Meeting Minutes

Advisory Committee on Immunization Practices

June 21-22, 2000

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GEORGIA
June 21-22, 2000
Atlanta

Agenda Item	Purpose/Action	Presider/Presenter(s)
June 21, 2000		
8:00 Welcome		Dr. J. Modlin (Chair, ACIP) Dr. D. Snider (CDC, OD)
8:30 ACIP recommendations for the Pneumococcal conjugate vaccine Update on revised cost-effectiveness evaluation VFC vote Are any revisions needed to current ACIP draft statement?	Information Discussion Decision VFC Vote	Dr. D. Johnson (Mich Dept of Hlth.) Dr. Tracy Lieu (Harvard) Dr. B. Schwartz (NIP,ESD) Dr. C. Van Beneden (NCID, BMD)
9:30 BREAK		
10:00 ACIP recommendations for the pneumococcal conjugate vaccine - CONTINUED		
11:00 VFC Update Analysis of survey	Information	Mr. D. Mason (NIP, ISD)
11:30 Vaccine Additives: Aluminum update Puerto Rico meeting report	Information	Dr. M. Myers (NVPO)
12:00 LUNCH		
1:00 Vaccine additives: Thimerosal update Introduction and background Progress reports and projections for supplies of vaccine without thimerosal as a preservative Studies of blood levels of mercury following vaccination Analysis of vaccine safety datalink data Overview Analysis Independent Assessment Consultants' Report Consultants' Report Policy Options Public Comment for Thimerosal Vote Future Research	Information Discussion	Dr. R. Bernier (NIP, OD) Dr. F. DeStefan (NIP,ESD) Dr. Wm. Egan (FDA) Dr. M. Gerber (NIH) Dr. P. Stehr-Green Dr. T. Verstraeten (NIP,ESD)

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Agenda Item	Purpose/Action	Presider/Presenter(s)
June 21, 2000		
3:00 BREAK		
3:30 Vaccine additives: Thimerosol update - CONTINUED		
5:30 Bioterrorism Working Group Draft anthrax recommendation Vaccine Health Care Center Network Update from smallpox working group	Information Discussion Decision Draft Statement	Dr. D. Ashford (NCID,DBMD) Dr. C. Helms (Univ of Iowa) Dr. M. McNeil (NIP, ESD) Dr. L. Rotz (NCID,DBMD)
6:15 Public Comment		
6:30 **ADJOURN**		
June 22, 2000		
8:00 Unfinished Business from Previous Day		Dr. J. Modlin (Chair, ACIP)
8:30 General Recommendations Progress towards recommendation Immunization records of foreign adoptees Format of harmonized schedule	Information Draft Statement	Dr. W. Atkinson (NIP, ISD) Dr. C. Le (Kaiser Permanente) Dr. D. Peterson (Minnesota Dept. of Hlth.)
9:15 Update on Influenza Vaccine Supply Who should receive the vaccine?	Information Discussion Decision	Dr. K. Fukuda (NCID, DVRD) Dr. R. Levandowski (FDA) Dr. J. Singleton (NIP, ESD)
10:45 BREAK		
11:15 Global Alliance for Vaccines and Immunization Progress in supporting global immunization programs and introduction of new vaccines	Information	Dr. S. Hadler (NIP, OD)
11:45 Progress Report on Vaccine Identification Standards Initiative (VISI) Any suggestions prior to disseminating for the "public comment" phase	Information Draft Report	Dr. Weniger (NIP,ESD)
12:00 Rotavirus Vaccines Update on Geneva meeting - effect of ACIP decision on rotavirus vaccination by WHO VSD analysis of intussusception and Rotavirus infection	Information	Dr. R. Chen (NIP, ESD) Dr. P. Kramarz, (NIP, ESD) Dr. P. Offit (Children's Hosp. Phili)
12:30 LUNCH		

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Agenda Item **June 22, 2000**		Purpose/Action	Presider/Presenter(s)
1:30	Status of High-Speed Needle-Free Jet Injectors for Mass Vaccination Campaigns, for Pandemic Influenza or Bioterrorism	Information Discussion	Dr. B. Weniger (NIP,ESD)
2:15	Vaccines and Autism Summary of data: American Academy of Pediatrics meeting Measles Vaccine and Inflammatory Bowel Disease	Information	Dr. F. Destefano (NIP,ESD) Dr. N. Halsey (J. Hopkins Univ.)
2:45	CDC/FDA Report on Two-Dose Schedule for Hepatitis B for Adolescents	Information Discussion	Dr. W. Egan (FDA)
3:15	Nabi Conjugated bivalent *S. aureus* Vaccine - StaphVax™ Introduction to StaphVax™ Use in populations at risk of *S. aureus* infection	Information Discussion	Dr. S. Fridkin (NCID,HIP) Dr. G. Horwith (Nabi)
3:45	Updates National Center for Infectious Diseases National Immunization Program Food and Drug Administration Vaccine Injury Compensation Program National Vaccine Program	Information	Dr. A. Mawle (NCID, OD) Dr. W. Orenstein (NIP, OD) Dr. W. Egan (FDA, CBER) Dr. G. Evans (HRSA) Dr. M. Myers (NVPO)
4:30	Public Comment		
4:45	ADJOURN		

ACIP June 21-22, 2000

ATTENDEES:

Committee Members
Dr. John Modlin (Chair)
Dr. Dennis Brooks
Dr. Richard Clover
Dr. Fernando Guerra
Dr. Charles Helms
Dr. David Johnson
Dr. Chinh Le
Dr. Paul Offit
Dr. Margaret Rennels
Dr. Lucy Tompkins
Dr. Bonnie Word

Ex Officio Members
Dr. James Cheek (IHS)
Dr. William Egan (FDA)
Dr. Geoffrey Evans (HRSA)
Dr. Randolph Graydon (HCFA)
Dr. Carole Heilman (NIH)
Dr. Martin Myers (NVPO)
Dr. Kristin Nichol (VA)
Dr. David Trump (DOD)

Liaison Representatives
Dr. Jon Abramson (AAP)
Dr. Stanley Gall (ACOG)
Dr. Bruce Gellen (IDSA)
Dr. Barbara Howe (PRMA)
Dr. Randolph Jackson (NMA)
Dr. Victor Marchessault (NACI)
Dr. Paul McKinney (ATPM)
Dr. Jim Norton (AAHP)
Dr. Georges Peter (NVAC)
Dr. William Phillips (AAFP)
Dr. Larry Pickering (AAP)
Dr. Jose Santos (HICPAC)
Dr. Bill Schaffner (AHA)
Dr. David Wilson (AMA)
Dr. Richard Zimmerman (AAFP)

Executive Secretary
Dr. Dixie Snider

Office of the Director
Dr. David Fleming
Mr. Don Schriber

Office of the General Counsel
Kevin Malone

Office of Public Affairs
Barbara Reynolds
Tom Skinner
Charlis Thompson

EPO
Sharon Bieh

National Center for HIV, STD, and TB Prevention
Tim Mastro

National Center for Infectious Diseases
Lynnette Brammer
Joe Bresee
Carolyn Bridges
Burnadette Burder
Scott Campbell
Suzanne Cotter
Nancy Cox
Roz Dewart
Thea Fischer Perch
Keiji Fukuda
Roger Glass
Rima Khabbar
Amy Khon
Jessica Llenig
Maureen Lynch
Eric Mast
Alison Mawle
Erin Murray
Jan Nicholson
Liza Rotz
Ann Schuchat
David Shay
Chris Van Beneden

National Center for Infectious Disease - continued

Thomas Verstraeten
Fran Walker
Cyndi Whitney
Mira Zader
Elizabeth Zell

National Immunization Program

Melissa Adams
William Atkinson
Angie Bauer
Roger Bernier
Bob Chen
Susan Chu
Gary Coil
Jose Cordero
D. Datta
Frank DeStefano
Elizabeth Fair
Bill Gallo
Paul Gargiullo
Edith Gary
Kristen Goliber
Penina Haber
Stephen Hadler
Wendy Heaps
Beth Hibbs
Saron Holmes
Erik Hummelman
Sonja Hutchins
Marika Iwane
Laurie Johnson
Suzanne Johnson-DeLeon
Laurie Kammoto
Sharon Katz
Duane Kilgus
Maureen Kolasa
Mary Lambert
Carla Lee
Hugh Mainzer
Tasneem Malik
Dean Mason
Mehran Massordi
Mary McCauley
Michael McNeil

National Immunization Program - continued

Gina Mootrey
Trudy Murphy
William Nichols
David Nelson
Rick Nelson
Glen Nowak
Dennis O'Mara
Walter Orenstein
Mark Papania
Bindi Patel
Tim Petersen
Robert Pless
Amy Poel
Bette Pollard
Vitalli Pool
Vishnu-Priya Sneller
Dianne Quarterman-Ochee
Susan Reef
Jameka Reese
Lance Rodewald
Susan Scheinman
Judy Schmidt
Joanne Schulte
Ben Schwartz
Aby Shefy
Jim Singleton
Bob Snyder
G.G. Sommerville
Shannon Stokley
Ray Strikas
Kathy Taevers-Solis
Jackie Tate
James Watt
Darma Weaver
Bruce Weniger
Melinda Wharton
Matt Widsom
Craig Wilkins
Skip Wolfe
Ed Yacovone
Masilu Zanaka
Fangian Zhou
Laura Zimmerman

NVPO
Sandra Browning
Shaunette Crawford
Brian Foy
Alicia Postema
Dan Riedford

Other Government Attendees
Leslie Ball, FDA
Norman Baylor, FDA
M.M. Braun, FDA
Lenore Gelb, FDA
Michael Gerber, NIH
LTC John Grabenstein,US Army SGO
Albert Kapikian, NIH
Roland Levandowski, FDA
David Morens, NIH
Phillip Pittman, DOD
Doug Pratt, FDA
Lone Simonsen, NIH
Barbara Stya, FDA
James Veazey, FDA

Others Present
Murray Abramson, Merck Company
Sherman Alfors, Glaxo Wellcome
Liz McKee Anderson, Wyeth Lederle
Bescom F. Anthony, Biologics Consulting Group
Lynn Bahta, Immun. Action Coalition
Sharraine Banks, ASTHO
Joe Beaver, Tennessee Dep't of Health
John Bluff, Merck
Michael Blum, Wyeth-Ayerst
Mike Borota, Connecting with Kids Network
John W. Boslego, Merck Company
Jerry Bowman, AAP
Jillian Caneton, Cohn & Wolfe
Dan Casto, San Antonio, Texas
Andrea Cawein, Lyeth-Lederle
Jill Chamberlain, Vaccine Bulletin
Ray Chiang, Merck
Hillel Cohen, Merck Company
Kevin Connolly, Merck

Others Present- continued
Lenore Cooney, Cooney/Waters
Louis Cooper, Nat'l Network Immunization Info
Mike Cooper, Reuters
Dack Dalrymple, Bailey & Dalrymple
Bill Darnall, Merck
Geroge Davis, ParkeDale Pharma.
Jaime Deseda, University of Puerto Rico
Natalie Devare, Wyeth Company
Richard Dinovitz, Wyeth
Frank Dzvonik, SmithKline Beecham
Craig Engesser, Wyeth Lederle
Michele Erstein, Cohne & Wolfe
Ali Fattom, Nabi
David Fedson, Aventis Pasteur
Helen Fingar, Wyeth-Lederle
Beverly Gaines, National Medical Assoc.
Ronan Gannon, SmithKline Beecham
Bruce Gellen, Vanderbilt
Jayne Gilbert, Chiron
Ruth Gilmore, GA Immunization Prog
Jesse Greene, SC Department Health
Kenneth P. Guito, Aventis Pasteur
Neal Halsey, John Hopkins University
Jannet Hammond, Glaxo Wellcome
Phil Hasegana, Merck
Bill Hausdroff, Wyeth Company
Penny A. Heaton, Merck
Luit Heyjes, SmithKline Beecham
Gary Horwith, Nabi
Phil Hosback, Aventis Pasteur
Sharon G. Humiston, Univ. of Rochester
Robbin Itzer, Merck
John Jabara, SmithKline Beecham
Van Hoff Johan, SmithKline Beecham
Erik Joller, CDC Immunization Hotline
Clare Kahn, SmithKline Beecham
Bronwen Kaye, American Home Products Corp.
Stephanie Keith, North American Vac.
Michelle Kirsche, Slack, Inc.
Ann Kohrt, Pennsylvania
Fred Lake, Cooney/Waters
Len Lavenda, Aventis Pasteur
Edgar Ledbetter, Nat'l Network Immunization Info.
Myron Levin, Univ. of Colorado

Others Present- continued
Tracy Lieu, Harvard
Rick Linder, SmithKline, Beecham
Scott Litherland, Parallax Comm.
Mike Lombardo, Merck
Harold Lupton, Aventis Pasteur
Ann MacSperi, SmithKline, Beecham
Lugene Maher, Wyeth-Lederle
Melissa Malhame, Merck
Michelle Mattie, Aventis Pasteur
Paul Mendelman, Aviron
Marc Merritt, Monarch Pharm. Inc.
Kathryn Metcalfe, Cohn & Wolfe
Marge Mitchell, Merck
Jean Mologerak, GA Immunization Program
Joanne Monahan, Merck
David Muth, Nabi
Stan Music, Merck Company
Brian Newby, Meningitis Foundation
Carla Newby, Meningitis Foundation
Sam Nickerson, Bioject
Susan Noonan, Merck
Gerry Outer, Policy Analysis Inc.
Emma Patten, Infection Control Advisory Network
Diane Peterson, Dept. of Health
David Pill, Assoicated Press
Wayne Pisano, Aventis Pasteur
Jane Quinn, Merck
Manuel Ramos, Wyeth
Scott Ratzan, Academy for Advancement of Hlth.
Kevin Reilly, Wyeth
Lynn Redwood
Anne Roger, Parallax Communication
Zeil Rosenberg, Becton Dickenson
David Ross, Merck
Fred Ruben, Aventis Pasteur
Jordon Rubenson, SmithKlein, Beecham
Jerald C. Sadoff, Merck

Others Present- continued
Paul Sanders, Merck
Robert Seith, Connecting with Kids Network
Kristine Severyn, Ohio Parents for Vaccine
Florian Schodel, Univ. of Munich
David Schoenfield, SmithKline, Beecham
Jodee Shay, Wyeth-Lederle
Judith Shindam, Aventis Pasteur
Alan Sievert, Cobb County Board of Hlth
Gary Siskowski, Nabi
Parkah Smith, International Medical News Group
Dan Soland, SmithKline, Beecham
Dale R. Spriggs, Biochem Pharma
Ted Staub, Aventis Pasteur
Paul Stehr-Green, Univ. of Washington
Stacy Stuerck, Merck
John Talarico, NYS Dept. of Health
Dirk Teuwen, Aventis Pasteur
Eric Thrash, Wyeth-Ayerst
Peter Tobar, Wyeth-Lederle
Miriam Tucker, Pediatric News
Joe Vazquez, Merck
Tom Vernon, Merck
Peter Vigliarolo, Conney/Waters
Ted Vigodsky, WABE-FM/CBS Radio
Robert Walker, Aviron
Richard Ward, AAP
Beth Waters, Cooney/Waters
Virginia Watson, Cooney/Waters
Tip Weniger, Atlanta, GA
Melanie Weniger, Atlanta, GA
Tim Wenz, Ketchum
Deborah Wexler, Imm. Action Coalit.
Matt Wilcox, Aventis Pasteur
David Wineadon, SmithKlien, Beecham
Steven Wright, Holland & Knight
Richard Zakark, McKesson Bioservices
Robert Zeldin, Marion, Pennsylvania

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Advisory Committee on Immunization Practices
June 21-22, 2000

June 21, 2000

The Centers for Disease Control and Prevention convened a meeting of the Advisory Committee on Immunization Practices (ACIP), June 21-22, 2000 at the Four Points Hotel in Atlanta, Georgia. Dr. John Modlin, Chairman of the ACIP, called the meeting to order at 8:30 a.m.

Dr. Snider welcomed everyone to the meeting and introduced two new ex-officio members joining the meeting: Dr. Carole Heilman, National Institutes of Health; and Dr. James Cheek, Indian Health Service. Dr. Snider recognized Dr. Phillips as an additional liaison representative of the American Academy of Family Physicians. Introduced to the Committee were Dr. James Nordin representing the American Association of Health Plans in the absence of Dr. Eric France and Dr. Bruce Gellin representing the Infectious Diseases Society of America for Dr. Samuel Katz. Dr. Snider expressed his appreciation to Dr. David Trump, Department of Defense who will leave his present position in July and is attending his last ACIP meeting as a DOD representative, and to Dr. Yvonne McHugh, who has resigned as the representative of the Biotechnology Industry Organization.

Dr. Snider asked all members to send an updated curriculum vita to Ms. Gloria Kovach by July 1 via email to acip@cdc.gov. He reminded the Committee that the telephone and fax numbers for the ACIP are 404-639-8096 and 404-639-8520, respectively. The next meeting of the ACIP will be held October 18-19 at the Marriott Century Center. The Year 2001 meetings are scheduled for February 21-22, June 20-21, and October 17-18.

Dr. Snider reviewed the instructions for public comment during the meeting; he cautioned that casual comments are received during the meeting, but must be kept within the time allotted for the topic. Those who wish to address the committee are requested to sign in at the back of the room. Dr. Snider then reviewed the seating of committee members, liaison representatives, and ex officio members. He reminded members of the audience and the Committee to use the microphones and identify themselves when addressing the Committee.

The ACIP charter gives the Executive Secretary, or designee, the authority to temporarily designate the ex officio members as voting members. This will not take place unless there are less than seven appointed members not qualified to vote due to a financial conflict of interest. The ex officio members will be formally requested to vote when necessary.

We will have 11 appointed members present. Seven members constitute a quorum, I urge the members to be prompt in returning from lunch and break.

Dr. Modlin welcomed the new representatives and guests. He briefly reviewed some of the contents of the members' notebooks. He informed the audience that there is a photographer in the room, and the possibility of television crews attending the meeting. Those who do not wish to be photographed, should take notice of their location. He announced that the working group would be meeting tonight, so there are no dinner plans for the whole committee.

Dr. Modlin then requested that ACIP members who may have a potential conflict of interest should make it known. Conflicts include any relationships with vaccine manufacturers. All members regardless of a conflict may participate in discussions of all issues provided that full disclosure of potential conflicts of interest have occurred. However, the person(s) with a direct

conflict may not vote on any issue related to the conflict. There is an exception to this requirement. There are particular requirements pertaining to attendance at scientific meetings. You are required to disclose both honoraria and travel support received during the past twelve months. Travel support is considered a de minimus interest which having been disclosed, does not prohibit you from voting. In addition, honoraria that does not exceed $1,000 per year per entity is also considered de minimus and does not require recusal from voting. Amounts over $1,000 annually do require abstention from voting.

Members with financial conflicts of interest must abstain from voting on the Vaccines for Children resolutions. Since a conflict may also appear to be present if such a member is allowed to introduce or second a VFC resolution, ACIP has adopted a policy that prohibits a member with financial conflicts of interest from introducing or seconding a VFC resolution. He asked voting members to disclose any financial conflicts and then reviewed the rules and exceptions.

Members who stated no financial conflicts of interest were:

- Bonnie Word, State University of New York
- Charles Helms, University of Iowa Hospital and Clinics
- Lucy Tompkins, Stanford University
- David Johnson, Michigan Department of Community Health
- Dennis Brooks, Johns Hopkins School of Medicine
- John Modlin stated he had no conflicts, but had participated in advisory board meetings for Smith Kline Beecham and Aventis Pasteur for which travel expenses were reimbursed.

Members who stated a conflict of interest were:

- Richard Clover, University of Louisville School of Medicine: he and his department have projects with Merck, Smith Kline, Wyeth Lederle.
- Chinh Le, Kaiser Permanente Medical Center: Kaiser Permanente has vaccine research projects with Wyeth Lederle, Merck, Aventis Pasteur, Smith Kline, and North American Vaccine. At times, he serves as sub-investigator, but no portion of his salary comes from these research activities. He received a $400 honorarium from Smith Kline for a lecture on lyme disease.
- Margaret Rennels, University of Maryland School of Medicine, has vaccine contracts with Merck, Wyeth Lederle, Aventis. She has participated on the Data Safety Monitoring Board for Smith Kline Beecham and has given grand rounds that have been supported by unrestricted educational grants from Wyeth Lederle.
- Fernando Guerra, San Antonio Metropolitan Health District: his department has projects with Smith Kline Beechman, Merck, Aventis. He serves as principal or co-investigator with North American Vaccine and has served as a consultant to Smith Kline, Merck, and North American Vaccine.
- Paul Offit, The Children's Hospital of Philadelphia, is a co-holder on a patent for a vaccine developed by Merck and has given grand rounds that were supported by an unrestricted grant from Merck.

ACIP Recommendations for the Pneumococcal Conjugate Vaccine

Dr. Modlin reviewed the reasons for scheduling this topic on the agenda. He stated that there is new information that bears on the economic impact and effectiveness of polysaccharide vaccine for those children over two years of age. Most children's risk drops after 24 months of age, and varies with some racial groups; early data did not show a natural place to draw the line for immunizations, catch-up immunizations, etc.

Dr. Dave Johnson summarized the presentations and introduced Dr. Ben Schwartz.

Dr. Schwartz stated that some major concerns of the Committee regarding the pneumococcal conjugate vaccine program were related to the cost and the previous analysis. The private sector cost is $58 per dose; $232 total cost for 3 primary doses and booster for each infant. The societal breakeven cost is $46 per dose. When this analysis had been done, not all data had been compiled and costs had come from Kaiser Permanente, so national costs may not be reflected. The vaccine manufacturer supported the analysis. Dr. Schwartz emphasized that the manufacturer's support had not caused a bias in fact, but could have some bias in perception. Therefore, several activities were initiated, including a reanalysis of the cost effectiveness and cost benefit. An evaluation of other outcome measures such as willingness to pay and cost per quality adjusted life year will be presented to the committee next year. Dr. Copeland's ethics panel will review ethical considerations. An evaluation of VFC costs will be presented later this morning.

Dr. Schwartz urged committee members to focus greater attention on the sensitivity and future areas of research – not the costs.

Dr. Schwartz explained the 3 categories of the re-analysis, which are:

- baseline analysis – impacts where data are sufficient to include in the model
- sensitivity analysis – some data exists, but magnitude of effect cannot be determined
- areas for future research – likely areas, but areas where data are currently insufficient.

Dr. Schwartz then turned the presentation over to Dr. Tracy Lieu.

Dr. Lieu acknowledged those who contributed to the analysis and reviewed the differences between the original analysis and the re-analysis. Meningitis, bacteremia, pneumonia, and otitis media were included in the re-analysis. The re-analysis included two different perspectives – that of the health care payer and the societal perspective. The health care payer perspective includes only medical costs. The societal perspective costs includes medical, non-medical, parent time costs, and losses from future productivity when a child dies or is disabled. Original analysis did not include psychological costs. She cautioned the committee that presenting only breakeven costs gives everyone a false sense of precision; there is a range of uncertainly around the analyses.

Dr. Lieu stated that the review panel had recommended more than a dozen revisions in baseline analysis, revisions in sensitivity analysis on issues thought to have important effect, and identified important areas for future research.

Dr. Lieu reviewed some of the differences in data used and how they affected the costs. The original analysis was conducted using1997 dollars; the reanalysis used 1999 dollars making the vaccine more attractive. New data on otitis media caused societal breakeven cost to go down by $4.

The review panel recommended using cost data from another source besides the original Kaiser Permanente and substituting Medicare data. The American Association of Pediatrics raised questions with using Medicare data for a population of children. The review panel contacted Medstet for data on outpatient visits with children. Using the Medstet data, the breakeven costs went down by $2. Wholesale drug costs were also used which further decreased the breakeven costs. The vaccine administration costs were changed to the average Medicaid reimbursement rate, decreasing the breakeven costs by $4. Two changes for calculating parent-time costs were recommended – use of the average national wage rates and inclusion of all time spent caring for

child, not just time away from work. Unfortunately, no data is available for non-work time lost. These changes resulted in an increase in societal breakeven costs by $4.

When all changes are incorporated, the breakeven cost goes down to $40 from a societal perspective. The cost per life year saved goes up to $110,000. From the health care payer perspective there's very little change in either number.

Sensitivity Analysis and Future Research

Dr. Lieu reviewed the various results from several sensitivity analyses conducted, which include:

- 40-100% of current testing and treatment for children 3-26 months – breakeven costs $2-5 increase
- Additional reduction in antibiotic use – increase of up to $1
- Adding the pneumococcal conjugate vaccine to the infant immunization schedule, an additional 10% of children would return to their health care providers for vaccines – increase of $1 to $2 dollars

The changes in cost of vaccination of children in daycare vary with the age group.

Dr. Lieu reviewed some of the issues flagged by the review panel such as, if the addition of the pneumococcal conjugate vaccine causes other vaccines to be deferred; will it hurt the coverage rates of other vaccines, and will it cause additional visits to health care providers. There is also a need to compare vaccines to other health care interventions, a need to develop a standard for determining effectiveness of vaccines, and a need to look at mortality and morbidity.

Dr. Lieu summarized other issues to be presented to the committee at a later date. They include:

- Herd immunity
- Estimates of uncertainty
- Complete querying Medstet for cost analysis data and possibly extending the model

Discussion

Dr. Le questioned two issues: the impact of day care centers in older age groups, and how the vaccine will decrease the work-up for febrile children. He expressed concern of making sweeping conclusions with limited data.

Dr. Modlin asked Dr. Abramson to elaborate on how the daycare center issue is handled by the American Academy of Pediatrics. Dr. Abramson stated that the risk in daycare is equal to the risk in African-American children. Dr. Le stated that the data from the paper by Levine et al. of daycare centers is contaminated by the high degree of African-American children and further questioned the validity of using the data.

Dr. Peter Paradiso from Wyeth updated the Committee on contract negotiations. Details such as delivery sites and monthly reports have not been finalized; reduction in costs for the VFC program has not been finalized, but is in the 20%-25% range.

Dr. Schwartz reminded the Committee that the two groups that will be considered in each vote.

Dr. Van Beneden reviewed the three options for the ACIP recommendations, which are:

Option 1: ACIP draft recommendations (February 16, 2000)
PCV7 is recommended for the following:

- Infant immunization
- Catch-up vaccination of children age less than or equal to 23 months
- Children 24-59 months of age from the following groups at high risk of disease: SCD/asplenia, HIV+, chronic illness or immunocompromised, Alaska Native, American Indian, and African-American descent

Vaccination with PCV7 should be considered for all children 24-59 months of age, with priority given to:

- Children attending group child care*
- Children who are socioeconomically disadvantaged
- Children who had frequent or complicated acute otitis media in the previous year

Option 2: AAP recommendations (May 31, 2000)
PCV7 is recommended for the following:

- All children less than or equal to 23 months of age
- Children age 24 to 59 months at high risk of invasive disease (greater than or equal to 150 cases/100,000), including HIV+, SCD/asplenia, chronic illness or immunocompromised

A single dose of PCV7 or PPV23** may be given to children 24 to 59 months of age, with priority given to:

- Children 24 to 35 months of age
- Children 36 to 59 months of age who
  - are of American Indian, Alaska Native, or African-American descent, and
  - attend out-of-home child care

Option 3: ACIP Working Group alternative (May 2000)
PCV7 is recommended for the following:

- Infant immunization
- Catch-up vaccination of children age less than or equal to 35 months
- Children 36 to 59 months of age from the following groups at high risk of disease: SCD/asplenia, HIV+, chronic illness or who are immunocompromised

Vaccination with PCV7 should be considered for all children 36 to 59 months of age, with priority given to:

- Children of Alaska Native, American Indian, and African-American descent
- Children attending group child care *
- Children who had frequent or complicated acute otitis media in the previous year

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* Group child care defined as: a setting outside of the home where a child regularly spends ≥ 4 hours per week with at least two unrelated children under adult supervision.

** PPV23 is an acceptable alternative to PCV7, although an enhanced immune response and probably reduction of nasopharyngeal carriage favor the use of PCV7 "whenever possible" (draft AAP recommendations as of 5/31/00).

Dr. Van Beneden highlighted the differences among the three options into four major areas:

- Upper age limit for universal childhood vaccinations
- Clarifications on the recommendations for Native Americans (including Alaska Natives and American Indians) and African Americans
- Recommendations for premature infants
- Use of the polysaccharide vaccine as an alternative in older children

Dr. Van Beneden reviewed statistics from Kaiser Permanente that supported the recommendations for premature infants, and compared the efficacy, immunogenicity, and safety of the conjugate and the polysaccharide vaccines using data from recent studies.

Dr. Modlin introduced Ms. Carla Newby of the Meningitis Foundation of America and she gave her comments on the pneumococcal conjugate vaccine. Ms. Newby, whose child died from meningitis, expressed concerns with the recommendations of the American Academy of Pediatrics. She urged the Committee to vote to recommend the routine use of Prevnar in all children up to age five. (A copy of her comments were distributed to all attendees.)

Dr. Modlin asked Dr. Pickering or Dr. Abramson for an update on the recommendations of the AAP. Dr. Pickering said that a recommendation has been approved, put on the organization's Web, and distributed to the AAP membership. The considerations for the recommendations include:

- Thorough evaluation of the scientific data
- Ability to implement these recommendations in physicians' offices
- Considerations of the FDA
- Input from the AAFP and the CDC

Dr. Modlin then asked Dr. Zimmerman or Dr. Phillips for an update from the American Academy of Family Physicians.

Dr. William Phillips reviewed the basic types of policy for the organization: standards, guidelines, practice options; and reviewed the history for the development of the recommendation. The recommendation is:

> *The AAFP recommends pneumococcal conjugate vaccine for children less than 24 months and for children less than 60 months with high risk conditions, that is sickle cell, HIV, functional and anatomical asplenia and pneumococcal conditions and chronic illnesses, and for African American, Alaska Natives and American Indians. The AAFP regards this a practice standard. Implementation will take time and resources. The AAFP regards the vaccination of the children 24-59 months, including those who attend child care settings and with frequent otitis media is a practice option.*

He expressed concerns about expanding the recommendation beyond the February meeting.

Dr. Modlin reminded everyone that a policy was adopted in February and that it can be used as a starting point. He reviewed the two major points surrounding the vote, which are:

- Age for routine recommendation
- Indications for catch-up vaccination

He then opened the meeting to discussion on the topic.

Dr. Rennels commented that any recommendations that are in conflict with the AAP recommendation for age would only cause confusion and economic as well as political problems. Dr. Le agreed and cautioned the committee on the efficacy of the vaccine for otitis media according to the data presented by Dr. Lieu.

Discussion followed regarding committee members' option preferences: inclusion of African-American, Alaska Native, and American Indian groups; effect of socioeconomic status; flexibility of decision making within the individual physician's office; word-smithing of the recommendation; inclusion of future benefit for populations that will be at risk for other conditions, such as Hispanics; and combining the vaccine with the annual flu vaccine.

Dr. Johnson made a motion that ACIP consider more emphasis on the conjugate vaccine in the 24-59 month age group; and that the African-American and Native American children 24-59 month age group should be considered for vaccination. He also recommended that the committee drop the inclusion of otitis media in the final recommendation.

Dr. Modlin asked Drs. Johnson and Van Beneden to work on the language and bring the topic to a vote after lunch or on tomorrow.

Dr. Schwartz reminded the committee of two issues that need to be included in any vote of the committee: the use of conjugate vaccine followed by polysaccharide vaccine, and the vaccination of premature infants. He also reviewed advantages and disadvantages for coverage for the permissive group, the recommended group, parts of each group, and cost information.

At full implementation (regardless of recommendation made by committee) the cost would be $491 million. Other options include covering children less than 24 months of age and in high-risk categories for a cost of $184 million for VFC; covering all children less than 59 months of age, the increment in cost would be $49 million for VFC; covering highest risk children in permissive group, the cost increment would be $24 million dollars for VFC.

Discussion followed regarding the inclusion of administration costs, how the VFC program affects other vaccine programs and funding, VFC eligibility, and ratios of VFC versus non-VFC covered populations.

Dr. Schwartz stated that he had prepared five options and presented the following recommendation: VFC coverage for all infants and children six weeks through 59 months of age with priority being given to groups identified as high-risk and as moderate-risk.

Dr. Graydon of the Health Care Financing Administration commented that we may be taking VFC coverage beyond what we are recommending for children in the general population, that we are taking data to turn the conversation around to make the case to extend VFC; and that maybe we need to look at the basic recommendation again.

Dr. Schwartz clarified that permissive and recommendations could all be included in the VFC program.

Dr. Word asked how a physician knows who's VFC eligible. Dr. Schwartz responded that VFC program information is distributed to VFC program providers.

Dr. Modlin asked that Dr. Schwartz review all of the other options, which are:

- Coverage through 59 months
- Coverage through 35 months
- Coverage reflecting the recommendations from the committee in February
- Coverage including out-of-home child care

Discussion followed regarding word-smithing of the recommendation. Dr. Schwartz suggested that he make the modifications during lunch and present to the committee later for the vote. Dr. Modlin agreed.

Vaccines for Children (VFC) Program

Dr. Mason provided a brief history of the Vaccines for Children (VFC) program. The program was enacted in 1993 and now has full participation in all 50 states to provide a more equal access to vaccines for all children. It places emphasis on service and minimizes bureaucracy. Vaccines covered by the VFC program are determined by the resolutions evaluated by ACIP. Funding is through the Grant 317 program and state support. Any child through 18 years of age, who is Medicaid eligible or uninsured, who is American Indian or Alaskan Native, or served through federally funded health centers is eligible. There are 44,500 sites, not providers, enrolled in the program. Both vaccine and administrative costs continue to increase, reflecting additional vaccine and vaccination of additional groups.

Dr. Mason reviewed the results of a recent survey in which 100% of the project participated: the program is fully operational and well-received; annual budget expenditures increase as new vaccines are added; project policies regarding provider choice, public purchase, and distribution of vaccines remain consistent from year to year. He emphasized that vaccine accountability must be a major focus for the future. However, funding to purchase vaccines will continue to remain complex.

Discussion and questions followed regarding the presentation.

Dr. Schwartz summarized the resolution including the proposed changes in wording. All infants and children from six weeks to 59 months of age would be eligible and would include the ACIP-identified groups at highest risk and moderate risk. The recommended schedule would reflect the content of the ACIP statement. It would be three doses and a booster for those children beginning the series at less than 6 months of age; those beginning between 7 and 11 months, it would be two doses and a booster; those beginning between 12 months and 23 months would be a two dose without a booster. After 23 months, healthy children would receive a single dose, others two doses. Children in high-risk groups would receive the polysaccharide vaccine after the conjugate vaccine. American Indian and Alaskan Native children 24-59 months of age may receive the polysaccharide vaccine after the conjugate vaccine. The dosage intervals is two months between dosages with the first dose beginning no earlier than six weeks; booster dose should be administered between 12 and 15 months of age. This resolution replaces the previous resolution and includes use of the polysaccharide vaccine. He also reviewed contraindications and precautions. He noted that the resolution would become effective after the vote and upon publication.

Dr. Zimmerman suggested that the minimal interval be changed from six to four weeks to harmonize with the recommendations of the Working Group.

Dr. Le pointed out that the package insert states "four to six weeks" for the interval.

Dr. Schwartz agreed to change the interval if the committee wishes.

Dr. Modlin asked for clarification on what committee members have conflict that would prevent them from voting. Doctors Le, Rennels, Guerra, Offit, and Clover stated they had conflicts. Dr. Snider stated that there was less than seven public members eligible to vote due to a financial conflict of interest, and therefore designated the ex officio members as voting members.

Dr. Johnson made a motion to accept the resolution as presented and Dr. Helms seconded the motion.

In Favor : Drs. Johnson, Tompkins, Helms, Word, Modlin, Myers, Brooks, Evans, and Trump
Opposed : None
Abstained : Drs. Lee, Rennels, Guerra, Offit, Clover, Egan, Heilman, and Mr. Graydon
Decision : Passed

Dr. Johnson presented highlights of the proposed recommendation: The conjugate vaccine would be recommended for infants and children less than or equal to 23 months of age and children 24-59 months of high risk. PCV7 should be considered for all children 24-59 months of age with priority given to children of Native American and African-American descent, children in out-of-home child care, and those aged 24-35 months.

Dr. Johnson noted the clarification for the conjugate vaccine, which has been added to the proposed recommendation, which is: PPV 23 is licensed for use with children 2 years of age or older who are at high-risk for pneumococcal infection. The PCV7 vaccine has advantages over the PPV23, which include: induction of immune memory, reduction in carriage, probable higher efficacy against serotypes causing most invasive disease, and likely effectiveness against non-invasive syndromes. If pneumococcal vaccine is to be used among healthy children 24 to 59 months of age, ACIP recommends that PCV7 be used and not PPV23.

Dr. Le questioned the use of the last three words "and not PPV23" in the statement. Discussion followed. Dr. Modlin asked for input from other committee members.

Dr. Tompkins stated that she prefers the way the resolution is currently written (with the strike out of the last three words). Dr. Peter asked if "children who are socioeconomically disadvantaged" group were intentionally omitted from the recommendation and urged that the group be included. Dr. Johnson stated that the group would be noted in the text, but not in the table.

Dr. Helms made a motion that the resolution be adopted with the minor changes as discussed. Dr. Tompkins seconded the motion.

In Favor : Drs. Johnson, Tompkins, Heilman, Modlin, Trump, Myers, Evans, and Mr. Graydon
Opposed : Drs. Word and Brooks
Abstained :Drs. Le, Rennels, Guerra, Offit, Clover, and Nichol
Decision : Passed

Dr. Le suggested some minor changes to the draft. Dr. Modlin asked Dr. Le to pass the changes on after the meeting. Dr. Modlin thanked the presenters and noted the accomplishment as a milestone.

Vaccine Additives: Aluminum Update

Dr. Martin Myers updated the committee on the proceedings of the Aluminum in Vaccines Workshop held in San Juan, Puerto Rico on May 11-12. Summaries of the meeting will be put on the National Vaccine Program Office's web site and proceedings will be published. The goals of the workshop were to: establish a better understanding of the role and need of aluminum as an adjuvant in vaccines; explore the possibility of adverse events due to the use of aluminum in vaccines; and develop a research agenda to expand existing knowledge on the impact of aluminum on the human body. Dr. Myers presented highlights of three sessions: Use of Adjuvants in Vaccines, Aluminum Pharmacotoxicology, and Macrophagic Myofasciitis (MMF); and a summary of the findings of the meeting, including:

- A variety of aluminum salts have useful physicochemical and immunogenic properties that lend these minerals to use in vaccines
- 70 years of experience: safe and effective
- Reduction in the number injections and the amount of antigen per dose
- Decreased toxicity of some antigens
- Enhanced Ag presentation; type 2 immune response
- IM is less reactogenic than SC
- More pharmacokinetic data are needed, but there is an apparent wide margin of safety
- MMF is likely a consequence of the normal immune response
- MMF may be a serendipitous finding in patients with ascending myalgias and fatigue

Dr. Modlin thanked Dr. Myers and asked for questions.

Vaccine Additives: Thimerosal Update

Dr. Bernier reviewed the history removing thimerosal from vaccines and previewed the presentations to follow. In July 1999 a joint statement was issued by the Public Health Service, AAP, and later agreed to by AAFP, to remove thimerosal from vaccines as soon as possible. In October 1999 ACIP issued a statement confirming the goal in the joint statement; and recommended that vaccines containing thimerosal be used until the goal could be achieved. He then asked representatives from each of the five vaccine manufacturers for an update on the activities for removal of thimerosal from their products.

Mr. Phil Hosbach of Aventis Pasteur stated that removal of thimerosal from the company's vaccine Tripedia is a high priority; it is reducing thimerosal until only trace amounts remain and is asking for an expedited review by the FDA. The company has an active license for the next generation of vaccine, which does not contain thimerosal.

Dr. Tom Vernon of Merck stated that all of the company's vaccines are thimerosal-free with the exception of a syringe-based hepatitis-B vaccine. Within six weeks the company will be filing a thimerosal-free version of the vaccine.

Dr. Steve Keith of North American Vaccine stated that the company's supply of thimerosal-containing vaccine is almost depleted, and that it expects to file a thimerosal-free vaccine with the FDA in the next couple of months. All future products will be thimerosal-free.

Dr. Barbara Howe of Smith, Kline, Beecham stated that the company has three products licensed for use in pediatrics, all thimerosal-preservation free as of April 2000.

Dr. Peter Paradiso of Wyeth stated that the company has a number of products that contain thimerosal; however, they are moving forward with eliminating the preservative from its vaccines.

Dr. Egan of the FDA reviewed progress of the removal of thimerosal-containing vaccines over the past year. He stated that letters were sent to manufacturers last July, requesting information on their plans for removal of thimerosal, and recently asked for updates on their plans. He then reviewed the FDA activity:

- Merck was licensed for a thimerosal-free hepatitis B vaccine.
- Smith-Kline Beecham was licensed for a greatly reduced-thimerosal-containing formula of hepatitis B vaccine.
- Wyeth announced that the HIB single-dose thimerosal-free vaccines would be available in July.

DTaP is the only remaining thimerosal-containing vaccine.

He commended the manufacturers on their accomplishments and stated that the FDA is committed to expedited reviews of the applications and supplements.

There were no questions for the manufacturers or Dr. Egan.

Blood Mercury Levels

Dr. Michael Gerber presented data from studies that looked at blood mercury levels in infants before and after receiving vaccinations.

Dr. Schwartz questioned the sensitivity of the assay used for all types of mercury. Dr. Gerber stated that the assay was sensitive to all forms. An unidentified speaker asked if the study would be extended to include children of other ages and look at gender differences. Dr. Gerber stated that was possible if done quickly before all vaccines become thimerosol free.

Analysis of Vaccine Safety Datalink Data

Dr. Frank DeStefano provided a background on the Vaccine Safety Datalink Project (VSD), a collaborative project between the CDC and four HMOs. The project began in 1991 with three HMOs. Adolescents and adults were added to the project later, but today's presentation focuses on the data surrounding children. The HMOs send various data from their administrative and medical databases to the CDC: vaccination records, medical event information (hospitals, emergency room and outpatient visits), and patient demographics. The Project links the various databases. He explained the basic study parameters for reviewing the data for thimerosal-containing vaccine related conditions, and then introduced Dr. Tom Verstraeten for a presentation on the analysis of the data.

Dr. Verstraeten described the findings from the VSD screen analyses. The study consisted of two phases: the first, a screening of the data for neurological and renal impairments related to thimerosal-containing vaccines; the second phase, a hypothesis testing of any hypothesis generated during phase I. The phase I study restricted the cohort to children born between 1992 and 1997 into the Group Health Cooperative of Puget Sound and Northern California Kaiser-Permanente HMOs, and had received at least 2 polio vaccines by one year of age. The investigation team calculated each subject's cumulative exposure to ethyl mercury at the end of the first, second, third, and sixth months of life using data from automated vaccination records.

Among the outcomes, the investigation team found a statistically significant positive correlation between the following measures of exposure and outcomes:

- Cumulative exposure to thimerosal-containing vaccines at 2 months of age and unspecified developmental delay;
- Cumulative exposure at 3 months of age and tics;
- Cumulative exposure at 6 months of age and attention deficient disorder (ADD);
- Cumulative exposure at 1, 3, and 6 months of age and language and speech delay;
- Cumulative exposure at 1, 3, and 6 months of age and neurodevelopmental delays, in general.

Based on these results, the investigation team concluded that a possible association exists between certain neurologic developmental disorders and exposure to mercury from thimerosol-containing vaccines before the age of six months.

Dr. Verstraten pointed out the limitations for the study and analysis:

- Potential for misclassification of exposure
- Use of thimerosal-free vaccines in the population is possible
- Limited information on weight of children
- Potential for misclassification of outcomes
- No information on some factors that could affect the medical care utilization, such as socioeconomic status or race and ethnicity
- Insufficient power for some conditions

He then reviewed some of the activities performed to overcome some of these limitations.

The design for phase II was similar to that of phase I. Harvard Pilgrim Health Care was the source of the data for phase II. These precise data contained information on the weight of children, which allowed for more analysis. However, the Harvard results do not confirm the VSD results for speech delay and ADD.

Dr. Modlin opened the discussion to questions for design and conduct of studies as well as the results.

Dr. Nordin expressed concern about using the group with no mercury exposure as a baseline. Dr. Verstraeten agreed and stated that the group was chosen for clarity. Dr. Modlin added that the children did get two polio vaccines, some had some vaccinations. Dr. Le asked if other compounding factors were considered for speech delay and family structure. Dr. Verstraeten said that they were, but did not affect the estimates. Dr. Jackson asked how the various terms for some diagnoses were standardized. Dr. Verstraeten agreed that that was a serious limitation of the study. Dr. Nichol asked if the study was able to adjust for health care utilization. Dr. Verstraeten said that it did not change the adjustments. An unidentified speaker from Aventis Pasteur asked if there were any differences in the way the disorders identified were treated; or if the diagnoses were clustered in any group of physicians. Dr. Verstraeten explained the differences and discussion followed. Dr. Offit asked what the working hypothesis is between the two phases and Dr. Verstraeten explained.

Dr. Paul Stehr-Green presented a report from a meeting of independent consultants on the review of Vaccine Safety Datalink information on thimerosal-containing vaccines. A group of 11 consultants and 49 other resource specialists were asked three major questions:

1. Did the data in the Vaccine Safety Datalink (VSD) Project warrant further investigation?

2. If the observations constituted a signal, did they support a causal relationship?

3. If the observations do constitute a signal, what are the next steps, in priority order, to further investigate a potential relationship?

He then reviewed the consultants' issues of concern:

- A reasonably strong possibility of an ascertainment bias related to the apparently increased health care-seeking behavior among parents of subjects receiving the highest doses of thimerosal-containing vaccines
- The inexactness of the diagnoses of the neurodevelopmental outcomes of interest and the consistency of these diagnoses across clinician, clinics, and HMOs
- The meaning and significance of the exposure estimates used in this screening analysis
- The possible impact on the lack of data reflecting familial/genetic predispositions to the neurobehavioral outcomes of interest in these analyses
- Limited ability of these analyses to distinguish between the possibility of elevated risks attributable to thimerosal from those that may have been induced by other components of the vaccines or other vaccine-related associations

The group felt that further investigation should be done as soon as possible. The consultants agreed that these results, by themselves, couldn't be used to support or deny a causal relationship. This opinion was based on consideration of the criteria for causality: temporal association, basic criterion met; strength of association, weak statistical association, consistency, minimal evidence; dose-response, modest evidence; biological plausibility, unconvincing evidence; specificity/reproducibility, minimal evidence. The consultants suggested the following next steps:

- Reanalysis of the VSD data
- Analysis of other administrative datasets
- Pharmacokinetic studies in humans
- Toxicological and neurodevelopmental studies in experimental animals
- New epidemiologic studies designed to control a priori for potential biases, to better define and ensure the quality of diagnoses on outcomes of interest, and to collect data on other relevant factors

Dr. Stehr-Green referred the committee to the full summary report for further detail.

Dr. Modlin opened the discussion to questions. An unidentified speaker asked if the consultants considered exposure to other metals. Dr. Zimmerman commented that the criteria become more negative with more data.

Dr. Modlin thanked Dr. Stehr-Green for his presentation, and asked Dr. Bernier for a presentation of the options before the committee.

Dr. Bernier again reviewed the events in terms of the vaccine supply, and presented the three options, which are:

A. Continue the current policy of moving rapidly to vaccines which are free of thimerosal as a preservation. Until an adequate supply of each vaccine is available, use of vaccines which contain thimerosal as a preservation and vaccines which do not is acceptable.

B. State an explicit preference immediately for vaccines which do not contain thimerosal as a preservation. If only vaccines which contain thimerosal as a preservative are readily available, vaccinate infants and children with these vaccines.
C. State an explicit preference immediately for vaccines which do not contain thimerosal as a preservative. If only vaccines which contain thimersol as a preservative are readily available, postpone vaccination until vaccines which are free of thimerosal as a preservative can be obtained.

Dr. Bernier then reviewed some of the factors important to consider in choosing any of these options.

Factors in favor of Option A: consistent with evidence existing at this time; would cause minimal disruption in coverage; would avoid adding complexity and confusion if product-specific recommendations were including; maintains current number of vaccine suppliers, keeping competition up and prices down; doesn't expose providers to great liability. Factors against Option A: would continue to exposure infants to mercury; may not fully address public concerns; does not provide the strongest incentive to manufacturers; if subsequent research finds mercury levels do have effects, then cases of disease would not have been avoided.

Factors in favor of Option B: further reduce exposure to thimerosal-containing vaccines; potentially better address public concerns; would give more incentives to manufacturers to remove thimerosal; potential number of infants harmed would be less than under Option A; would achieve the goal faster than Option A. Factors opposing Option B: supply of thimerosol-free vaccines is not available; would risk decreasing in coverage and increase in disease might occur if supply or understanding of the policy occurred; more liability to suppliers; evidence does not justify this option at this time; risk of financial loss due to unused supply.

Factors in favor of Option C: provide greatest amount of reduction in exposure to thimerosal; provides the strongest incentive to manufacturers; sends the strongest signal regarding vaccine safety; eliminates the possibility that additional infants would be harmed. Factors opposing Option C: increased disease incidence; favors a specific manufacturer, thereby possibly harming other manufacturers; current evidence does not support this Option; possible financial losses due to loss of use of current supplies.

Discussion
Dr. Tompkins pointed out that Option B might have a boomerang effect in public confidence and preferred Option A. Dr. Brooks concurred. An unidentified speaker asked for clarification with "thimerosol-free" and "thimerosol-reduced" wording. Dr. Bernier stated that "thimerosol-free" is used to refer to both in his presentation. The amounts of thimerosal in vaccines containing such are considered clinically insignificant. Dr. Offit stated that he supports the view of Dr. Tompkins and Dr. Brooks, as did Dr. Le. Dr. Guerra asked for comments on substitutes planned for thimerosal. Dr. Egan pointed out that a switch to single-dose vials would eliminate the problem as they have no preservatives.

Dr. Modlin asked for a summary of what substitutes are available. Dr. Bernier stated that there are two preservatives – 2-phenoxyethanaol and phenol – used in pediatric vaccines.

Dr. Modlin asked for comments from the representatives of the academies. Dr. Pickering stated that he would need to check with the AAP board, but thought that they would favor Option A. Dr. Phillips of the AAFP stated that they would be concerned about the mixed message to providers, and supports Option A and to move toward thimerosal-free vaccines. Dr. Helms

stated support for Option A. Dr. Neil Halsey made a couple of points: there still is some vaccines that contain thimerosal; he suggested a limit of one thimerosal-containing vaccine per visit; there will be an underestimation of the public reaction; it will take several years of follow-up to determine the evidence, but it is important to act now. Other speakers commented on various aspects of the data. Dr. John Clements from the World Health Organization congratulated all those involved and stated that the WHO supports the removal of thimerosal from vaccines. He voiced concerned that the data are based on microclimates, and explained the move toward single-dose options in developing countries because of increased costs and volume. The majority of the world's children depend upon multi-dose vials. He encouraged finding an alternative to thimerosal.

Discussion followed regarding data in different countries. Dr. Modlin asked for any comments on Dr. Halsey's recommendation for limited exposure to thimerosol-containing vaccines.

Dr. Modlin asked for those scheduled to give public comment on thimerosal-containing vaccines. Ms. Lynn Redwood, a nurse practitioner in Fayette County, Georgia and a mother of a child with pervasive developmental disorder, a mild form of autism briefly reviewed her child's health history and her awareness of applicable research. Dr. Modlin then read lengthy verbatim comments from Dr. Enayati, Heide Roger, Sallie Bernard, and Teresa Binstock. Each provided examples of family members and research supporting the development of health problems related to mercury, and urged the committee to vote to eliminate the use of vaccines containing thimerosal.

Dr. Snider clarified the policy on public comment. Reading comments into the record is not standard operating procedure; however, this was an exception.

A motion was made by Dr. Johnson to accept Option A. Dr. Brooks seconded the motion. Dr. Snider clarified what committee members could vote: Drs. Brooks, Helms, Johnson, Modlin, Tompkins, and Word. Dr. Snider stated that there was less than seven public members eligible to vote due to a financial conflict of interest, and therefore designated the ex officio members as voting members.

In Favor : Drs. Johnson, Tompkins, Helms, Word, Modlin, Brooks, Myers, Evans, Trump, Mr. Graydon
Opposed : None
Abstained :Drs. Clover, Offit, Guerra, Rennels, Le, Egan, Nichols
Decision : Passed

Dr. Bernier then reviewed the proposed policy of the joint statement on thimerosol-containing vaccines, the policy being:

> The AAFP, AAP, and the PHS reaffirm the goal set in July 1999 to remove or reduce thimerosal from vaccines as soon as possible for the following reasons: 1) the removal or substantial reduction of thimerosal from vaccines is feasible, 2) the progress in removal which has been made to date is substantial, 3) the collaboration of the Food and Drug Administration and the vaccine manufacturers in removing thimerosal is ongoing, and public concern about the use of mercury of any sort remains high. Based on information from the FDA and manufacturers, the PHS projects that the United States will complete its transition to a secure routine pediatric vaccine supply free of thimerosal as a preservative (i.e., at least two vaccine products each for Hep B, Hib, and DTaP) by the first quarter of 2001.

The use of any Hib or DTaP vaccine should continue according to the currently recommended schedule until early 2001. The risk of not vaccinating children on time with DTaP to protect them against pertussis or with any remaining Hib vaccine is believed to far outweight the risk, if any, of exposure to thimerosal containing DTaP and hib vaccines which are still available or still being produced. Any new information from ongoing investigations will be monitored carefully by the PHS to determine if any change in this assessment and in existing recommendation is warranted.

Other vaccines such as diphtheria-tetanus, meningococcal, and influenza vaccines will still contain thimerosal after the first quarter of 2001. Diphtheria-tetanus and meningococcal vaccines are not recommended routinely for children. Influenza vaccine is not recommended routinely for infants under 6 months of age, but should be given to infants and children 6 months of age and older who are at high risk of morbidity and mortality from the influenza virus. Continued use of these products as indicated is recommended until thimerosal is removed or until new products without thimerosal are licensed.

Dr. Bernier then reviewed each section of the joint statement.

Dr. Modlin cautioned the members on getting too involved on wordsmithing, but asked the members for suggestions for change.

Dr. Johnson expressed concern about the clause at the end of the second paragraph, "until early 2001." Discussion followed. Dr. Myers suggested striking the phrase entirely. A speaker identified only as Dr. Offit pointed out that some people only read the summary and suggested adding a statement regarding the evidence to establish some reassurance. He would also suggest restating the actual policy in the statement. Dr. Guerra suggested adding to the third paragraph or as a separate paragraph; something recognizes the importance of continuing to protect developing countries.

Dr. Helms made a motion to accept the policy with the modifications as discussed. Dr. Tompkins seconded the motion. Dr. Modlin asked counsel for clarification on who could vote. Eligibility is the same as the last vote. Representatives of the AAP and AAFP stated that they would need approval from their respective boards for the final wording.

In Favor : Drs. Tompkins, Helms, Word, Modlin, Brooks, Trump, Myers, Egan, Heilman, Evans, and Mr. Graydon
Opposed : None
Abstained :Drs. Offit, Guerra, Rennels, Lee, Nichols
Decision : Passed

Bioterrorism Working Group

Dr. Modlin introduced Dr. Helms who previewed the presentations for this topic:

- the draft of the anthrax recommendation by Dr. David Ashford;
- an update on the Vaccine Health Care Center Network by Dr. Michael McNeil;
- an update on smallpox vaccine by Dr. Lisa Rotz.

He then reviewed the history of the drafting process.

Dr. Ashford reviewed the draft of the statement, which states:

The recommendations concern the use of the aluminium hydroxide adsorbed cell-free anthrax vaccine (Anthrax Vaccine Adsorbed [AVA], BioPort Corporation; Lansing, MI) in the United States for protection against disease caused by *Bacillus anthracis.* Also included is information on the use of chemoprophylaxis against *B. anthracis.*

He then highlighted the changes in the draft since the last meeting. Data from studies have been updated, and statements regarding the DOD studies, long-term health effects of the vaccines, Gulf War illnesses, management of adverse events have been added. Two new sections under "Precautions and Contraindications" have been added – Vaccination during Lactation and Illness. Dr. Ashford reviewed the recommendations and use of anthrax vaccine adsorbed for pre- and post-exposure, as well as the research agenda. Recommendations include antibiotic susceptibility and treatment studies, safety and toxicology studies among pregnant animals.

Dr. Helms opened the discussion to questions. Dr. Stanley Plotkin questioned the completeness of list of proposed research priorities. He suggested adding two: finding a serological correlate of protection and development of second-generation vaccines. Dr. Le pointed out that a statement was noted on page 17. It was suggested to further emphasize the point. Dr. Guerra suggested more emphasis on bioterrorism preparedness efforts on the public health side. Dr. Modlin questioned the appropriateness of such a comment in this document. Discussion followed. Dr. Snider suggested adding a reference to the CDC bioterrorism plan.

Dr. Tompkins made a motion to accept the draft as written as an ACIP Statement of Policy. Dr. Guerra seconded the motion.

In Favor : Drs. Johnson, Tompkins, Helms, Word, Modlin, Offit, Guerra, Brooks, Rennels, Le
Opposed : None
Abstained :None
Absent : Dr.Clover
Decision : Passed

Dr. Helms thanked all contributors to the project.

Vaccine Health Care Center Project

Dr. Michael McNeil described a proposal to establish collaboration with the Department of Defense and the CDC for anthrax activities – Vaccine Health Care Network. Benefits of such as collaboration would be:

- Enhanced reporting of adverse events
- Production of standards of practice for vaccine administration
- Development of standard case definitions for adverse events
- Evaluation to improvement of management of adverse events
- Better detection of adverse effects through data mining and artificial intelligence

He then described the organization, which includes clinical advisory board, a lead center at Walter Reed Army Medical center, and five peripheral sites; and described the composition, requirements and functions of the board, and suggested the name of "Subcommittee for Bioterrorism Agent Vaccines" for the ACIP subcommittee governing the project.

Dr. Snider raised the following issues:

- a subcommittee must be established in the charter of the committee and suggested that a working group could be formed
- conflicts of interest of some members

Discussion followed.

Dr. Modlin expressed an interest and willingness to work on the proposal.

Dr. Rotz updated the committee on activities of the smallpox working group. A statement is being drafted and she reviewed several aspects of the basic outline of the statement, which were:

- Purpose of revising the 1991 statement
- Introduction and background
- Previous recommendations regarding viruses and vaccine usage
- Vaccination recommendations
- Precautions and contraindications in routine and emergency use
- Vaccination administration and interpretation of responses
- Vaccine availability
- Prophylactic use of vaccine
- Research
- Future research and studies

Dr. Modlin thanked Dr. Rotz for the presentation. He reminded those participating in the working group that the meeting would begin at 7:30 p.m. in the restaurant. The second day will start at 8:30 a.m. He adjourned the meeting at 7:05 p.m.

June 22, 2000

Dr. Modlin called the meeting to order at 8:40 a.m. and introduced Dr. Chinh Le for a presentation on the General Recommendations Work Group.

General Recommendations

Dr. Le stated that this is his last meeting and begged indulgence of the committee for him to point out two issues that he has with the pneumococcal conjugate vaccine data presented on Day One of the meeting. He thanked all the mentors who guided him over the years. Dr. Modlin thanked Dr. Le for his service.

Dr. Le stated that the work on the revision of the general recommendations has stalled due to workload, but hopes to have a draft ready in October. He turned the program over to Dr. William Atkinson.

Dr. Atkinson reviewed the current wording of the Acceptability of Vaccines Received Outside of the U.S. recommendation, which is:

> The acceptability of vaccinations received outside the United States depends primarily on whether receipt of the vaccine was adequately documented and whether the immunization schedule (i.e., age at vaccination and spacing of vaccine doses) was comparable with that recommended in the United States. Any doses [with written documentation] administered at the recommended minimum intervals [and ages] can be considered valid.

Dr. Atkinson reviewed available data from several studies: one done by Dr. Margaret Hostetter, who performed diphtheria and tetanus antitoxin titers on 55 children adopted from China, Russia, and Eastern Europe; a study performed by Dr. Jane Aronson at Columbia University, looking at hepatitis B serologic marked among children adopted from other countries. Dr. Hostetter found that 38% of children with written records of 3 or more doses of DTP had adequate antitoxin titers. Only 18% of adoptees who received 3 or more doses of DTP in orphanages had protective levels of antibody, compared to 65% of adoptees who received at least one dose in the local community. In the study performed by Dr. Aronson, she found that about half of the children were adopted from China, and another third from Russia. Among the 96 children with a history of hepatitis B vaccination, only about 53% had detectable hepatitis B surface antibody. Forty-five percent were antibody negative, and 2% were HbsAg positive.

Discussion followed. Numerous comments were made regarding the conflicting data. Dr. Gall pointed out that the pregnant women are also underimmunized. Dr. Abramson repeated that he felt the data were insufficient to make a decision on options 2 and 3. Dr. Modlin asked Dr. Atkinson to present the three options, which are:

Option 1: No change in the current recommendation. Accept doses if supported by written documentation, and if doses comply with current recommended ages and intervals for an accelerated vaccination schedule. All written vaccination records should be examined carefully to ensure compliance with U.S. ages and intervals. Doses not in compliance with U.S. age or interval recommendations should be repeated.

Option 2: Accept documented doses that comply with U.S. recommended ages and intervals, except for children adopted from orphanages from China, Russia, Eastern Europe (or other groups). For these children, all vaccines should be repeated. An alternative method could be to

evaluate and repeat based on the type of vaccine and number of documented doses. For example, repeat all doses of MMR and Hib, repeat all doses of DTaP if 3 doses or fewer of DTP are documented. For children with more than 3 documented doses, consider serologic testing for some antigens (e.g., tetanus antitoxin) to determine the need to repeat some or all doses. Could also suggest testing for other antibody (e.g., rubella, measles).

Option 3: Ignore records and repeat all doses of all vaccines as age-appropriate (i.e., MMR for children 12 months and older, Td rather than DTaP for children over 7 years). This approach assures that all children are fully protected. It also increased the change of local reactions with excessive doses of tetanus and diphtheria toxoids. To avoid this, an algorithm could be suggested for reducing the number of doses of DTaP similar to that given above for Option 2 (e.g., children with more than 3 documented doses, consider serologic testing for diphtheria and/or tetanus antitoxin to determine the need to repeat some or all doses.

Dr. Offit asked if there is an interest in doing another study that would be better powered. Dr. Atkinson said that would be a huge study. Dr. Modlin disagreed. Dr. Guerra suggested that the AAP and AAFP could by survey get more data. Dr. Peter pointed out that these children will be entering school in a few years and what records will be accepted; also questioned the risk with additional doses. Dr. Schwartz questioned the benefit of additional doses versus serology in options 2 and 3. Dr. Kristen Severen from the Vaccine Policy Institute pointed out the varying immunity from vaccines and the lack of a control group in these cited studies.

Dr. Clements of the World Health Organization noted that he made comments quoted in the draft. The WHO's position is that it is more practical to go ahead and give an immunization, than to test because of costs and availability of testing.

Dr. Santos stated that most countries in Latin America have adequate vaccine coverage; the questions come in the supply of vaccines; records are adequate.

Dr. Modlin asked the committee how they felt about making a decision at this time. Dr. Offit said that he felt uncomfortable about making a decision at this time. Dr. Le voiced concerns about enough time to truly bring more data. Dr. Atkinson suggested a prototype wording for the foreign vaccines sections, which is:

> Although some vaccines with inadequate potency have been produced in other countries, most vaccines used worldwide are produced with adequate quality control standards and are reliable. As a result, the acceptability of vaccines received outside the United States depends primarily on whether receipt of the vaccine was adequately documented and whether the immunization schedule (i.e., age at vaccination and space of vaccine doses) was comparable with that recommended in the United States. Only written documentation should be accepted as evidence of prior immunization. Written records may be considered valid if the type of vaccine and exact date of administration (i.e., day, month, and year) are present.
>
> Immunization records for some children, especially those adopted from orphanages from some areas of the world (e.g., Eastern Europe, Russia and other countries of the former Soviet Union, and China), may not accurately reflect protection because of inaccurate or unreliable records or lack of vaccine potency. If there is any question as to whether the immunizations were administered or were immunogenic, the best course is to repeat them.

Administration of vaccine to a child who is already immune, either from prior vaccination or disease, is generally not associated with an increase in adverse reactions, except possibly for tetanus and diphtheria toxoid. Excessive doses of diphtheria or tetanus toxoid-containing vaccines (i.e., DT, DTP, DTaP) may increase the risk for local adverse. For children whose records indicate 3 or fewer doses of diphtheria or tetanus toxoid-containing vaccine, the series may be repeated. For children whose records indicate 4 or more doses, consideration should be given to serologic testing for diphtheria or tetanus antitoxin. Those whose serologic test is negative should have the series repeated. Those with low titers should receive one or two additional doses.

Dr. Modlin and the committee agreed to wait on a decision.

Format of Harmonized Schedule

Ms. Diane Peterson of the Minnesota Department of Health presented a summary of the changes made to the annual childhood immunization schedule based on feedback obtained from immunization providers throughout the year. The formatting changes were made to make the schedule more user friendly. Changes include:

- Expanding the age range to 18 years
- Eliminating the ovals and extend the age range for catchup vaccination
- Introducing color into the bars
- Replacing the instructions with color-coded phrases
- Adding footnotes for new vaccines
- Changing passive to active voice
- Formatting the schedule to fit on one 8-1/2" x 11" page
- Including catch-up charts on the reverse side

Ms. Peterson also reviewed the distribution of the schedule, and noted the availability of schedules for adults and travelers.

Discussion
Dr. Zimmerman would suggest that a catch-up schedule become part of the schedule in the 2000 recommendations.

Dr. Modlin welcomed Dr. David Fleming to the meeting. Dr. Snider recognized the three members whose terms will expire on June 30: Dr. Le, Dr. Fleming, and Dr. Guerra, and expressed appreciation for their efforts. Drs. Le and Guerra expressed their thoughts on leaving the committee. Dr. Modlin noted that Dr. Guerra is completing his second term on the committee and chaired the working group on influenza.

Update on Influenza Vaccine Supply

Dr. Fukuda announced that the influenza working group will be meeting during lunch. He noted that there are some concerns about the vaccine supply for the fall and previewed today's presentations on the subject.

Dr. Roland Levandowski of the Food and Drug Administration (FDA) presented an overview of the influenza vaccine supply for the upcoming season. He began by listing the licensed manufacturers of the influenza vaccine, which are: Aventis Pasteur, Medeva, Parkdale, and

Wyeth-Ayerst. They produced 80 to 90 million doses last year. Vaccine production is expected to be delayed and possibly reduced for the 2000-2001 influenza season, and Dr. Levandowski explained the reasons why. Two of the four manufacturers are experiencing manufacturing problems. Both are working with the FDA and are making corrections. It is unlikely that the other two manufacturers will be able to produce sufficient vaccine to eliminate the shortfall. Second, the yield for this year's influenza A(H3N2) vaccine component appears to be lower than anticipated.

Dr. James Singleton of the National Immunization Program gave an overview of past and expected influenza vaccine use in the United States. He pointed out that not all vaccine produced is actually used. Vaccine manufacturers report to the CDC their total doses distributed, the number of doses returned to them, and the net total (gross-returns). Data compiled from the U.S. Census bureau, the National Health Interview Survey, the Behavioral Risk Factor Surveillance System, the National Nursing Home Survey and manufacturers reports of distributed vaccine, show an upward trend in self-reported influenza vaccination from 1989 through 1999 in the U.S. The highest coverage is among persons aged 65 years of age or older. An upward trend was seen in influenza vaccination coverage among persons with diabetes aged 50-64 and 18-49. He presented data on the estimated number of doses needed for the 2000-2001 year for several groups: persons at increased risk (the majority of which are older adults), health care workers, healthy persons less than 65 years of age, resulting in a total of 56 to 82 million needed doses. The expected demand among persons at increased risk, and health care workers, could be met if at least 45 million doses were available. If 51 to 67 million doses are available, the expected demand from persons at increased risk, health care workers and household of persons at increased risk could be met.

Discussion
Dr. Offit asked what the likelihood of having 45 million doses would be. Dr. Levandowski said that where the supply will be is currently unknown. Dr. Abramson asked if the severity of the disease affect the number of doses given. Dr. Levandowski said probably not; vaccine sales usually decrease in the beginning of November; most of the vaccine is given before the influenza season starts. Dr. Le said that his HMO wastes 50,000 to 70,000 doses in a year, and that getting a flu shot is very much a behavioral issue. In a vaccine shortage, the behavioral aspect becomes more of a factor. David Fenstein of Aventis Pasteur asked if manufacturers would be permitted to export vaccine in a shortage. Dr. Levandowski stated that no curbs are in place affecting the distribution internationally.

Dr. Modlin asked what are the cost implications. Fred Ruben of Aventis Pasteur stated that prices are set prior to the season and contracts are negotiated with the customer, so there would be no change in costs in a vaccine shortfall.

Dean Mason, from the National Immunization Program, stated that the return rate from private doctors is 10% to 14%. The CDC has two contracts with Wyeth and Aventis Pasteur for one million doses each, which have been maxed out with the states. The vaccine price per dose is $2.36.

Dr. Carole Heilman of the National Institutes of Health explained a future project that will look at the 18 to 49 year old population. Previous reports have indicated that a smaller dose of vaccine antigen might produce an acceptable antibody response in this age group. Information from this project may be available in October. Dr. Egan commented on how this information might be important to the FDA.

Dr. Fukuda summarized the scenarios. Best vaccine estimates range widely and the start of the influenza season is never certain. Publicity around the situation could create an artificial vaccine crisis. Clear messages to providers and the public are paramount. Because the majority of vaccine clinics are already planning for vaccination in the fall and the vaccine supply is largely committed already, the window for acting is small. Options for the Committee are:

- Option 1: wait for events to evolve; defer any changes in recommendations and publication of the article in *Mortality and Morbidity Weekly Report*
- Option 2: adopt the proposed modified vaccine recommendations and to implement those recommendations for the coming season; or adopt the recommendations in principle but delay implementation until a certain threshold is met

He then reviewed a draft of the Modified Influenza Vaccination Recommendations for the 2000-2001 Influenza Season. The document focuses on the vaccination of high risk persons and health care personnel in October and November; contingent upon the availability of vaccine, vaccination of other persons who are most likely to transmit influenza virus infection to high risk persons would being in December; after December vaccination would begin of other persons who desire to receive the influenza vaccine.

Issues to consider if the recommendations are approved: implementation of the recommendations would be purely voluntarily, requiring more education of the providers and the public; and, the ability to steer vaccine is limited as the majority of the supply is already committed.

Dr. Modlin summarized the two issues: the recommendation and the timing.

Dr. Zimmerman suggested that all campaigns be delayed one month and a third option for the Committee to consider. Dr. Nichol asked when more information would be available on the nature of the delay and the supply issue, and plan strategies for delay and supply shortfall. Discussion followed regarding the logistics of planning and delaying campaigns. Dr. Levandowski reminded the Committee that only four manufacturers produce the vaccine supply, and every year produce a brand new vaccine. He suggested that the Committee might consider the issue in long term planning as delays and shortfalls may occur annually.

Dr. Modlin stated a consensus: that it is important to get a message out now for planning purposes; that campaigns should be delayed one month; if a true shortage of supply does materialize that high risk groups should be prioritized. Dr. Abramson stated that a delay would not be feasible, considering that many children must have two shots. Others agreed that a delay was not feasible. Discussion followed. Dr. Word suggested adding a statement regarding children receiving multiple doses. Dr. Clover expressed a concern about some of the subsets of the high-risk categories, such as frequent visitors to nursing homes. Fred Ruben of Aventis Pasteur stated that the company is informing its customers of a three-to-four week delay of shipment of vaccine.

Dr. Modlin stated that there is general comfort among the committee members with the content of the draft article and requested Dr. Fukuda to move to publish the MMWR article as soon as reasonable. Dr. Fukuda asked for clarification on the modifications, which are:

- delays are expected, shortages might occur;
- providers should consider delaying adult clinics/campaigns; but pediatric clinics/campaigns to continue on schedule.

Dr. Schwartz asked Dr. Fukuda if written input from the members on wordsmithing was possible. Dr. Fukuda agreed and also asked for input from the manufacturers as soon as possible.

Global Alliance for Vaccines and Immunization

Dr. Hadler presented an overview of the Global Alliance for Vaccines and Immunization (GAVI), a partnership of the World Bank, UNICEF, WHO and the Bill and Melinda Gates Foundation, the Rockefeller Foundation, national governments that are responsible for delivering vaccinations, technical agencies, and the vaccine industry. The goal of the alliance is to accelerate the introduction of new vaccines, to revitalize childhood immunization programs globally, and to support development of new vaccines for less developed countries. The objectives of GAVI are:

1. to improve access to sustainable immunization services
2. to expand the use of all existing cost-effective vaccines
3. to accelerate the development and introduction of new vaccines
4. to accelerate research and development efforts for vaccines and related products specifically needed by developing countries
5. to make immunization coverage an integral part of the design and assessment of health systems and international development efforts

The organization of GAVI is not a vertical structure; it is a series of work groups and committees. The working group (a group of eight members) is the main driving force. GAVI has already received monies to fulfill its mission and Dr. Hadler reviewed the sources. The Gates Foundation has provided a $750 million over five years; the Norwegian government pledged $125 million over a five-year period; the U.S. government has requested $50 million in Fiscal Year 2001; other countries are considering contributions. The fund has three operating accounts: procurement of new vaccines; access and infrastructure for immunization; and research and development of new vaccines (priority on malaria, TB and HIV).

The first meeting of the board was held July 1999 and followup meetings in January and June 2000. Plans are to make funds for procurement of new vaccines and access and infrastructure available for application by July 1, 2000 with review of initial applications the followup month. Awards will be made in August. Eligibility for funds for new vaccines and for access to infrastructure differs with the vaccine coverage. Only countries with per capita GNP less than $1000 and population <150 million are eligible to apply for funding. India, China and Indonesia will be considered separately for funding. Funding will be for a five-year period; coverage surveys and audits will be used to monitor the funding effectiveness.

Fifty-five countries have expressed interest in applying for GAVI funds. Most interest has been shown in the hepatitis B vaccine.

There is a research and development task force in the early organizational stage. Dr.Hadler explained the other activities in immunization of the Gates Foundation, and added that the demand for technical capacity is stretched thin.

Discussion
Dr. Tom Vernon pointed out that there is full collaboration of industry in GAVI, noting that John Jacque Petran of Aventis Pasteur and Dr. Tim Cook of Merck Vaccine Division sit on the board

and working group, respectively. He urged that the collaboration achieved by GAVI be continued in the future in other endeavors.

Dr. Guerra asked about the Rotary International membership in GAVI. Dr. Hadler stated that Rotary was invited to the board meeting, and is not yet a member. He added that there is a concern with GAVI's existence possibly detracting some countries from completing the eradication of polio in their countries. Unidentified speaker pointed out that some previous organizations with similar objectives had failed due to the limited funds and time commitments of donors.

Vaccine Identification Standards Initiative

Dr. Bruce Weniger presented an update of the Vaccine Identification Standards Initiative (VISI). The VISI is a voluntary, cooperative effort among various partners in the vaccine and immunization system to develop guidelines for vaccine labeling in order to enhance the safety of vaccination administration, and avoiding errors in record keeping, written communications, publications and surveillance systems for adverse effects of vaccine. He reviewed the status and gave examples of the components of the initiative, which are:

- Peel-off, bar-coded, stickers on vials and syringes with vaccine identifying information
- Full bar-coding of National Drug Code, lot, number, expiration date on vaccine cartons
- Uniform Vaccine Administration Record Form to receive peel-off stickers
- National Drug Code Database Search Engine for medical practice and immunization registry software developers
- *Vaccine Facts* information sidebar on vaccine cartons
- Standardized vaccine and manufacturer abbreviations

The next steps in the initiative are:

- Develop standardized language for each field in the Vaccine Facts information sidebar
- Announce public comment period
- Review comment, revise, redraft
- Solve challenge of printing small barcodes at high speeds during vaccine filling process
- Find resources for editorial / web / graphics services to reformat narrative text and website
- Publication
- Identify long-term responsibility for ongoing maintenance of NDC database and abbreviation lists

Discussion
Dr. David Fedson of the Aventis Pasteur MSD joint venture asked how the process would be applied outside of the U.S. Dr. Hadler stated that they had a domestic focus on this initiative; the packaging for the U.S. market would need to be changed for marketing in other countries.

Rotavirus Vaccines

Dr. Paul Offit reported on the meeting in Geneva held in February entitled "Future Directions of Rotavirus Vaccine Research in Developing Countries." He focused on the reaction of the World Health Organization to the ACIP decision to withdraw its recommendation for rotavirus vaccine, and presented two issues for committee consideration:

- Risk-benefit ratios of rotashield vaccine in the United States – the WHO criticized the ACIP for not considering the risk benefit ratio
- Strategies to encourage the use of the vaccine in developing countries

Dr. Offit presented data from poster sessions and lectures held during the meeting on the first issue. He stated that final data on intussusceptions and Rotavirus infections are needed before a determination of the risk-benefit ratio can be made. For the second issue, he made three suggestions:

- manufacturers conduct trials in developing countries, so that those countries could make a decision based on data obtained from their own countries, rather than extrapolating it from clinical trials performed in the U.S.
- incentives be given to manufacturers to develop vaccines for use in developing countries even though the vaccines are not recommended for use in the U.S.; sources of funding could be the United Nations or GAVI
- incentives be given to manufacturers for local production of vaccines

Dr. Kramarz presented data from the Vaccine Safety Datalink on intussusception and Rotavirus infection and from the Managed Care Organization Study. He concluded that the Vaccine Safety Datalink data don't confirm association between Rotavirus vaccine and intussusception; and the follow-up data don't support the triggering hypothesis.

Discussion
Dr. Le asked if ACIP reconsidered the cost analysis, would Rotashield come back, considering that the vaccine had already been withdrawn from the market before the ACIP vote was taken. Dr. Egan stated clarified that the vaccine license is still effective, but that no vaccine has been distributed.

Dr. Schwartz asked how ACIP weighs the impact of a decision to remove a vaccine affects how new vaccines are introduced. Dr. Offit replied that we should make the best decision based on how it will affect children in this country. Dr. Abramson stated that what we really need is a safer vaccine. Discussion followed regarding safety. Dr. Zimmerman offered the suggestion of moving into more shared-decision making in vaccines with risk and benefit. Dr. Roger Glass stated that changed in doses and the age in which the vaccine is given could have proven beneficial; and that there was a concern that the vaccine contained more killed antigen than live virus.

Dr. Chen announced that Dr. Kramarz would be leaving the NIP and returning to his native Poland to work with the Ministry of Health, and acknowledged his contributions to NIP.

Status of High-Speed Needle-Free Jet Injectors for Mass Vaccination Campaigns for Pandemic Influenza or Bioterrorism

Dr. Bruce Weniger covered the history, use, and safety concerns of needle-free jet injectors. Several cases of hepatitis B were transmitted in California in 1985 in a weight loss clinic which a needle-free jet injector was used to administer growth hormone. More recently, five devices were studied in several safety tests. In late 1997, the manufacturer of the Ped-O-Jet withdrew the product from the market, and the Department of Defense recalled it from military use. The WHO no longer recommends the use of high-speed devices until they can be proven safe. The current ACIP policy recommends balancing risk and benefit and leaves the decision to health authorities. Dr. Weniger demonstrated several FDA-approved products. Several key challenges

to future development remain: having the end-user fill cartridges; lack of standardized cartridge size, auto-reconstitution of vaccine, size of market, and scarcity of funding for a new generation of devices.

Without safe, high-speed vaccination devices, we may not be prepared to administer vaccine quickly enough in response to a pandemic disease or bioterrorism event. Dr. Weniger presented calculations on the manpower needed to vaccinate a selected population with and without the use of high-speed vaccination devices, indicating manpower may be insufficient without high-speed vaccination devices.

Discussion
Dr. Jackson pointed out that slippage of the injector on the skin could cause a laceration. Dr. Weniger stated that the problem is known and it is recommended that the arm where the vaccination is being given be held firmly to avoid this complication. Dr. Modlin asked how the Committee could be of help. Dr. Weniger asked for moral support to justify financing by CDC and others. Dr. Le suggested exploring routine clinic use as a possible market, especially in consideration of the new OSHA regulations. Discussion followed regarding what is acceptable risk for such a product. Dr. Trump added that without a device, we don't have a trained population for mass immunizations. Dr. Snider suggested considering blood and blood products risk data for information on what is acceptable.

Dr. Modlin departed from the agenda for one topic that was omitted on June 21 – the future research in thimerosol. He spoke for the committee stating that the committee strongly supports future research and hopes to see the fruits of that research.

Vaccines and Autism

Dr. Halsey reported on the "New Challenges in Childhood Immunization" meeting held in Chicago in June. The meeting reviewed three hypotheses generated by investigators in the United Kingdom:

- Measles virus can persist in intestinal tract and possibly contribute to chronic inflammation
- Concurrent exposure to more than one viral infection in childhood can have an increase risk and severity of autism
- Use of MMR has resulted in increased autism

Lectures at the meeting highlighted the history of autism, risk factors, recent data, and review of studies in the planning phase. A writing panel has been formed to pull all of this information together and a draft report will be submitted to the American Academy of Pediatrics by the end of the summer.

Discussion
Dr. Le asked if there was anything in the meeting that changed what Dr. Halsey wrote in an editorial. Dr. Halsey stated that he did learn a lot, but hasn't changed his mind; the process hasn't ended; he's still in the process of gathering data to determine causal effect.
Dr. Pickering said that his mind was not changed but the meeting did elevate the need to devote more funds to the cause, treatment, prevention of autism; ensure that these funds are devoted to the appropriate function; enhance the communication with autism groups. Dr. Jackson requested information on imaging studies. Dr. Halsey stated that the study that he refers to has not been done. Dr. Guerra asked how the meeting information would be disseminated. Dr. Halsey said

that is an Academy decision. Dr. Seven asked how many people attended the conference, and asked who in addition to the CDC funded the meeting. Dr. Halsey said that approximately 100 people attended the meeting; he was not sure who else funded the meeting in addition to the Academy, but no corporations sponsored the meeting.

Measles Vaccine and Inflammatory Bowel Disease

Dr. DeStefano presented data from a study using the Vaccine Safety Datalink. The hypothesis that measles vaccine may be related to inflammatory bowel disease and Crohn's Disease first surfaced in 1995. Subsequent studies did not find an association with the measles vaccine. The debate has since shifted to the question of separating the three antigens in MMR vaccine.

The study using Vaccine Safety Datalink data is the first to specifically study MMR vaccination. Data were from the four HMOs as previously noted in other presentations throughout the meeting. All types of measles-containing vaccine, including MMR were assessed, and disease was restricted to definite or probable cases. One hundred fifty-five cases (one half Crohn's Disease and one half ulcerative colitis) were identified. Most cases had onset between 11 and 19 years of age. The data showed a slightly decreased risk for Crohn's Disease; no increased risk for ulcerative colitis; The relative risk for all inflammatory bowel disease is less than one for MMR vaccine; for other measles-containing vaccines the relative risks are all near one.

If MMR was given at less than 12 months of age the relative risk was less than one, but the decreased risk was not seen for other measles-containing vaccine. No suggestion of an increased risk was shown in any category of MMR or other measles-containing vaccine.

Discussion
Dr. Le asked why children receiving two doses were not studied. Dr. DeStefano agreed that would be a good future study. Dr. Guerra asked if there were any differences in race or ethnicity. Dr. DeStefano said he was not familiar with those data.

CDC/FDA Report on Two-Dose Schedule for Hepatitis B for Adolescents

Dr. Egan of the FDA reported that an FDA decision on Smith-Kline Beecham related to a two-dose adolescent hepatitis B vaccine was tabled until further discussion with the CDC. A harmonized schedule with Smith-Kline Beecham and Merck should be done, and expressed a need for more communication with CDC.

Discussion
Barbara Howe of Smith-Kline Beecham explained that the reasoning for bringing the application for recommendations because of the compelling data. Dr. Egan emphasized the need for communication between the FDA and the CDC. Dr. Snider stated that new language would be included in policies and procedures to facilitate communications among FDA, CDC, and ACIP.

Nabi Conjugated Bivalent *S. Aureus* Vaccine

Dr. Gary Horwith presented an overview of the effects of *S. Aureus* infections. There are 25 million patients hospitalized in the United States each year. S. Aureus is the second most common nocosomial infection, with increased morbidity, mortality and increased health care costs. He reviewed the obstacles in the development of immunological strategies to prevent and treat staphylococci infections, staphylococci physiology and serology, and the mechanism of action of Nabi-StaphVAX®, a polysaccharide conjugate vaccine, new approach to the prevention of S. Aureus infections in high-risk populations.

Dr. Ali Fartom presented an overview of selected data from the phase I, II and III clinical trials, concentrating primarily on the Nabi 1356. The Nabi 1356 is a multi-center, prospective, randomized, stratified, double-blinded, placebo-controlled, phase III trial focusing on the value of active vaccination for the prevention of S. aureus bacteremias in hemodialysis patients. Beginning in April 1998, 1809 patients dialyzed at 70 hemodialysis centers located in Northern and Southern California, some of which are part of Kaiser-Permanente of Northern and Southern California, were vaccinated with StaphVAX. Based upon the estimated infection rate of 0.046 bacteremias per patient year from Kaiser Permanente records, the 1800 subjects would be expected to experience approximately 83 infections during the 2-54 week period. An interim analysis of the data from the trial was undertaken in August 1999 by an independent third party. The analysis included data from 1774 subjects and occurred at a time-point when there were 31 confirmed *S. aureus* bacteremias. The results of the analysis indicated that there was a trend toward protection, and the study was continued. Approximately 56 *S. aureus* bacteremias were recorded for the primary analysis period (weeks 2-54 post-vaccination).

Other studies are planned for groups such as individuals anticipating surgery and nursing home populations.

Discussion
Dr. Guerra asked if diabetes was a co-morbitity for any of the study subjects. Dr. Horwith said they were and Dr. Modlin commented that could be another potential group that would benefit from the vaccine. Dr. Offit asked for clarification on the cause of death of the animals in the study. Dr. Le asked what is the protective level of the vaccine. Dr. Fridkin said that defining the protective level is an objective for future studies. Dr. Pickering asked what were the antibody concentrations in individuals who were not immunized and developed bacteremias. Dr. Fedson of Aventis Pasteur asked if there are plans to study the vaccine in health care workers in preventing nasopharyngeal colonization. Dr. Horwith indicated there are plans for studies in several areas. Speaker identified only as "Stan" asked if localized stalphylococcal disease could be prevented.

Updates

National Center for Infectious Diseases

Dr. Mawle updated the committee on the outbreak of meningococcal disease following Hajj. There have been over 300 cases in 13 countries, including four cases in the United States, two of whom were Hajj pilgrims, and all were presumed vaccine failures. The NCID has been looking at the isolates from Saudi Arabia and other countries and identified the same clone in all of these cases as W-135. The NCID has been invited to Saudi Arabia to review the situation.

Discussion
Dr. Tompkins asked how many different strains there are. Dr. Mawle said that she is not sure how many strains have been identified. Dr. Peter asked if these cases were true vaccine failures and Dr. Mawle clarified that they are presumed vaccine failures.

National Immunization Program
Dr. Orenstein reported on the Institute of Medicine Study on Immunization Finance Policies and Practices. The committee's charge was to:

- Assess overall spending during the 1990s
- Identify state spending patterns
- Recommend current and future funding requirements
- Recommend method for distributing Federal funds
- Identify how to target funds for high-risk populations
- Recommend role of CDC in supporting State adult vaccination efforts

The IOM report recommended that: current vaccine purchase budget is adequate; additional funds are needed for purchasing adolescent/adult vaccines; increase spending for infrastructure; Federal funding should be awarded through a formula, and that the State take more of a role; consistent and comparable measures are needed to monitor coverage in private and public sectors.

Dr. Orenstein reported the progress toward measles elimination in the United States. There is under one case of reported measles per million in this country now. About 100 cases have been reported for each of the last two years; compared to 27,000 in 1990 alone. More and more cases are documented to be due to importations. The NIP concludes that measles is no longer an endemic disease in the United States, but recommends efforts be maintained and improved to ensure immunization coverage levels remain very high and surveillance is of high quality, and that the support for global measles control be strengthened.

Food and Drug Administration
Dr. Egan reported on two topics discussed at a recent meeting of the Vaccines and Related Biologic Products Advisory Committee. They were:

- Potential future rotavirus vaccines. It was a unanimous approval of the Committee to go forward with research into this area.
- Cell substrate use in the development of viral vaccines in tumor cell lines and [/].

Vaccine safety, especially thimerosol and mercury, continues to be a leading issue, and he emphasized that in March, Smith Kline Beecham's thimerosol-free vaccine was approved. He announced that there will be a joint meeting of the TSE Advisory Committee and the Vaccines and Related Biologic Products Advisory Committee on July 27 to discuss two issues: use of fetal calf serum and the use of European-sourced bovine components in preparation of some vaccines.

Vaccine Injury Compensation Program
Dr. Evans of HRSA presented highlights of the report. The Vaccine Injury Compensation Program continues to receive about 12 claims per month. He pointed out that the large increase in the number of claims in 1999 was due to the filing deadline for hepatitis B vaccine claims in August 1999. Of the 285 claims received, only 68 have medical records information. The process is expected to take four to five years because the science surrounding the adverse effects of hepatitis vaccine is fairly new. Many of the claims will have to be reviewed on a case-by-case basis. He pointed out that France has a compensated program and that in about half of the claims they have compensated for multiple sclerosis.

There are only 12 claims to date. The program has paid $1.1 billion to date with $1.5 billion in the trust fund. There has been some controversy on the amount of money in the trust fund. Dr. Evans reviewed the GAO report on this issue. However, the report had no recommendations.

Legislation to include hepatitis A vaccine has been introduced. As of October 1998, rotavirus vaccine has been covered; two claims have been received, both injuries requiring surgical intervention. He noted one problem with some people being covered under the program: anyone who receives compensation must show six months of continual effects. Language has been included in a House Bill to alleviate this concern.

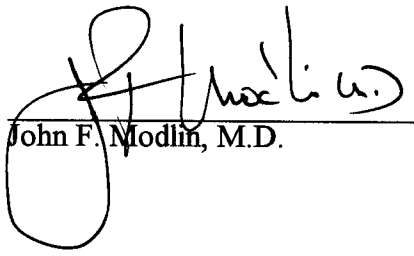
National Vaccine Program
Dr. Myers of the National Vaccine Program Office (NVPO) reviewed the activities of the organization, which facilities and coordinates policy regarding vaccines across agencies:

- Joint statement of AAFP, AAP, ACIP, PHS
- Development of vaccine registry report, with privacy and confidentiality statements
- Workshop on understanding the complexities of vaccine development to prevent chronic diseases such as diabetes
- Establishing a work group to develop guidelines to inventory wild type polio viruses
- Drafting revisions of the Pediatric Immunization Standards and Adult Immunization Standards
- Sponsoring a benefit/risk communication workshop in November
- Development of a benefits/risk assessment economic model for future vaccines
- Establishing guidelines for states in implementing mandates.

Dr. Peter added that comments on the pediatric and adult immunization standards are very much desired.

Dr. Modlin adjourned the meeting at 4:40 p.m.

I hereby certify that to the best of my knowledge, the foregoing summary of minutes is accurate and complete.



19 Oct 00

John F. Modlin, M.D. Date