and procedures call for a recommendation, but do not specify how that should be done. The committee’s consensus was to include the indication of evidence strength in the text. The standard needs to be consistent across ACIP documents. HICPAC’s system is simple but differs from that used in recent statements. It could be based on either efficacy or immunogenicity, but which is used should be specified..

Schedules for infants born to surface antigen negative mothers, surface antigen positive and then untested mothers, and for children, adolescents and adults. The data supporting the schedules

are in the background, but some of the schedules are not from the package insert and FDA-approved, but are those used in practice.

ACIP response:

- Provide a distinction between the package insert FDA-approved schedule and those supported with other data, in the text and the background, but not necessarily in the table.
- Since many people reference the tables more than the text, try to make them as stand-alone as possible, including as much of the richness of detail in the text. And cite in the Preamble the success to date of hepatitis B vaccination and the accompanying lowered incidence.
- Include in the recommendations better discussion about how to manage non-responders, as done on page 46.

VOTE on the hepatitis document with the suggested changes. Conflicts with Merck or SmithKline Beecham were reported by Drs. Rennels, Offit, Clover and Levin, preventing achievement of a quorum. Dr. Snider requested the ex-officio members to vote on this issue.

Dr. Tompkins moved that the ACIP accept the hepatitis B statement as presented. Dr. Smith seconded the motion.

In favor: Drs. Word, Brooks, Smith, Tompkins, Deseda, Modlin, Heilman, and Mr. Graydon.

Opposed: None

Abstained: Drs. Rennels, Offit, Clover, Levin, Midthun and Evans, Groom and Diniega.

The motion passed and Dr. Margolis was thanked for his efforts. The final document will be circulated to the committee members.

Inclusion of the Twinrix™ hepatitis vaccine in the VFC program.

Dr. Melina Wharton presented for discussion the topic of inclusion of the Twinrix™ hepatitis vaccine, only for adolescents aged 18 years, in the Vaccines for Children Program (VFC). Twinrix™ is Glaxo SmithKline's licensed hepatitis A/hepatitis B combination vaccine. Since this vaccine is labeled for use in persons 18 years of age and older, its use by the VFC program is limited to children in their last year of eligibility at age 18. She offered for ACIP approval a set of resolutions to revise the relevant statements.

Hepatitis A statement. The previous resolution would be revised to incorporate the use of a 3-dose combination hepatitis A/hepatitis B vaccine for use in persons aged 18 years, to add: a) the Twinrix™ schedule to the Hepatitis A vaccine schedule; b) minimum intervals to the dosage interval table; c) Twinrix™ to the contraindications and precautions, for use in persons under 18 years of age (due to its labeling); d) pregnancy listed as a precaution; and e) a notice at the statement's end that vaccines approved by ACIP for inclusion in the VFC program are not available for use in the program until the recommendations are published and CDC has established a purchase contract for the vaccine.

Hepatitis B resolution, similarly, revises the previous resolution to incorporate the use of the combined hepatitis A/hepatitis B vaccine for use in persons aged 18 years. The resolution adds: the age distinction to the eligible groups; the Twinrix™ schedule to the catch-up vaccination schedule; minimum intervals to the dosage interval table; contraindication of use of the vaccine among persons 18 years of age and older; and the same pregnancy precaution as for use of hepatitis A vaccine.

Dr. Brooks moved to accept the hepatitis A and hepatitis B resolutions as stated. Dr. Tompkins seconded the motion.

Vote: Again, the Merck, SmithKline Beecham conflicts prevented votes by Drs. Rennels, Offit, Clover and Levin. The ex-officio members again voted.

In favor: Drs. Word, Brooks, Smith, Tompkins, Deseda, Modlin, Heilman, Evans, and Mr. Graydon.

Opposed: None

Abstained: Drs. Rennels, Offit, Clover, Levin, Midthun, Groom and Diniega.

The motion passed and Dr. Wharton was thanked for her efforts.

REVIEW: HARMONIZED CHILDHOOD IMMUNIZATION SCHEDULE.

Dr. Modlin noted that the NIP harmonized immunization schedule now specifies “childhood” since an adult schedule has also been formulated. Dr. Wharton presented the schedule, which incorporated the ACIP guidance provided in June. Changes since the June iteration included:

- A bar now specifies a pre-adolescent assessment for 11- and 12-year-olds. Otherwise, all the ages normally considered adolescent (13-18) are grouped together.

- A green bar now indicates age groups warranting special effort for immunization if not previously vaccinated, with explanatory text.
- The hepatitis B wording will remain as it is, not specifying the birth dose for infants born to hepatitis B antigen positive mothers, until the AAP, AAFP, and ACIP concur. However, the bar will extend from age zero to two to emphasize the desirability of the birth dose.
- Language was added that DTaP/Hib combination products should not be used for primary immunization of infants at ages two, four or six months, but can be used as a booster beginning at age 12 months following any Hib vaccine.
- Reconsider the DTaP/Hib text about vaccination it at age 12 months (the label specifies 15 months). Perhaps it could be marked as a useful booster dose beginning at 15 months of age rather than 12 months.
- A second sheet of contraindications to vaccination will be developed in future. Currently, text was added to refer readers wanting additional information about the vaccines and immunization contraindications to the NIP Website. There was agreement to list the partners' (e.g., AAP, AAFP) Websites, and one for information about vaccine supply.
- In light of the Td shortage, a planned green bar to highlight the special efforts needed to administer the Td dose, was not done. If the supply issues are resolved, that could be done next year to indicate catch up needs for missed doses.

Discussion included:

- Dr. Neuzil: Consider listing, as done on the adult schedule, the risk factors for influenza for children aged >6 months, depending on the space available.
- Dr. Wexler: Consider putting only the hepatitis B dose 1 in column #1 for birth, and a green catch-up vaccination bar through 1-2 months, to remind about the possibility of catch-up while recommending the birth dose. However, this should be left it as is now, until the AAP, AAFP and ACIP concur.
- Dr. Vernon: Indicate in the footnote that hepatitis A is a two-dose vaccine.
- Dr. France: Serology is recommended for those children born to hepatitis B positive mothers, but serology is rarely done (for only ~30%). Specifying that serology be done at 9-15 months to confirm conversion would probably raise the number of those tests done, suggesting the addition of that statement to that section.
- Dr. Pickering: Emphasize the screening of newly-pregnant woman to ensure it is done, and delete the text about individual influenza viruses.
- Dr. Zimmerman: Delete the now-redundant statement that children and adolescents

unimmunized against hepatitis B may begin the series at any visit.

- Dr. Pickering: Ensure that the interval for dose 4 of IPV parallels that of the General Recommendations.
- Dr. Evans: Add a reference to the NVICP to the section on reporting adverse reactions.
- Dr. Modlin: Twinrix™ and other combination vaccines are covered by text stating that licensed combination vaccines may be used whenever any components in the combination are indicated in the vaccines and other components are not contraindicated.

Reverse side of schedule: The presented catch-up schedule for children behind in their immunizations was presented, more for formatting comments than for content accuracy. Two approaches were outlined: 1) comprehensive tables with short footnotes, based on the successfully field-tested Minnesota schedule; and 2) more concise tables and more extensive footnotes, based on the NIP's "Pink Book" on the epidemiology and control of vaccine-preventable diseases. The committee was split in its preferences between the two and suggested that the NIP select the format and assess its success in a year or two.

Dr. Rennels moved that the ACIP adopt the harmonized schedule as presented. Dr. Tompkins seconded the motion.

Vote:

In favor: Drs. Rennels, Offit, Word, Clover, Brooks, Levin, Deseda, Tompkins, Smith, Modlin.

Opposed: None

Abstaining: None

The motion passed.

ADULT IMMUNIZATION SCHEDULE

After a short break, Dr. Vishnu Priya-Sneller of the NIP presented the Adult Immunization Schedule developed by that Workgroup with the ACP, the AAFP and the ACOG. Recent work discussed the format, content, table and footnotes, changes in the color scheme, and inclusion of the Lyme disease vaccine. She reported coordination with the ACP's Green Book and ACOG's Technical Bulletin, both of which are being updated.

The table footnotes include indicator conditions, the risk of exposure, the vaccine dose and the

interval between the doses on the bars. Additional footnotes for persons with indicator conditions cite contraindications and special notes. A companion table will list vaccinations recommended for people with chronic diseases and/or conditions, and share the same footnotes.

Remaining issues:

1. Td booster: recommended by ACIP as a decennial booster; ACP recommended a single Td booster at age 50 for persons who completed the primary series.
2. Complete the table of immunizations recommended for persons with chronic diseases/conditions.
3. Finalize the age-based recommendations.
4. Present the harmonized schedule to the ACP/ASIM Adult Immunization Initiative Physician Advisory Board (October).
5. Incorporate recommended changes for publication in the January, 2002 *MMWR*.

Discussion included:

- Dr. Zimmerman: Include the AAFP's recommendation of periodic health exams.
- Dr. Mahoney: Make the table colors consistent with the childhood schedule. Consider a black and white version to assist copying.
- Dr. Gall: ACOG has been part of this process and endorsed these recommendations.
- Dr. Rennels: Since this is a "recommended" scheduled, insert text that Lyme vaccine "may be considered", or code with another color, or separate it with a red dotted line.
- Include the occupational risks of microbiologists under meningococcal vaccine.
- Dr. Overturf: Note that the Red Book does not consider splenectomy or asplenia a risk for meningococcus, based on no data.
- Dr. Plotkin: Two doses of measles vaccine are recommended, but only one dose of mumps vaccine. The effectiveness of mumps vaccine is not equal to measles and rubella. It cannot be collapsed into one dose of MMR due to issues of rubella seronegativity in pregnant women and immigrants, who may be naturally immune to mumps or rubella, but not measles.
- Dr. Neuzil: Such fine points will be considered in the full statements, which the schedule faithfully reflects. Identify the research gaps.
- Dr. Salisbury: Drop the reference to serogroup C text in point 10 on meningococcal vaccine, since it is for all four serotypes. However, Dr. Sneller responded that the ACIP vaccine efficacy recommendations for outbreak control cite the effectiveness against group

C. Again, this parallels the statement.

- Dr. Salisbury: Consider a bullet to include travelers under “Occupational and Other” since they will be one of the biggest groups for whom vaccination is indicated.
- Dr. Evans: Include citation of the VAERS reporting requirements and availability of that and the compensation program.
- Dr. Overturf: Under hepatitis A, indicate CDC's recommendation for high risk states, if that applies to adults as well as children.

There was general committee agreement to indicate that licensed combination vaccines may be used whenever components are indicated, and to avoid trade names. The schedule is near finalization. The committee’s further comments on colors to reflect adult/child recommendation consistencies and differences were solicited.

USE OF OPV FOR OUTBREAK CONTROL

Dr. Ben Schwartz reported the departure of Dr. Joanne Cono, who had worked on this issue, which will delay further work. He referenced recent cases of vaccine-acquired paralytic polio (VAPP) in the Philippines, similar to those reported recently in Haiti and the Dominican Republic. Considering the persistence of vaccine-derived or wild polio, an OPV stockpile for the U.S. is deemed wise, despite our successful vaccination program. He discussed the development of that stockpile and progress toward reaching an IND application for OPV use in an outbreak setting.

Unresolved issues include

1. The reasonableness of the proposed investigation and vaccination strategy.
2. Whether there are situations in the draft IND where IPV should be used rather than OPV.

The ACIP has recommended OPV use for outbreak control due to the greater degree of seroconversion following a single dose versus IPV; the decrease in intestinal replication of wild polio virus following OPV; the increased community immunity; and successful use of OPV in outbreak situations. No new doses of OPV are being manufactured in the U.S. The 850,000 expired OPV doses would require an IND license to be administered. Quarterly testing shows them to still be potent, but FDA data indicates that this will soon diminish. CDC is contracting with another manufacturer for a long-term stockpile of a vaccine not licensed for use in the U.S.; it also would be given under an IND.

Dr. Schwartz presented a draft CDC/FDA protocol for OPV use:

1. Confirm the index case with laboratory testing of clinical specimens.
2. Obtain information from the case patient, including travel exposure and immunization histories.
3. Identify close contacts and their clinical and vaccination histories, as well as stool cultures from household contacts, family members, day care contacts and staff, teachers of an older child, and health care workers.
4. Pending case confirmation, administer IPV to close contacts of the case patient who was not completely immunized.
5. Investigate the level of complete polio vaccination coverage in the surrounding community, and any pockets of lower vaccination rates.

In investigation of the case/outbreak community, outbreak control depends on:

1. Whether this is a primary case, someone incompletely vaccinated or immunosuppressed, with contact with the case or traveled to an endemic area. If this is not a primary case or there is evidence of ≥ 1 cases, community infection levels are likely, which advises a broad-based outbreak control strategy.
2. The age groups affected. Polio virus spread is most likely in children.
3. The level of complete vaccination coverage in the community; if $< 80\%$, significant infection spread is likely, indicating a more broad-based vaccination response.
4. The epidemiological situation and the results of the cases, the community, and the environmental investigations.

He outlined proposed vaccination scenario strategies, in which OPV use is expanded alongside greater community risk:

1. Primary polio case, no secondary cases or dissemination within the community: OPV for household and other close contacts aged < 60 months; IPV to health care workers with potential contact with that case patient and non-household close contacts aged ≥ 60 months.
ACIP Response: OPV is better for primary protection; IPV is a better booster; and an IPV injection could cause provocation paralysis.
2. Non-primary polio case, no additional cases in a community where $> 80\%$ had three or more doses of vaccine: OPV to young and older household and close contacts as well as all community children aged < 60 months and not completely vaccinated; IPV to the health care workers and unvaccinated or incompletely vaccinated persons aged > 60 months (due

to their higher risk of VAPP).

Response: Again, OPV would provide quick immunity with immunization.

3. Either primary or non-primary cases in a setting of additional cases or community immunity at <80%: OPV for unvaccinated/incompletely vaccinated persons aged >60 months. OPV given according to the cases' age distribution or lab evidence of infection; IPV given to all those not included under the OPV recommendation.

Discussion: This strategy is for the period of continued polio immunization in the U.S., still with susceptible, naive infants; not after eradication.

4. OPV use in young children during an outbreak: OPV for those aged 3 days to 59 months, regardless of vaccination history. But the follow-up would differ: none would occur for those with recorded full vaccination. A second OPV dose for those partially vaccinated and further doses of IPV from their health care provider would be administered if necessary. Those unvaccinated would receive 2 OPV doses 4 weeks apart.

Discussion included:

- Dr. Plotkin asked the rationale for 3 days rather than 1 day; and if using an IND, suggested that the IND use a monovalent rather than trivalent OPV, which requires 2 doses for 100% seroconversion. The prevailing serotype can be determined within 24 hours. VAPP risk was higher among adults, the health care workers, etc., being considered for vaccination here, involving the issue of informed consent. Any introduction of polio in the U.S. will be in an under-immunized population, which is also vulnerable to VAPP.

Dr. Schwartz cited the low risk of vaccine-derived virus spread in a highly immune population; the currently existing trivalent lots; and that 100% seroconversion is not the goal. The goal is to give one dose to decrease intestinal replication and shedding and to increase immunity. Three days rather than one was recommended by the international polio staff. They will be re-consulted.

- Dr. Katz: Since, aside from vaccine-derived strains, no Type 2 polio is circulating, a Type 1 or 3 monovalent could provide an advantage. And, since the Type 2 of the trivalent replicates better than the Types 1 or 3, the best protection may not be against the original paralytic strain. Those comments will be useful in CDC's negotiation with the other manufacturer, and will be considered in developing the IND protocol.
- Dr. Modlin: If vaccine is unavailable in an outbreak, immune globulins are also effective preventatives.
- Dr. Halsey disagreed with the caution about IPV use due to potential provocation polio.

Any community with low immunization rates and with a case of paralytic polio should immunize un- or partially-vaccinated children with IPV. And OPV and IPV given at the same time enhance the immune response without interference.

- Dr. Vernon: *How is the 80% population coverage measured, and how is the “community” defined?* 80% is the proportion to be vaccinated to provide good herd immunity in the community. The “community” is harder to define. There may be pockets of groups who object to vaccine, surrounded by larger groups in which the coverage is higher. In that case, OPV in the smaller (<80% coverage) community and IPV in the broader surrounding community may be a reasonable approach. The National Immunization Survey, community surveys, and local/state health department data may also aid that definition.

IOM RECOMMENDATION ON THIMEROSAL

Dr. Kathleen Stratton, Executive Secretary of the Institute of Medicine’s (IOM) Immunization Safety Review Committee, and Dr. Marie McCormick (by speakerphone link) summarized the committee’s recently-released report.

That committee was charged to investigate the evidence of biologic plausibility and the hypotheses of a relationship between thimerosal and neurodevelopmental disorders. To do so, they conducted: 1) a plausibility assessment, which evaluated the evidence of causality, biologic plausibility, and the strength of competing hypotheses; and 2) a significance assessment, which considered the number of persons affected, and the seriousness and treatability of the adverse event and natural disease. Based on those assessments, the committee was asked to advise the government on potential future activities (e.g., research, surveillance, communications, and policy review).

Dr. McCormick summarized that biologic plausibility exists in a range, without any agreed-upon hierarchy of evidence or associated terminology. The committee reviewed data on the toxicokinetics of mercury, ethyl mercury, and methyl mercury; on the potential health effects of high-dose exposures to thimerosal or the mercuries (including data in VAERS reports); and the effects of low-dose exposures to thimerosal or methyl mercury. No published epidemiological studies could be examined, but some unpublished VSD analysis data were examined. The report included caveats on the lesser weight given to the latter data. Public input was accepted, and the report was peer-reviewed.

The IOM committee's conclusions of plausibility were:

- An association between exposure to thimerosal-containing vaccines in the recommended childhood immunization schedule and neurodevelopmental disorders could not be established.
- However, the hypothesis is biologically plausible, based on demonstrated neurodevelopmental effects for prenatal but not postnatal exposures to low doses of methyl mercury.
- Vaccine thimerosal exposure was not proven to result in the mercury levels associated with toxic responses. The signs and symptoms of mercury poisonings are not identical to autism, ADHD, or speech and language delay.
- Indirect information does support biological plausibility:
 - High-dose thimerosal exposures are associated with neurologic damage.
 - Methyl mercury, a close chemical relative, is a toxicant to the developing nervous system.
 - Some children who received the maximum childhood immunization schedule vaccinations had ethyl mercury exposures in excess of federal guidelines.
- The evidence is inadequate to either accept or reject a causal relationship between exposure to thimerosal from vaccines and the neurodevelopmental disorders of autism, ADHD, and speech or language delay, based on insufficient data, published or unpublished.

Their findings for significance were that:

- Immunization is important to continue against serious vaccine-preventable diseases.
- Neurodevelopmental disorders are pervasive and impose significant burden.
- Mercury is a well-known toxicant.
- It cannot be predicted that removing thimerosal will decrease the prevalence of neurodevelopmental disorders.
- There is no reason to believe that switching to thimerosal-free single-dose vial vaccines will pose a risk to children.
- Replacing thimerosal with less effective preservative in multi-dose vials may increase the risks.
- Decreased immunization due to fears may increase the prevalence of vaccine-preventable diseases. Therefore, continued public health attention is advised.
 - Thimerosal was used in vaccine for several decades and the risks/benefits must be determined.

- ▶ Future concerns about thimerosal need to be resolved to restore, maintain, and build trust in vaccines.
- The committee supported the 1999 ACIP, AAP and AAFP call for removal of thimerosal from vaccines as soon as possible. Such precautionary steps are justified even if cause-effect relationships are not fully established scientifically.
- The committee also recommended use of the thimerosal-free DTaP, Hib, hepatitis B vaccines in the United States (defining as “thimerosal-free” those with remaining trace amounts).
- Professional societies and government agencies should consider recommending thimerosal removal from vaccines administered to U.S. infants, children, or pregnant women, and review their policies about the non-vaccine biological and pharmaceutical products containing thimerosal that are used by the same populations.
- The committee also recommended policy analyses to inform these discussion in the future, and in particular, review/assessment of how public health policy decisions are made under uncertainty; and to recommend research on the strategies used to communicate rapid changes in vaccine policy. Also recommended: a) analysis of the differing risks and benefits of thimerosal vaccines’ use in other countries; and b) implementing a diverse public health and biomedical risk/benefit research portfolio.
- Clinical research recommendations: Careful, rigorous and scientific investigation of chelation, which is not necessarily a benign intervention; identification of a safe, effective and inexpensive alternative to thimerosal for those countries now using it; and appropriate animal models to explore the neurodevelopmental effects of ethyl mercury.

Dr. Modlin thanked Dr. McCormick. He also reported the formation of an ACIP work group to discuss the IOM report’s implications, chaired by Dr. David Johnson.

Thimerosal Update. Mr. Dean Mason updated the committee on the remaining thimerosal-containing vaccines and DTaP vaccine supplies. Prior to April 2001, 11-12 vaccines were thimerosal-containing; now, only ~6 vaccines purchased through the CDC contracts are, none of which are on the routine pediatric schedule for all children. Tetanus, diphtheria, pediatric DT and other products may contain it, but these are not part of the CDC contracts.

To roughly evaluate the remaining supply of thimerosal-containing product, a nationwide convenience sample of VFC provider offices was done from August 10-17 (16 states, 3 large

urban areas, 225 site visits, 22% public clinics, 31% private pediatricians, 47% family practitioners). It focused on DTaP, Hib and hepatitis B pediatric vaccines. A later analysis of lot number determined that 5.5% were t-containing. Another analysis was done of a convenience sample of t-containing product in GIV and Belco depots, who supply 8-12 states, . They have fresher vaccine than health care provider inventories. Only 1% was t-containing (80% DTaP, 14% DTaP/Hib, and 6% hepatitis B).

DTaP Update. The ~867,000 doses on back order (>15 days late) through CDC's contracts in February was down to 268,000 doses by June. But Aventis Pasteur's supply of DTaP vaccine to the public market was dropped, and the CDC contract moved to Glaxo Smith-Kline. As of October, 15 CDC grantees had no DTaP inventory, and 42 have a ≤ 15 -day supply (>60% at critical inventory). Projections through December reflected an average national need of 1.44 million doses per month (4-year supply analysis) for all providers. GSK can fill ~1.64 million doses/month, relieving some of the present pressure (only ~61% are timely orders). Reported spot shortages in provider practices may last 3-5 months. Aventis Pasteur is filling private sector orders at ≤ 80 doses/month per doctor, unless otherwise justified by the physician. Aventis Pasteur will restart filling CDC contract orders in the second quarter of 2002.

Discussion included:

- *Can you repeat the providers office survey September through December to see if the supplies received are being rapidly used?* Yes, if the states agree. NIP will continue to monitor the situation. In an alternative approach to the labor-intensive convenience sample, NIP reviewed VAERS reports, which were consistent with the sample results.

Manufacturer Perspectives

Glaxo Smith-Kline: Dr. Tom Zink, Vice President of Immunization Practices and Scientific Affairs, reported CBER's release the previous day of 400,000 vaccine doses; hopefully, another 400,000 will be released shortly. GSK is aware of continuing public concern about thimerosal in vaccines, despite any scientific evidence of a causal link to neurodevelopmental harm. To preserve public trust in the immunization programs:

1. Only the GSK Andrax B adult and Andrax B pediatric vaccines have thimerosal. The DTaP and hepatitis A vaccine never did.
2. GSK worked with the FDA to remove thimerosal as a preservative from their adult and pediatric vaccines.

3. GSK no longer distributes any vaccine in the U.S. in any presentation with thimerosal as a preservative. They are instituting a free voluntary exchange program for previously released thimerosal-containing adult and pediatric vaccines.

Mr. Mason summarized that the ~38% of the October 1-December 31 product will come out in October; but the 62% percent will arrive November and December, *if* everything goes perfectly. There are questions of equitability among the states about distribution to the public and private sectors. While 800,000 doses will certainly help, 1.4 million doses are waiting to be filled and 67% of that is backordered, and that is only for the public sector.

Merck Vaccine Division. Dr. Tom Vernon reported that their hepatitis B vaccine Recombivax® contained thimerosal until late 1999; it is now completely thimerosal-free. They discontinued their CDC contract for thimerosal-free pediatric vaccines in April 2000. Merck is also considering a return policy.

Wyeth-Lederle Vaccines. Dr. Peter Paradiso reported Wyeth-Lederle's response as quickly as possible to the ACIP's recommendations on thimerosal. The Hib titer vaccine and Prevnar® are thimerosal-free,

Aventis Pasteur. Dr. Phil Hosbach reported the March approval of a thimerosal-free Tripedia®. All current products for routine pediatric use are thimerosal-free: IPV, Hib, DTaP and the DTaP/Hib combination vaccines. They are struggling with DTaP production somewhat due to the quick changeover to preservative-free vaccine and the loss of one manufacturer of that and tetanus diphtheria (Td).

Discussion included:

- Dr. Abramson: *So, will we have a shortage?* If "shortage" is defined as the inability of doctors to serve all DTaP-eligible children at any visit, yes. Hopefully that will be corrected before year-end, but those hopes have been dashed before.
- Dr. Modlin: *Would using the thimerosal-containing remaining supply help?* About 9-10% of providers' vaccine DTaP supply is thimerosal-containing. An immediate cessation if use would be a substantial problem. The shortage is independent of the thimerosal issue; as the manufacturing improves, so will the supply.

Workgroup Presentation to ACIP

Dr. Johnson reported the Workgroups's conference call discussions and presented six different options for ACIP to consider and deliberate in response to the shortage.

1. Issue a strong recommendation of immediate cessation in use of thimerosal-containing vaccines.
2. Express a preference for thimerosal- free vaccines.
3. As of January 1, 2002, express a preference or recommend use of only t-free vaccines.
4. Identify a preference/recommendation of t-free vaccine administration by age group (i.e., <6 or <12 months).
5. Address the issues based on vaccine supplies (e.g., t-free Hib or hepatitis B vaccines).
6. Continue the current ACIP statement developed in 1999.

The workgroup reached some, but not universal, consensus on one of those options, and therefore suggested development and adoption of a joint statement. To do so, they drafted some principles for use.

Dr. Roger Bernier clarified that the ACIP was not being asked to vote on the options presented, preferring to issue a third joint AAP, AAFP, and ACIP statement to end the transition of the June 2000 statement. He then outlined the workgroup's suggested process:

1. Review the IOM report and respond to their recommendation to use thimerosal-free or trace-thimerosal vaccines for DTaP, Hib and hepatitis B. To do so, complete the transition from the June ACIP statement that reaffirmed that either t-containing or t-free vaccine could be used.
2. After review of the report, issue a unified policy position that recommends with the support of the pediatricians and family physicians.
3. Create a framework that describes all points of agreement and use those as guiding principles to charge a drafting committee in developing the joint statement.
4. Develop a provisional joint statement, share that with the four organizations, vaccine manufacturers, and other key stakeholders to gather and consider their comments on the provisional joint statement.
5. Incorporate those comments into a final statement, also to be shared, and hopefully to have approval within 30 days from the four organizations.
6. Publish this document in 30 days, post it on the Internet and an *MMWR* Notice to Readers.

The guiding principles to be used in developing the statement are:

1. Issue a single unified policy position supporting completion of the transition that was begun in July of 1999 and reinforced June 2000.
2. The statement's main purpose is to convey how the transition from using t-containing to t-free vaccines should be done.
3. The transition should be done as rapidly as possible to eliminate the theoretical risk of harm from t-containing vaccines.
4. An important principle is that the transition policy should cause children no delay in receiving scheduled DTaP, Hib and hepatitis B or any other vaccination.
5. The transition policy should attend to the current and anticipated vaccine supply and not seriously jeopardize vaccine availability, even at the provider level.

Two communication messages were also identified:

1. Convey that this transition is precautionary and not driven by evidence of harm to children from these vaccines that contain thimerosal as a preservative.
2. Continue to emphasize previous statements that the t-containing vaccines are still considered to be safe and effective.

Discussion included:

- Dr. Word: *Include influenza vaccination in the "no delay" wording as it applies to children for whom that is indicated, or specify that elsewhere.*
- Dr. Offit: *Is the theoretical risk limit referred to that of EPA, WHO, FDA, or ATSDR? And to how many children do you expect this to apply?* Dr. Snider: *We are concerned not only with the mercury in vaccines, but with that overlaid on other potential exposures. ACIP response: Then change the last clause (e.g., "to further reduce the amount of mercury that a child may receive, not only from vaccines, but from the environment generally"). And, include in the communication the issue of benefit/risk: that is, unvaccinated children are at far more risk than that from the thimerosal.*
- Dr. Abramsom: *It seems we are placing this in a crisis context, when no guidelines are exceeded any longer. We have dealt with the problem, as advised by the IOM. We need to address mercury and mercury exposures from other sources, such as fish consumption. While the ACIP should respond to the IOM report, the transition "as rapidly as possible" makes it sound like a crisis. In these days of terrorists and anthrax, "emergency" needs*

careful definition to allow prioritization.

- Dr. Johnson: The ACIP cannot really address those larger exposure issues, but there is a need to quickly respond to this new report, which suggests a fairly rapid changeover. While this is not a “crisis,” an ACIP response to the independent IOM committee’s report is necessary to avoid any suspicion of complicity by ignoring it. In addition, federal agencies may feel pressured to make their own statements about this issue and would appreciate the guidance of a joint statement, which can be word smithed.
- Dr. Overturf: Make clear that the ACIP’s initial response was very successful in removing thimerosal and restate that the mutually agreed-upon goals by ACIP and the IOM report will be met in a reasonable time. The only remaining issue is whether to use the small remaining t-containing supply
- Dr. Offit: It is of concern that, upon the recommendation against giving the hepatitis B vaccine to babies of surface-antigen positive mothers, 9% of hospitals stopped that immunization entirely. Beware of conveying that t-containing thimerosal is dangerous.
- Dr. Snider: A response is needed to avoid any perception that the ACIP is refuting the IOM report, which poses implications to the acceptance of their future reports; to further clarify the issues for the litigation that is already beginning; and to maintain public confidence, perception, and trust in the immunization programs.
- Dr. Halsey: There is still the possibility that some children may receive all three of the t-containing vaccines in some clinics. Separate the vaccines in the statement to avoid potential harm to some children in some clinics.
- Dr. Brooks: Address the principle in conflict with the established recommendations, to delay dose 4 if there is a shortage of DTaP.
- Dr. Peter: This response supports the IOM recommendations to review and assess how public health policy decisions are made under uncertainty, as well as the strategies to communicate rapid changes in vaccine policy. It also provides something of an answer of how those are now done.
- Dr. Chen: The joint statement workgroup should be sure to clarify that "inadequate evidence to accept or reject" does not equate to no evidence to accept a causal relationship. Rather than “as rapidly as possible," use text such as “expeditiously.” All risk has not been eliminated, but the removal as rapidly as possible to reduce the total dose of mercury was achieved almost immediately.
- Dr. Reilly appreciated the acknowledgment of the manufacturers’ positive response to the committee’s July 1999 recommendations. He emphasized that the maximum likely

inventory in the field at any time is probably two months, which means that the t-containing vaccine out there is probably 5% of only two months' inventory.

PUBLIC COMMENT

Ms. Sally Bernard, Executive Director of Safe Minds, thanked GSK for their voluntary recall of their thimerosal vaccines, and supported the IOM's balanced set of recommendations. She stated, from a parent's perspective, the importance that the ACIP state a strong and decided preference for t-free vaccines, and to support that this be implemented immediately, as the IOM advised. She also asked for a parent representative on the joint statement workgroup.

Ms. Lynn Redwood, President of Safe Minds, reported their petition to FDA, with other organizations, to recall of all remaining infant t-containing vaccines. She also thanked GSK for their responsiveness to the public concerns and asked the other vaccine manufacturers to consider doing the same. She advised the ACIP that Safe Minds has documents, including a VSD document, which independent statisticians found to show statistically significant associations with increasing levels of thimerosal exposure, with neurodevelopmental delays, including autism. That makes a statement of insufficient evidence premature. She also cited this document's discrepancies to those were presented to ACIP in June of 2000 and to the IOM in June of 2001. Other internal documents also cast doubt on the VSD process. Therefore, Safe Minds will call for a Congressional and a Department of Justice investigation into the generation and manipulation of these reports. She asked ACIP's support in these investigations, to ensure accurate data. They also will ask the IOM's support, since they relied on the VSD data in the causality assessment.

Ms. Terry Polling is a parent, a registered nurse and an attorney; her husband is a neurologist, scientist and was a Johns Hopkins resident. Although she believed in immunization, their daughter, now nearly 3, could not be vaccinated from age 7 months to ~18 months old due to chronic otitis media and rhinitis. Their pediatrician recommended giving her all 9 vaccines at once; she developed an encephalopathy, a body rash, and was later diagnosed with autism. Ms. Polling attended this meeting to raise the issue that, if scientific evidence is found to be insufficient to show a causal relationship between neurodevelopmental problems and vaccines, that absence must also be acknowledged to support the timing of immunizations at birth, 1, 4, 6, and 12 and 15 months. And, while there was no reliable evidence found to connect thimerosal and neurodevelopmental problems, neither was there evidence of *no* causal connection. In her

opinion, that is because, until now, no one has been looking. She made the point that thimerosal is neurotoxic, and as the use of t-containing vaccines rose, so did the number of neurodevelopmental problems in children. She asked that all this be considered as the ACIP deliberates what policy to advance, and warned of a potential backlash reaction from parents unwilling to be an “experimental group.”

Dr. Plotkin commented that the rationale behind thimerosal removal and the philosophical principle invoked by the IOM report is the principle of precaution. This may not always be totally desirable, because it can lead to actions based on only concern. That same principle prompted the partial withdrawal of hepatitis B vaccine by the French authorities, despite studies showing no relationship between the vaccine and multiple sclerosis. Rather than that principle, discussion of the inevitability of a risk for every benefit, and the need to balance those, is needed.

Dr. Johnson summarized that additional communication principles had been raised for the drafting group, as well as modifications to guiding principle 3. The workgroup is in formation and includes representatives from AAP, AAFP, ACIP, NVAC, and the Public Health Service (CDC, HRSA and FDA). If a conference call is necessary, it will be held in public.

Finally, Dr. Wexler reported the availability of the “Immunization Techniques” video, which her organization hopes to place in every clinic in the United States. It provides teaching guidelines on appropriate IM and subcutaneous injections, and a skills checklist with which to review staff immunization techniques. She provided order forms. Also available is a related poster to hang in the clinic. Dr. Modlin reported the enthusiastic acceptance of these tools in his office. With that, the meeting adjourned at 7:10 P.M. and reconvened at 8:10 A.M. the following morning.

OCTOBER 18, 2001

THIMEROSAL-CONTAINING VACCINES WORKGROUP REPORT.

Dr. Johnson distributed and reported on the provisional draft of the Third Joint Statement to be issued by the AAFP, the AAP, the ACIP, and the Public Health Service agencies. The Workgroup members were: Drs. Overturf, Zimmerman, Johnson, Offit, Midthun, Baylor, and Evans. Drs. Joel Kuritski, Roger Bernier, Sam Katz, and Georges Peter also participated. Appreciation was expressed of the manufacturers’ efforts to reduce or eliminate thimerosal in

vaccines.

Dr. Bernier requested the members' comments by November 5 in order to circulate a final joint statement to the four organizations by November 15 for approval by November 30. That would enable publication with the new Harmonized Schedule to avoid any sense of urgency or crisis, and provide 1-3 months for implementation for a transition period.

Discussion included:

- Dr. Plotkin: Clarify that the general phrasing about "vaccine" not to be used after March 31 does not include influenza vaccine, and be clear that the statement's focus is on the three routine pediatric vaccines.
- Dr. Snider requested NVPO's assistance to engage and coordinate all the PHS agencies' responses.
- Dr. Chen emphasized that the VSD report was a screening analysis of administrative data, not a stand-alone finding; a more definitive validated study is needed. And, while he understood the advocates' intent to protect children through thimerosal removal, he urged them to pursue a collaborative approach with public health rather than engaging in conspiracy theories and questioning researchers' personal integrity. He recommended caution, noting the U.K.'s report of similar rises in their autism rates alongside no change of their vaccines' thimerosal content since the 1950s.

AGENCY UPDATES

National Immunization Program

Dr. Walter Orenstein reported:

- Immunization coverage for 19-35 month-old children as of first quarter 2001 was unchanged for polio, Hib and MMR. Hepatitis B is at >90% coverage, and varicella is at a high of 75% coverage; DTP-3 is at almost 95%, and DPT-4 is at ~82%, the lowest-coverage antigen. Measles incidence continues to be extremely low. The effects of September 11 on global polio eradication work remain to be seen.
- FY 2002 budget: The President requested \$575 million, a \$22 million increase (\$14 million for vaccine purchase, \$4 million for vaccine safety, \$1 million each for extramural research and global polio eradication, and \$2 million for mandatory salary increases). The House passed \$25 million more; the Senate passed a version \$62.5 million over the President's request. Most of whatever is passed in the Conference Committee will fund state grants for

vaccine purchase and infrastructure.

- An NIP-IOM public- and private-sector vaccine financing study focuses on the stakeholder roles and responsibilities of the immunization system, best finance strategies, current needs, and best ways to introduce/finance new vaccines (particularly in mid-budget periods and for future vaccines). The study director is Dr. Rosemary Chalk.
- CDC funded an annual study to be done by the Gallup organization, which is a longitudinal survey of family practitioners' and pediatricians' attitudes and practices regarding childhood immunization, including vaccine safety. This could be expanded to survey attitudes about adult immunization.
- CDC-military partnership to develop the Clinical Immunization Safety Assessment Network (CISA). This will create academic centers of excellence to study post-immunization adverse events (adverse event definition, reviewing, protocols for potential therapy). Contracts were awarded to Johns Hopkins University, Boston Medical Center, and the Kaiser Research Institute Foundation (Stanford, Vanderbilt, and New York Presbyterian-Columbia).

Discussion included:

- Regarding financing for studies of anthrax and smallpox vaccines, and dosing for children, NIH reported a focus on the 18-30 year age range. Vaccination studies of pediatric, elderly, and pre-vaccinated populations will be done incrementally.

Food and Drug Administration (FDA)

Dr. Karen Midthun reported VRBPAC's review of Aviron's biologic license application for live-attenuated influenza virus (LAIV) vaccine, summarized the previous day. FDA approved Evans' supplement for thimerosal-reduced formulation of their influenza virus vaccine. VRBPAC will meet again November 28-29 to discuss efficacy endpoints for human papilloma virus vaccine studies.

National Vaccine Injury Compensation Program (NVICP)

Dr. Geoffrey Evans reported.

- Claims filed this fiscal year (pre-1988 claims are no longer eligible for filing): 212.
- Pending claims: hepatitis B (awaiting the IOM report on hepatitis B vaccine and neurological disorders); Hib vaccine (4) and varicella (18); rotavirus (11 claims, one including an intussusception death following rotavirus vaccination); acellular pertussis vaccine (36).

- Awards: >\$1 billion dollars paid for pre- and post-1988 program. The Trust Fund continues to grow.
- A Notice of Proposed Rulemaking was issued this summer to add intussusception to the Vaccine Injury Table (VIT) for injury sustained from 0-30 days post-rotavirus vaccination. The Advisory Commission on Childhood Vaccines also approved a distinct category by specific vaccine related to intussusception. Future vaccines that are not live, oral, and rhesus-based will be added under the general category. Since infants who suffered rotavirus recovered quickly, the 2000 legislation allowed compensation for those hospitalized and receiving surgical intervention if their effects lasted <6 months. That applies to all vaccines under the program.
- Technical VIT changes included:
 - ▶ The Hib polysaccharide vaccine will be removed from the VIT. It was added in 1997, when the IOM determined the relation of early-onset Hib disease to the Hib polysaccharide vaccine, whose use ended in 1989. The eight years of retroactive compensation application was nearly expired and no claims for the polysaccharide vaccine were filed.
 - ▶ Residual Seizure Disorder will also be removed; there is no longer any condition listed on the table for RSD. The Hib vaccine and the Residual Seizure Disorder will both be removed from the qualification for AIDS to interpretation.
 - ▶ The pneumococcal vaccine will be added in its own box category (from the current general category of CDC-recommended vaccines for routine administration). Coverage was effective since the excise tax was levied. No public comment on related injury is expected.
- Active legislation includes:
 - ▶ The Bunning legislation to lower the excise tax.
 - ▶ The Weldon-Nadler Bill would set a non-scientific standard for deciding the pertinence of table and non-table injury claims to vaccines. That would create problems for the program and would create an almost-limitless statute of limitations.
 - ▶ The Government Reform Committee has scheduled another hearing at month's end.
- An ACIP general use recommendation for inactivated flu vaccine would make all ages eligible to file with the Compensation Program.
- Only one thimerosal-related injury claim has been filed, although a litigation group specializing in class action lawsuits has advertised nationally to find plaintiffs. Current status of the suits is unknown.

In discussion, clarification of the new requirements for intussusception was requested (i.e., if the general application of “surgical intervention” cover sequella unrelated to the vaccine, such as an abscess at the site of the injection that as surgically drained in hospital with antibiotics prescribed. Dr. Evans answered yes, but those kinds of scenarios are very rare.

National Institutes of Health (NIH)

Dr. Carole Heilman reported on two areas of NIH activities:

Influenza

- Epidemiology activities include a contract to research the ecology of zoonotic influenza viruses to identify the H5, H7, and H9 zoonotic infections; and evaluation of community-based strategies to create herd immunity and interrupt the spread of influenza.
- Vaccine development: The Partnership for Controlling Infectious Disease (2003), which addresses LAIV, and more recently, the Challenge Grant Program, share 50% of costs for development of high-importance vaccines not now aggressively pursued by industry. The two current activities are development of a DNA-based influenza vaccine and production of non-egg vaccine substrates. Research to maximize the availability/delivery of vaccines includes response of healthy individuals to lower (half) doses; and novel delivery methods (e.g., intranasal delivery).

NIAID studies on thimerosal:

- Pichichero and Treanor conducted a brief clinical study to identify the amount of mercury in infants after vaccination (University of Rochester). The cohort was 20 each of 2-month-olds and 6-month-olds, whose whole blood, urine, and stool samples were sampled at varying times within 30 days of vaccination. The results were that: 1) blood mercury levels in full term infants within 30 days were below EPA safety guidelines; 2) blood mercury levels in these infants were lower than predicted by the 45 days half life for mercury; but 3) mercury was detected in the stools of infants receiving vaccines containing thimerosal, suggesting that mercury is eliminated faster than is methyl mercury.
- Evaluation of mercury’s kinetics and tissue distribution in infant macaques is being considered to look at post-vaccination levels at various time points.
- A pharmacokinetic study (infant macaques) of the distribution of methyl versus ethyl mercury examined IM-plus vaccines over 4 weeks, monitored behavioral patterns and collected and analyzed specimens. The results were that: infant formula/food showed low background mercury levels; brain tissue of normal infant macaques held low and

nondetectable mercury levels.

Discussion included:

- Dr. Snider: *Please outline NIH's response to the IOM report's research proposals.* The IOM report called for ongoing research, as is being done by many of these studies and the NIH DTaP study done in Sweden. Those children are still being followed for neurological outcomes and hopefully will be linked to an autism database.
- Dr. Chen: NIP is funding a pilot study of the logistics necessary to do such follow-up among the now-older children at different neurodevelopmental stages. Standardized tests will be done in one visit to indicate whether the cohort approach will be the best, or if a multiple simultaneous case-control study will be appropriate.
- Ms. Redwood asked if the mercury levels in the stool samples were ~50-80 µg/g, and whether the mercury would have had to be blood borne to the stool. Not having the data with her, Dr. Heilman could not respond, but added that the John Treanor study should be published soon.

National Vaccine Program Office (NVPO)

Mr. Steven Sepe reported in Dr. Martin Myers' absence.

- NVPO is awaiting the return, and hopefully approval, of the National Influenza Pandemic Preparedness Plan, submitted to DHHS in July, with revisions made from agency input.
- NVPO coordinated report preparation for the House and Senate appropriation committees on the 2000-2001 influenza season vaccine delay. Submitted in August, it explained the basic procedures for annual influenza vaccine production and distribution, the 2000-2001 problems, DHHS responsive actions, continuing vaccine supply issues, and DHHS recommendations being implemented to improve future vaccine distribution. The Secretary identified vaccine supply as high priority. One thing which has already been done is the NVAC and NVPO's convening of a related work group. The Secretary signed a recommendation to all DHHS agency health clinics to prioritize initial influenza vaccinations to those at high-risk.

National Vaccine Advisory Committee (NVAC)

Dr. Georges Peter, NVAC Chair, reported an NVAC teleconference held on October 2, in place of the NVAC meeting, canceled due to the September attacks..

- Dr. Kathleen Stratton presented the IOM report and the committee discussed two

recommendations on the public health response: 1) public health policy decisions made under uncertainty; and 2) strategies to communicate rapid changes in vaccine policy. An NVAC work group will examine these issues. Also discussed were topics for the IOM Safety Review Committee, which will review nine topics over three years. The next report will be on the potential of immune overload from the administration of multiple antigens. NVAC recommended as the subsequent topic the putative association of hepatitis B vaccine and neurological disorders. A matrix with which to consider other topics was created.

- The report on the NVAC workshop on intussusception and rotavirus vaccine will be reviewed at the next meeting. That will be interesting in view of NVAC's role to foster new vaccine development, and since the priority for rotavirus vaccine differs greatly between the developed and developing world.
- The NVAC Standards for Adult Immunization Practices, reviewed by many partner organizations, should be published in *JAMA* in December. Companion standards on child and adolescent immunization practices were developed and approved by NVAC, and reviewed by ten partner organizations. Upon incorporation of their comments, the standards will be recirculated. Publication in early 2002 is hoped.
- Three regional meetings will be held to provide a framework with which states can decide their immunization policies: Nashville (September), Denver (November) and Boston (December). They will review public health policy creation and implementation at the national, state, and local level, as well as address consumer perspectives. A report will be issued. The decision framework will also help public health agencies assess which vaccines may warrant school immunization laws, which are better fostered by universal recommendations, and which are better based upon elective utilization.
- The NVAC Vaccine Supply Workgroup developed a list of concepts for the IOM committee's discussion, including supply options and strategies. A workshop of all stakeholders is planned in early 2002.
- The pandemic influenza preparedness plan is well advanced.
- NVAC's Workgroup on the Introduction of New Vaccines is awaiting the IOM Committee's report on the related financial elements before making any further recommendations.

National Center for Infectious Diseases (NCID)

Dr. Alison Mawle reported.

- Updated brochures have been published of the "Emerging Infectious Disease Plan, Strategy

for the 21st Century”, originally published in 1998. The activities covered include:

- ▶ Surveillance and response: Development of molecular immunologic tools for surveillance of organisms causing vaccine preventable disease (VPD). This reflects NCID's leap from no lab capacity three years ago to a state-of-the-art varicella lab tracking and collecting varicella strains worldwide.
- ▶ Applied research: Investigation of naturally-acquired protective human immune responses to disease. For example, a Kenya longitudinal cohort study of malaria now in its fifth year helped to develop a prototype peptide vaccine about to go into Phase I trials with the Malaria Vaccine Initiative).
- ▶ Infrastructure/training: Establishment of laboratory networks' diagnosis/molecular epidemiologic study of VPDs. A protocol for lab diagnosis of Hib, pneumococcal and meningococcal disease was created and networked in Africa. Two trainings (in English and French) were done and are on the Web and may be part of GAVI's integrated disease surveillance in Africa.
- ▶ Prevention and disease control: Polio eradication remains the priority goal. NCID holds the world reference lab and is working on lab containment of polio after eradication, conducting the U.S. lab surveys.

Discussion included:

- Dr. Plotkin: *Are there plans for surveillance of anticipated biowarfare agents?* The CDC Website lists the agents being addressed for bioterrorism response, and domestic movement of the select agents are tracked between labs.
- Dr. Snider: CDC routinely shares information with CSTE and the various states to reinforce messages already crafted and on the CDC site, and is considering broadening those messages to more clearly explain the surveillance and reporting roles of lab workers, practicing physicians and infection control staff. report.
- Dr. Modlin: The ACIP Bioterrorism Workgroup, chaired by Dr. Helms, will be reactivated to consult with CDC as needed.

PROPOSAL TO DECREASE THE TIME INTERVAL RECOMMENDED TO AVOID PREGNANCY AFTER RECEIPT OF RUBELLA VACCINE

Dr. Susan Reef, of the NIP/ESD, presented data to serve as a basis on which to decide about a proposal to decrease the time interval recommended to avoid pregnancy after receipt of rubella vaccine. The current recommendation to avoid pregnancy for 3 months post-injection with

rubella-containing vaccine is based on 1970s data of vaccine-like virus found in the fetus of a mother inadvertently vaccinated with HPV77 duck embryo 7 weeks before conception. That vaccine is no longer used in the U.S. and these findings have never been reproduced. All available data show no evidence of Congenital Rubella Syndrome (CRS) after inadvertent vaccination in the mother.

Rubella infection in pregnancy can result in miscarriages, still births, fetal deaths, asymptomatic infections in infants, and the CRS group of birth defects (cataracts, hearing impairment, heart defects). The timing of maternal viremia infection and gestational age upon infection are important. In organogenesis, weeks 3-6 are most critical for heart and CNS; the eyes are to week 8; and hearing is to week 16. Viremia normally occurs 7-11 days post-vaccination and usually clears well before 21 days.

Rubella and CRS cases in the U.S. are at a record low level. Most rubella occurs among foreign-born adults and most U.S. CRS cases are born to foreign-born mothers. An estimated 40% of U.S. CRS cases stem from missed opportunities to vaccinate women of childbearing age, some of whom could be immunized by decreasing the time interval from three months to one. That would also allow vaccination of women who are trying to get pregnant or undergoing fertility treatments, and who are unwilling to wait three months. Dr. Reef briefly reviewed past rubella vaccination policies. The current RA 27/3 vaccine was introduced in 1979.

Data on women inadvertently vaccinated 3 months pre- and during pregnancy was presented. For the 3-month waiting period, the *observed* risk was zero. The maximum *theoretical* risk was 0.5% [95% confidence interval (CI)]; 0.9% for only RA 27/3; 1.3% in the high-risk period for all vaccines (lower than background for serious malformations or birth defects); and 2.3% for RA 27/3 alone.

Additional supportive data comes from studies of inadvertently vaccinated women in the Caribbean (241 live births with no CRS cases) and Canada (81 live births, no CRS). Finally, rubella in the United States occurs among adults, and adult women are a high-risk group for whom decreased barriers are key to assure immunity.

Dr. Reef summarized the current recommendation's wording, which advises against administering MMR and its components to women known to be pregnant. Pregnancy should be

delayed for 3 months after administration of MMR or other rubella-containing vaccines, but only 39 days after measles and mumps vaccination. Pursuant to the ACIP's agreement, the wording would be changed to "becoming pregnant for 30 days after receipt of measles, mumps, or rubella vaccine."

Dr. Gall commented, in view of the epidemiologic data and that the 3-months wait after rubella vaccination delays MMR and risks rubella-contaminated pregnancy, that the data support a change in the recommendations.

Discussion included:

- Dr. Salisbury and Dr. Marchessault reported their countries' change from a three- to one-month recommendation with no change of CRS cases after an inadvertent immunization.
- Dr. Abramson found the data to be compelling.
- Dr. Ray Strickus, NIP, asked the proportion of woman expected to have viremia at ≥ 28 days after vaccination. Dr. Plotkin reported none seen at ≥ 21 days; the average is 7-11 days. He supported this change, adding support from a German study that included a rare case of a rubella-infected infant, who was normal upon follow-up for two years.
- Dr. Wharton announced that the change would be published as a brief Notice to Readers.

Dr. Johnson moved that the ACIP recommend a decrease in the time interval from vaccination prior to pregnancy down to one month. Dr. Smith seconded the motion.

Conflicts with Merck by Drs. Rennels, Offit, and Clover required the ex-officios to vote on this issue.

Vote:

In favor: Drs. Word, Brooks, Johnson, Smith, Tompkins, Deseda, Modlin, Mr. Graydon, Mr. Sepe, Drs. Groom, Diniega, Heilman, Evans.

Opposed: None

Abstaining: Drs. Rennels, Offit, Clover, Levin, Midthun.

Dr. Bill Atkinson, of the NIP, requested that this recommendation be made consistent with the General Recommendations to be published in the *MMWR*, which define a month as four weeks or 28 days. The committee agreed.

Dr. Offit commented that the credit for the RA 27/3 vaccine, which brought 20,000 annual cases of CRS down to <10, goes to its inventor, Dr. Stanley Plotkin. He received a round of applause.

UPDATE ON PNEUMOCOCCAL CONJUGATE VACCINE

Dr. Cindy Whitney, of the NCID Division of Bacterial and Mycotic Diseases, reported for Dr. Chris Van Beneden on a significant decline in pneumococcal disease cases, which is attributable to the new pneumococcal conjugate vaccine, Prevnar®.

Background: U.S. cases of invasive pneumococcal disease declined in 2000. This seems to result from the use of Prevnar,® the pneumococcal conjugate licensed in February 2000. It was recommended for use by the AAP in August of 2000 and by the ACIP that October. ACIP recommended the vaccine for all children aged <2 years and for a subset aged 2-5 years with certain chronic illnesses and immunocompromising conditions. Administration was optional for children aged 2-5 with these three situations. Therefore, the vaccine effect should be strongest in children aged <2, and be lesser in children 2-5. And, since wide use began late in the year, the effect should have been visible by September.

Efficacious effects found in pre-licensure research were:

- Against invasive disease due to serotypes contained in the vaccine.
- Possible protection against vaccine-related strains (both for invasive disease and otitis media).
- Reduced carriage in the vaccine-type strains and potentially reduced transmission of those strains.
- However, some data suggested potential replacement carriage with non-vaccine-type strains, including those of otitis media.

Surveillance objectives to measure reduction of transmission were to assess: 1) reduction of invasive disease due to vaccine serotypes in young children (and perhaps in older age groups), and 2) reduction of replacement disease for both vaccine-related types and non-vaccine types. The Active Bacterial Core Surveillance (ABC) system, with 7 participating states, was used. The methods were defined, beginning with the case definition: pneumococcus isolated from a normally sterile site.

Results for 1998/99 versus 2000, by year and age group, were:

- 800 cases in 1998-99 dropped to 634 cases in 2000, a 20% reduction.
- 15% reduction for those aged 2-4, and 5-39 (the latter was assessed to gauge household transmission).
- 3% and 4.8% reduction respectively, for ages 40-65 and >65.
- The effect was also reflected by the time of vaccine purchase, with case number reduction strongest in the second half of the year. A small reduction for children aged <2 in from January-June rose to ~40% in the latter half and ~20% in the next two age groups. The results were almost as strong for non-vaccine serotypes (34% for those aged <2), but the numbers were smaller, preventing any specific conclusions.
- As coverage increases, additional surveillance data will be needed to indicate the magnitude of vaccine-preventable disease and further examine the potential for a replacement disease.

Discussion included:

- Dr. Offit: *Was there any indication of decreased invasive pneumococcal disease due to a herd effect?* No current data allow that examination; vaccine histories of all reported cases were not available. A multi-state case-control study to examine vaccine effectiveness is being done with the ABCs, which may provide some herd data after another 2 years.
- Dr. Paradiso: The Kaiser data, part of the Phase IV studies, were recently presented at the IDSA conference, and confirmed these reported patterns.

Dr. Whitney also reported on the vaccine failure system to be launched. It will track instances of vaccine failure to generate hypotheses about in what subgroup situations even a highly effective vaccine such as Prevnar® might be less effective. This surveillance system will define a case as a child aged <5 years with pneumococcus isolated from a normally sterile site (e.g., blood, spinal fluid) who received at least one dose of Prevnar.® The strain will be serotyped from isolates collected and recorded to determine what may have contributed to the failure (e.g., chronic or immunosuppressing conditions, age at/time since immunization, number of doses, vaccine lots, concurrent immunizations). The state health lab will send a failure case report and CDC report for with the isolate to the NCID streptococcus laboratory. Cases may also be reported through VAERS.

Vaccine Supply. Dr. Schwartz noted the good acceptance of Prevnar,® with doses similar to

those of the Hib conjugate vaccine. Overall public and private sector demand is estimated at 1.5-1.6 million doses a month, but there is a shortage of pneumococcal conjugate vaccine. The rapid increase in demand exceeded expectations and production, resulting in backorders by health departments for most of 2001. This was exacerbated in August by lot release issues that suspended distribution, resulting in a September *MMWR* Notice to Readers of vaccination recommendations during a shortage.

The NIP data indicated:

- 28 of CDC's 56 grantees have ≤ 15 days inventory, a serious shortage.
- 11 projects have a 16-29 day inventory.
- 17 projects have an acceptable but not optimal amount of vaccine.
- The 3-day turnaround period at the beginning of the year vanished; the current longest pending order was placed in mid-June. An average $\sim 700,000$ doses/month were shipped January through August, when delays began, and 383,000 doses were shipped in September to the public sector. The total distribution is about double that to the public sector.

The *MMWR* recommendations were to:

- Continue vaccinating infants at 2,4,6 months.
- Continue vaccinating those aged 1-5 years at high risk based on the ACIP definitions.
- Defer vaccination of children between ages 2-5 and not at high risk.
- In more severe shortage situations, defer vaccination in those aged 12-23 months, including those who had not received any previous doses.
- Defer dose 4, generally given at age 12-15 months.
- Maintain records to recall those deferred for vaccination later.

These recommendations were intended to cause minimal disruption of infant vaccination and to provide the greatest protection of infants before the high-risk period of ~ 6 months-2 years. Since pre-licensure studies showed good vaccine efficacy from three infant doses, deferring the 12-15 month dose 4 was felt not to be that detrimental. The manufacturer also expected increased vaccine delivery in the fall and to catch up by year's end.

Comments received by NIP on these recommendations included:

- They should have been more definitive rather than flexible for providers to adjust their practices based on their own supply situation.

- They should have recommended vaccination for unvaccinated kids aged 12-23 months, who are at higher risk for pneumococcal disease than some other children.
- Some suggested dropping one of the first three infant doses in serious shortage situations, (e.g., to vaccinate at 2,4 months or 2,6 months only).
- Some suggested vaccination only at >6 months of age and delivering an entire series of three rather than four doses (i.e., a schedule of 6,9, and 12-15 months, both the latter required visits for other vaccines).

Wyeth-Lederle Perspective. Dr. Kevin Reilly provided Wyeth-Lederle's perspective. He agreed that the very strong acceptance of Prevnar® and compliance (~90%) with ACIP/AAP recommendations led to a shorter ramp-up than anticipated. Total distribution to October 1 was 11.4 million doses to the private and public sectors, in roughly equivalent amounts for both backorder and delivery. Shipments are tied to batch releases, as discussed the previous day about DPT vaccine. Wyeth is working to reduce the current large backorder and is working with CDC, individual physicians and group practices to ensure the best use of the product. Shipping is done on a first-in, first-out basis, but product availability to those most critically in need is also pursued.

The backorders are due to changes being made in the manufacturing process of preparing for and obtaining batch releases. Manufacturing capacity exceeds 30 million doses, and has been scaled up to introduce Prevnar® internationally. Total manufacturing capacity is in excess of 30 million doses, which surpasses the U.S. demand, but bottlenecks are still occurring in product releases. Extra resources are being used to resolve that. Wyeth expects to have no backorders by the end of the second quarter of 2002.

Dr. Schwartz expressed CDC's concern that the recommendations previously published in the *MMWR* will be insufficient to guide public and private sector clinicians on optimal vaccine use. He asked the ACIP to reassemble the Pneumococcal Conjugate Vaccine Workgroup, to ACIP, AAP, CDC and FDA representatives. The Workgroup was asked to evaluate manufacturer and other sources data¹ and to suggest a published revision to the September guidelines that the ACIP could review and approve, either before or at the next meeting in February.

¹ For example, on production issues, vaccine demand, doses used for infants versus catch-up, and on the immunogenicity of more frugal vaccination strategies for infants.

Discussion included:

- Dr. Modlin recalled that the September guidelines were CDC's, not ACIP's, but agreed to the Workgroup's reorganization. The issue could perhaps be addressed in the already-planned committee conference call about thimerosal and vaccines. Dr. Abramson hoped for a speedy process, reporting that the COID planned to discuss vaccine distribution concerns at their next meeting.
- Dr. Smith expressed concern that providers with no doses could result in some children being missed entirely.
- Dr. Rennels: *What numbers support good vaccine efficacy after three primary doses?* The pre-licensure NCK study showed >90% efficacy from after the third dose to the fourth dose given at one year. But there are no data on how many people missed dose 4 and on vaccine efficacy among those vaccinated with only three doses for a longer period. It is hoped the company may have unpublished data that the Workgroup could review. Another issue to consider is the use of a dose of the polysaccharide vaccine; again, manufacturers data would be helpful.
- Dr. Brooks: *We received our private patient supply of Prevnar®, but not that for the VFC.* Dr. Orenstein: CDC receives 50% of the overall production, but that is inadequate. CDC is trying to prioritize vaccine delivery to states with zero inventories.
- Dr. France: *Quick communication to change providers' practices is needed.* Dr. Schwartz: A letter and the *MMWR* recommendations to groups that order this vaccine has been suggested. CDC can work with the company on that document.

VARICELLA DISEASE/VACCINE UPDATE.

Dr. Jane Seward introduced the presentation of data compiled in the six years since varicella vaccine was licensed. The data were gathered by CDC, state and local health departments, special studies, FDA with VAERS, and others.

Disease burden. In the five years before licensure (1995), an average of 4 million varicella cases per year resulted in ~11,000 hospital admissions and 100 deaths, in both children and adults. Varivax® is a live-attenuated vaccine made by Merck. The AAP and ACIP recommended it in mid-year, but signing of the federal contract was delayed. The vaccine was not available in the public sector until the end of 1996.

Recommendations. The updated AAP and ACIP recommendations were published in 1997:

- One dose of vaccine for children aged <13 years.
- Routine vaccination at 12-18 months .
- Vaccinate any older child before their 13th birthday.
- For people aged >13, a two-dose schedule 4-8 weeks apart.

Original ACIP recommendation: Vaccinate health care workers and family contacts of immunocompromised patients. The updated recommendations also advised vaccination of susceptible persons at high risk of exposure or transmission (e.g., day care center employees, teachers, people in institutions). The updated statement defines the vaccine as desirable for all other susceptible adults and adolescents.

The updated recommendations advise vaccination for post-exposure use, for outbreak control, for HIV-positive children with adequate CD4 percentage counts, and suggested that states implement school entry and child care requirements.

Surveillance is done for:

- Coverage by the National Immunization Survey, and specifically for varicella and herpes zoster vaccine
- Safety by VAERS, and through special post-licensure studies
- Effectiveness by outbreak investigations and special studies

Varicella distribution reflects rapid uptake in the private sector and delayed uptake in the public sector due to vaccine unavailability. However, since it has been available, a more rapid uptake has been seen in the public than the private sector.

Uptake in 2000: 6.2 million vaccine doses among a birth cohort of 4 million. Coverage in 2000 of 68% rose to 75% nationally in the first quarter of 2001. Coverage of >90% is hoped for by 2010. State coverage rankings shared for coverage and for school entry requirements showed a clear association between child care requirements and high coverage.

Vaccine safety surveillance. Data from the Merck/CDC Varivax® in Pregnancy Registry of exposures three months prior to and through pregnancy were shared. The registry followed 412 pregnancy outcomes from licensure through six years thereafter. Results showed that 97 women were sero-negative and no cases of congenital varicella syndrome identified. Women continue

to be enrolled in this registry. The registry and VAERS reports indicated some varicella vaccine given to women where VZ was indicated. An *MMWR* alert was issued several years ago; monitoring continues.

Post-licensure vaccine effectiveness (VE) and breakthrough disease. Dr. Karin Galil presented data from ten post-licensure studies, some published or about to be so. Pre-licensure trials showed 70-90% effectiveness against all disease and >95% protection against severe disease. Post-licensure vaccine effectiveness estimates range from 42-100% and 75-100% protection against all disease.

Breakthrough disease is defined as a compatible rash illness occurring >42 days post-vaccination (to avoid confusion with vaccine virus strain replication), and clinical diagnosis. However, the latter may underestimate VE, while PCR positivity may overestimate the VE.

Pre-licensure trials' definitions of disease severity differ: <300 lesions as mild and ≥ 300 as severe; more recent outbreak investigation definitions of mild as <50 total and no complications, and severe as >500 lesions or any severe complications.

- Izurieta *et al*: highest estimate overall in a 1997 Atlanta outbreak; effectiveness was 86%.
- Lee *et al*: lowest estimate to date in a New Hampshire investigation: vaccine effectiveness of 42%.
- Berrios *et al*, vaccine effectiveness: 59%; 75% for moderate to severe disease.

Risk factors for vaccine failure since licensure:

- Asthma and reactive airways disease (RAD) was indicated by a multi-variate analysis of the number of asthma medications taken and for how long. However, a VSD study that attempted to separate out those two things found that asthma was not a risk factor; its treatment was.
- Systemic steroids taken at the time of, or shortly before, breakthrough disease but not at the time of vaccination produced a >2-fold increase in risk.
- Eczema produced a >3 times increase in risk.
- Receipt of MMR vaccine within 30 days before varicella vaccine, which is a contraindication in the ACIP General Recommendations.
- Age at vaccination.
- Effective age.

- Time since vaccination: ≥ 3 years, and for some children, ≥ 5 years.

One caveat offered was that some estimates are uni-variate and some are continuing; multi-variate analyses are hoped for soon.

The significance of breakthrough disease depends on how infectious it is, its mode of transmission, and its severity. Data on these were shared. The New Hampshire school outbreak strongly suggested airborne spread from one child. Data from 1995-2000 of the Varicella Active Surveillance Project were shared. They demonstrated a dramatic decline in overall case counts but a rising proportion of breakthrough cases (27% in 2000); 81% of vaccinated children who developed breakthrough disease had mild disease (<50 lesions and no complications); and 36% of unvaccinated children had mild disease. Complications tend to occur less commonly in vaccinees.

There were more cases of super-infection among unvaccinated children and no cases of ataxia, cerebellitis, or pneumonia amongst the vaccinees. No breakthrough cases were hospitalized. Breakthrough cases missed less school or work on average than unvaccinated cases.

Preliminary conclusions: Post-licensure vaccine effectiveness was found to be similar to the pre-licensure estimates, although there have been some recent low estimates. Risk factors identified for breakthrough disease include early vaccination at 12-14 months of age, a longer time since vaccination, vaccination given within 30 days of MMR, steroid use, RAD, or eczema. Breakthrough disease can in certain cases be highly infectious and involve airborne transmission. Both breakthrough-to-breakthrough and breakthrough-to-natural varicella cases have been recorded. Most of the breakthrough cases are mild, but ~20% percent are not.

Immunogenicity of Varivax® and Breakthrough Disease

Dr. Rupert Vessey, of Merck and Company, presented data from the Varivax® clinical trial database, on: 1) possible effect of age at vaccination on the immune response, and 2) on breakthrough rates over time from a post-licensure study. The primary assay used was the gpELISA test, measuring varicella antibodies against partially purified varicella glycoproteins. The results of clinical studies demonstrating the varicella antibody titer 6 weeks post-vaccination, and the cumulative varicella breakthrough rate over seven years of follow-up in a cohort of children, were as follows:

- The data demonstrated an inverse relationship between the 6 week post-vaccination varicella antibody titer and the risk of breakthrough disease. That established the clinical relevance of this immunity measure. Also demonstrated was a relationship between children with high titers and milder breakthroughs (median of 50 lesions).
- However, there is no absolute correlate of protection; varicella antibody titer ≥ 5 gpELISA units was used as an approximate correlate of protection.
- *Antibody responses relative to age of vaccination of varicella history negative children:* similar geometric mean titers and the percentage of subjects achieving response at ≥ 5 gpELISA units in all groups suggested no gross effect of age at vaccination on the humeral immune response.
- *Presence of residual maternal antibody and potentially inferior resulting response:* 20-40% of children aged 12-14 months had detectable antibody pre-vaccination, which dropped by age 15-16 months to background seropositivity. Analysis suggested that these low antibody levels do not interfere dramatically with the humeral immune response, but the numbers were small.
- *Antibody responses 6 weeks postvaccination in children aged 12-14 months according to prevaccination serostatus:* Most children seropositive prior to vaccination have very low levels of circulating antibodies: $\sim 70\%$ at < 1.25 gpELISA units and 7% at ≥ 5 gpELISA units. All the categories of children appear to have good anamnestic responses to repeat-challenge antigens, suggesting that the first dose did induce immunologic memory. However, the numbers in these groups in particular were again very small.
- *Post-licensure data on varicella breakthrough rates* (Black and Shinefield study of 7,500 children aged 12-23 months in 1995, will be followed by telephone survey every six months. Results of the first 5.5 years were showed the rate of varicella per 100 person-years to peak at ages 3.5-6 years, the time of maximum exposure to the virus. The breakthrough rate declines thereafter; there is no evidence of waning protection.

Surveillance Data: Varicella and Herpes Zoster. Varicella is not nationally notifiable, and so lacks any national passive surveillance system. CDC began active surveillance in three sites² in 1995. Some states voluntarily report to the National Notifiable Disease Surveillance System; Massachusetts incorporated it into their BRFSS survey; and the VSD project examined varicella/herpes zoster incidence with the GHC.

²Antelope Valley, Los Angeles County, CA; West Philadelphia, PA; Travis County, TX

- Active surveillance at the three CDC sites showed a dramatic decline of disease with increasing vaccine coverage in 1999 and attenuation of seasonality in all three sites. From 1995-2000, a 70-80% decline in cases was seen overall. The decline indicated reduced disease transmission and exposure in these communities.
- Passive disease surveillance data in Michigan and West Virginia were very similar to the active data, with a ~50% disease decline in 1999 continuing in 2000 and still further in 2001.
- The surveillance data from Massachusetts and the Seattle GHC on varicella and herpes zoster were shared. Massachusetts' pre-vaccine era 8% incidence declined in all age groups. Herpes zoster data are more limited, but show no change in age-specific incidence as varicella declines.
- Summary: Vaccine coverage is 75% and rising as states implement child care and school entry requirements. The vaccine has a good safety profile and robust protection against severe disease.

Discussion included:

- Dr. Modlin: *Is a second vaccine dose for children being considered?* There are plans to review with Merck data from a two-dose schedule and the public health significance of breakthrough disease. That will occur within 3-6 months along with some cost-effectiveness analyses.
- Dr. Abramson: *At what point should we revisit the decision not to vaccinate HIV-infected children with a live varicella vaccine? At some point the risk of having wild-type virus is so low that neither wild-type nor attenuated virus is desirable as these children become more immunosuppressed.* That point may come, but there are still exposures from herpes zoster. Dr. Modlin also noted that the successful treatment of HIV-infected children has produced some maintenance of t-cell immunity among them, which may mitigate those special concerns.
- Dr. Smith: *Why are there such striking differences in state coverage rates?* Some relate to vaccine delivery, due either of supply or logistics of rural delivery; some are due to state practices in promoting the vaccine more slowly than others. With child care and school entry requirements, those disparities are expected to fade.
- Dr. Neuzil: An alternative explanation of no sustained breakthrough with duration of time from vaccination may be that peaking disease incidence at age 3 may leave subclinical infection that boosts immunity. As wild-type virus circulation wanes, there may be more

breakthrough because that duration effect may be more profound. Dr. Vessey: We do recognize that. That question cannot be answered in an environment where wild-type virus is still circulating and children may get subclinical boosts.

- Dr. Offit: Consider not using the word "breakthrough," since the fact that 80% of the disease is very mild constitutes a success. That is an important concept to convey to parents who may bring in a child with only 10-15 lesions post-vaccination. Mucosal infections such as influenza or rotavirus, when modified, are not termed "breakthrough," even though there probably is some remaining transmission capacity.
- Dr. Levin: *Why were two studies' breakthrough rate significantly higher than others?* There was no good explanation found, even with the risk factors identified. They were immunized by different sources and the vast majority with different lots, over five years.
- Dr. Levin: *One risk factor was early immunization, and maternal antibody made a difference; but that did not carry over to those children's response.* Dr. Galil: Cell-mediated immunity may be the more important factor for protection. A correlate of protection that is good at age four may not be so at 13 months of age. The age of vaccination for measles also was raised from nine months, an original decision based on good response data among children, that was changed to 15 months after vaccine failures. That was only lowered when most U.S. mothers had vaccine-derived immunity. This merits more investigation, perhaps by mediated immune studies of young children to see whether they really are adequately protected when vaccinated at 12 or 13 months of age. Dr. Vessey commented that a robust and consistent cellular assay is needed for little children.
- Dr. Florian Schoedel, Merck: However, the measles example also holds some differences. Re-immunization with measles vaccine or vaccination with pre-existing antibodies did not produce a good take. The second dose boosted antibody titers little; the increased vaccine effectiveness pertains mostly to catch-up or converting people not yet converted. As seen from Dr. Vessey, this is dramatically different with the varicella vaccine, which provides a ten-fold higher antibody titer with dose 2.
- Dr. France: *Have you checked for different responses among atopic children and children with eczema and asthma?* Dr. Vessey: Yes. A couple of risk factors appeared to be supported by atopy. Those children's immune-generated immune response may differ, but we could not detect that with our method of measuring antibody response.
- Dr. Orenstein: *Did you analyze other outbreaks to see if the epi curve seen in the explosive New Hampshire outbreak was paralleled, and perhaps due to intense exposure rather than*

waning immunity? Dr. Galil: Our review of published and available unpublished information on overall attack rates among unvaccinated susceptible children showed most to have a fairly high cumulative attack rate. We will look with Merck at some of the risk factors in the trial data, which has 700-800 breakthrough cases.

- Dr. Phil Krause, FDA.: The pre-licensure data indicated a likelihood that people with more severe or greater exposures to wild-type virus would develop breakthrough disease. In household exposure studies, vaccine efficacy was ~70%, but the population estimate was 70-90%. It is reasonable to assume that the amount of virus circulating in an outbreak setting is much greater. There may also be reporting bias because the most severe outbreaks will be examined. But overall, the vaccine is performing as expected on approval.
- Dr. Vernon: In 5-10 years, low immunization rates in some areas may result in more serious disease in adolescents, young adults, and pregnant women. Factors contributing to the rate of variability include a lack of enthusiasm about the vaccine and about school attendance requirements, and opposition in some states against government mandates in general, by small citizen groups or even just a few key legislators. Those persons must be convinced to allow the vaccine to progress.

IMPLICATION TO CHILDHOOD IMMUNIZATION DELIVERY FROM OSHA REQUIREMENTS FOR SAFETY ENGINEERED NEEDLES

Ms. Linda Chiarello, RN, MS, of NCID's Division of Health Care Quality Promotion, led this presentation for NCID and also for OSHA, in the absence of the latter's scheduled speaker.

NCID Perspective. *Prevention of needle stick injuries during immunization.* There is limited information on needle stick injuries during immunization. Although the overall associated risk of transmission of blood-borne virus transmission is low, those events are costly in terms of treatment (post-exposure prophylaxis – PEP) and emotional costs (particularly exposures to HIV or hepatitis C). Most needle sticks are preventable, but that requires a multi-faceted approach, including safer technology.

Epidemiology. One published Canadian study showed an injury rate during immunization of 1:9000 vaccinations, but that fell to 1:19,000 when clean injuries were dropped. Descriptive data of the National Surveillance System for Health Care Workers (NSSH) indicate 80% of 16,000 blood exposures to be sharps-related injuries. Of 239 immunization exposures, 37%

were IM and 66% were subcutaneous or intradermal. Almost half (44%) of injuries occurred during needle insertion or withdrawal, or when the patient moved. The latter are largely not preventable with current technology. The other 56% occurred post-vaccination (e.g., clean-up, recapping, disposal). An NCID analysis of needle stick preventability determined that no current injection procedure can prevent injury during use in the patient. Prevention is only effective after the device's withdrawal.

Risk factors for occupationally bloodborne virus transmission, shown in prospective studies of exposed health care workers, are: 1) percutaneous injury exposure to hepatitis B virus: 6-30% risk; 2) hepatitis C: 1.8%; HIV percutaneous exposure: 0.3%. Virus-specific differences influence transmission risk.

ACIP recommendations and OSHA regulations have greatly reduced the annual incidence of hepatitis B transmission to health care workers. With more workers being immunized, this should decline even further. The risk for hepatitis C virus is believed to be similar to HIV. HIV data on occupational transmission is the most complete: through June 2000, 49 health care workers acquired HIV through a percutaneous exposure and most (38%) involved a hollow-bore needle.

Prevention strategies include safer device technologies, work practices (point-of-use sharps disposal, discouraging needle recapping); safety awareness (training, an institutionalized “safety culture”). The challenges to a safer technology include the absence of a clear definition of a safe syringe for injection. Current options include sliding sheaths that lock after use, additions to needle construction to cap the needle after use, and retractable needles. Product selection in immunization programs include clinical considerations, worker concerns (e.g., ease of use), safety features (e.g., ability to activate with one hand), and patient considerations (completeness of medication delivery, minimized discomfort). *Future strategies* for immunization needle stick prevention include needle-less administration (e.g, intranasal, skin patches, and jet injection).

OSHA Perspective

Ms. Chiarello provided a brief time line of OSHA's sharps-related regulations:

The OSHA Blood-Borne Pathogen Standard was implemented in 1991. It applied to all employers with staff who could reasonably anticipated exposure to blood or other potentially infectious materials. Only three aspects have significantly changed: the exposure control plan

(engineering/work practice controls and PPE) and record keeping requirements (maintenance of a sharps injury log).

Subsequently, a September 1998 OSHA request for information on safer technology in health care settings convinced them that safer technology could prevent needle stick injuries, especially in health care settings. Twenty-three states mandate the implementation of safer technology, some of which overlap with OSHA laws. In 1999, OSHA updated their compliance directive, providing guidance to interpret and enforce the blood-borne pathogen standard in health care settings.

Finally, in November 2000, the Needle Stick Safety and Prevention Act mandated OSHA to clarify and revise the 1991 Blood-Borne Pathogen Standard. The update added definitions of engineering controls and implemented new requirements in the exposure control plan. Non-managerial staff (representative, front-line workers) must participate in selecting safer technology, and a new sharps injury log was instituted.

OSHA requirements for immunization programs in this performance-oriented standard are that; 1) the employer must identify worker exposures to blood or a potentially infectious material; 2) review all processes and procedures with exposure potential (e.g., how immunizations are provided in a health care setting) 3) ensure that processes are in place to reduce the opportunity for a needle stick injury to the workers; and 4) annually re-evaluate processes or procedures.

The requirements of engineering and work practice controls are admittedly confusing. “Appropriate engineering controls” are determined on a case-by-case basis. An engineering control could be a sharps disposal container, self-sheathing needles, or safer medical devices that isolate or remove the blood-borne pathogens hazard from the workplace.

Needle-less systems were defined as any needleless injection equipment that is currently available. A non-needle sharp or a needle with a built-in safety feature mechanism that reduces the exposure risk is termed an engineered safety device, or a SESIP. Several were outlined.

The employer must:

1. Evaluate available engineering controls that would be applicable in this case to an immunization setting, implement those that are appropriate for the setting, and train

- employees on the safe use and disposal of these devices.
2. Document how the devices were evaluated prior to implementation, and document the implementation in the exposure control plan.
 3. Update this at least annually regarding new devices or technologies and determine their appropriateness for implementation.

NIP Survey

Dr. H. Yusuf, of the NIP's Division, of Immunization Services, reported on an August e-mail survey done of immunization program managers on their awareness of revised OSHA standards, use of SESIPs for immunization, staff training on SESIPs, perceived barriers to SESIP implementation. Results were:

- 88% responded.
- 90% were aware of the revised OSHA standards.
- 40% of immunization programs had disseminated SESIP-related information to their public sector clinics.
- 25% conducted SESIP-related training in public clinics.
- Very few programs disseminated information or conducted training in private sector clinics.
- 30% reported SESIPs currently used to vaccinate children in most or all of their public sector clinics, and about the same percentage to vaccinate adolescents and adults at those sites.
- In order, barriers to SESIP use were: additional cost, identification of suitable SESIPs, securing new contracts for manufacturers of SESIPs, need for additional space on availability of pre-filled syringes with SESIPs, disposing current pre-filled stocks that do not have SESIPs, and staff resistance to change.
- Preliminary national cost estimates to use SESIPs to vaccinate children aged 0-3 annually depended on various factors (device used, private or public sector, etc.).
 - ▶ Standard syringes were estimated at ~\$.05/syringe and SESIP syringes at ~\$.43.
 - ▶ ~31 million annual vaccine injections are given to children aged 0-3 years using public purchase vaccines, for a total SESIP cost of ~\$11.6 million. The ~28 million vaccine doses administered to 0-3 year-old children using private purchase vaccines involves an additional cost for SESIPs of ~\$10.6 million. The public sector vaccines administered in the private sector (e.g., through VFC) would cost ~\$5.4 million and ~\$16.8 million for the private sector.

Partnership options to disseminate information to immunization providers include OSHA, the AAP, ASTHO, and other organizations' fact sheets and Websites. The NIP and OSHA could jointly develop tools to help immunization providers meet the requirements (e.g., describing criteria for evaluating SESIPs, evaluating/documenting evaluation, and documenting needle stick episodes).

Discussion included:

- Dr. Modlin: *Has there been a cost utility analysis of these expensive devices' prevention effectiveness?* The Government Accounting Office attempted that nationally, mostly in hospital settings, but that is hard to extrapolate to all health care settings. It also depends on, and was most cost-effective with the cost of severe injuries, high PEP, and high frequency of seroconversion. Dr. Modlin wished to see that analysis.
- This is seen as another federal mandate no reimbursement increase. The AAP also has expressed its own concerns about the feasibility of implementation.
- Dr. Foster reported attempting to implement some of these devices' use. OSHA provided little guidance on the mandates, which include a requirement to keep records for 30 years post-employment. He felt that an educational program alone would decrease some injuries. The new devices require an extra step before readying the syringe, and the needle shield also has a significant (0.1) dead space, inferring potential under-vaccination and wastage during a vaccine shortage. Dr. Yusuf reported NIP' receipt of inquiries about the dead space issue. Discussions with FDA revealed that they consider that in the licensing procedure, but such concerns should be brought to the attention of the FDA's Compliance Division and the manufacturer.
- Dr. Smith: California's legislation preceded OSHA's and has been implemented, aided by a Sharps Workgroup. Some devices were found to be more useful than others.
- Dr. Chen: While injection safety was probably "the single largest iatrogenic disaster of the 20th century" globally, immunizations is only a small part (<5%) of all injectable use. The OSHA rules are driven by non-immunization-related injection safety concerns.
- Dr. Wexler: *Does OSHA require medical settings to have a plan to be in place by July 21 or actually to be using safety devices?* Ms. Chiarello: The new requirements took effect in April, and there are several months for implementation prior to the enforcement phase. An inspection would look for an exposure control plan that considers the safer technology and has implemented what is "appropriate," however that is defined. Questions should be directed to OSHA. But she agreed with Dr. Chen that many immunizations occur in the

context of other health care, so injections may not be the immediate priority for some health care settings.

- Mr. Zeal Rosenberg, of Beckton Dickinson: Federal and state health workers are not covered by this, but there is a House bill vote expected soon that would extend all these regulations to state and federal health workers. Ms. Chiarello: Some states have OSHA plans, so some public workers are not covered and others are.
- Dr. Pickering: This may be a self-correcting problem, since already two hepatitis preparations include such protective devices, but educational materials are needed to guide physicians. Dr. Yusuf: Yes. CDC would like to develop a tool to educate immunization providers. OSHA and NIOSH and others have expressed an interest in partnering on that.
- Dr. Zink: Glaxo SmithKline provides an optional purchase of a safety needle device with their pediatric hepatitis vaccines, and are monitoring its adoption in immunization practice. They plan to use it with Infanrix® and eventually for adult vaccines as well. The estimated added cost is ~30-40 cents. Dr. Yusuf: The cost analysis used 43 cents per SESIP, but the costs vary by device.

ADAPTATION OF A VACCINE FORMULARY SELECTION ALGORITHM TO A WEB-ACCESSIBLE TOOL

Dr. Bruce Weniger, of the NIP, introduced a new Website tool, inspired by the greater number of selections required by providers since the introduction of combination vaccines. The NIP developed a vaccine selection algorithm tool to help them select among competing monovalent or combination vaccines. The principles were: 1) to achieve the lowest overall cost according to objective economic criteria, and 2) to provide such transparent formulae and methods so as to allow the manufacturers to reverse-engineer the process to assist pricing decisions for a new vaccine; and 3) to recognize the difference between vaccine products. This technique of an industrial engineering laboratory was adapted to be accessible on the Web.

The algorithm involves several potential economic criteria. Vaccine price involves the number of doses required, preparation time, administration route, cold chain and other storage issues, safety/efficacy profile, etc.

The model, developed by industrial engineers at the University of Illinois and Southern Illinois University, was then adapted to the Web by Austral Engineering and Software, Inc., with CDC funding. Dr. Sheldon Jacobson, of the University of Illinois at Urbana-Champaign, described that

adaptation. A collaborative effort across government, industry, and academia, its purpose is to assist health care professionals in making some vaccine formulary choices, and ultimately to automate this procedure to help determine a “best value” formulary in a very user-friendly environment.

The operations research model, which helps find optimal ways to allocate scarce resources, includes the ACIP recommended childhood immunization schedule, the cost components described by Dr. Weniger, vaccine constraints (e.g., brand matching of DTaP) and other factors. The model can be updated to address new constraints and more cost components. The vaccine selection algorithm rapidly searches through a large possible set of vaccine products to ultimately determine the “best value,” lowest-cost vaccine formulary. Potential Website users include vaccine purchasers (public and private sector), health insurance companies, and vaccine manufacturers.

Dr. Enrique Medina, of Austral Engineering and Software, then demonstrated the Website (www.vaccineselection.com). It lists the vaccine by number and brand name, federal and private sector price, package mode (vial, syringe, powder), and cost per dose (which depends on the packaging; e.g., liquid 0.75). Vaccines can be added, a useful tool for manufacturers to estimate the competition for a hypothetical product. The clinic visit and injection costs (if additional) are entered and matched to the vaccines considered, producing a “shopping list” for that particular vaccine formulary selection.

In discussion, Dr. Clover asked: 1) if the same manufacturers' vaccines were used for the routine 2,4,6-month vaccinations; and 2) if the algorithm prioritizes price as the sole outcome or the number of different types of vaccines the provider would have to have in order to get the lowest price. Dr. Weniger answered that every vaccine available in the U.S. in all its product formulations is accessible on the table, by formulation (e.g., 10 single-dose vials or 5 single-dose vials). The practitioner can specify any detail for calculation. But one variable not in the algorithm is the economic value of reducing the total number of different vaccines stored in a physicians refrigerator. It only looks at the cost of the vaccine, the preparation costs, and the number of doses required and then optimizes the lowest cost mix.

Closing Comments. Dr. Clover announced that the Yellow Fever Workgroup would hold a conference phone call in the next three weeks.

Public Comment. Dr. Modlin called for any comments from the public, to no response. He and Dr. Snider thanked Ms. Kovach and her staff for all the work they do throughout the year, to committee

applause. Thereupon, the meeting adjourned at 1:14 p.m.

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

John Modlin, M.D., Chair

Date