Department of Health and Human Services
Public Health Service
Centers for Disease Control and Prevention

Advisory Committee on Immunization Practices

October 21-22, 1998

Meeting Minutes

Record of the Meeting Held At:
Atlanta Marriott North Central
Atlanta, Georgia

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Atlanta Marriott North Central - Atlanta, Georgia
October 21-22, 1998

October 21, 1998

Agenda Item		Purpose/Action	Presider/Presenter(s)
8:30	Welcome		Dr. J. Koplan (Director, CDC) Dr. J. Modlin (Chair, ACIP) Dr. D. Snider (CDC, OD)
9:00	Updates	Information	
	Food and Drug Administration		Dr. K. Goldenthal (FDA)
	National Immunization Program		Dr. W. Orenstein (NIP, OD)
	Vaccine Injury Compensation Program		Dr. G. Evans (HRSA)
	National Vaccine Program		Dr. R. Breiman, (OD, NVPO)
	Accreditation for MMWR's		Dr. J. Ward, (EPO,OD)
	Infectious Disease Society of America Vaccine Initiative		Dr. Wm. Shaffner (Vanderbilt Univ.)
10:00	Revised Rabies Recommendation	Discussion	Dr. P. Arguin (NCID, DVRD)
	Inclusion of evidence table	Decision	Dr. C. Rupprecht (NCID,DVRD)
10:30	**BREAK**		
11:00	Public Comment		
11:10	Recommendation for Lyme Disease Vaccine	Information	Dr. D. Dennis (NCID, DVBID)
	Approve background information on Lyme disease	Discussion	Dr. D. Fleming (Oregon Hlth. Div.)
	Approve background information for Lyme disease vaccine	Guidance	Dr. N. Hayes (NCID, DVBID)
	Consider for approval or modification, the specific recommendations for use of Lyme disease vaccine		
12:30	**LUNCH**		
1:30	Progress on *The Guide to Community Preventive Services* Chapter on Methods to Raise Vaccination Coverage Levels Among Children, Adolescents, and Adults	Information	Dr. P. Briss, (EPO, OD) Dr. J. Harris (EPO, DPRAM) Dr. L. Rodewald, (NIP, ISD)
	Overview of the Guide		
	Intervention and what it means to the program		
2:00	Harmonized Immunization Schedule	Discussion	Dr. P. Kilgore (NIP,ESD)
	Approval of changes in the harmonized schedule	Decision	Dr. J. Livengood (NIP, ESD)
3:00	Update on Recent Hepatitis B and DTaP Vaccine	Information	Dr. J. Livengood (NIP, ESD)
	Approval of *Notice to Readers* for Hepatitis B	Decision	
	Approval of *Notice to Readers* for DTaP		
3:15	**BREAK**		

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3:45	**Revised Recommendation for Vaccination of Children Against Hepatitis A** **Routine childhood vaccination in states with rates of hepatitis A greater than the national average** **Discussion on change in current recommendations**	**Discussion**	**Dr. B. Bell (NCID, DVRD)** **Dr. C. Shapiro (NCID,DVRD)**
4:30	**Vaccines for Children Program** **Resolution to include Rotavirus in the VFC Program** **Consolidate resolutions for vaccines included in the VFC Program**	**Discussion** **VFC Vote**	**Dr. J. Livengood (NIP,ESD)**
6:00	**ACIP General Recommendation** **Should ACIP form a working group to revise the present General Recommendation?**	**Discussion**	**Dr. J. Watson (NIP,ESD)**
6:30	**ADJOURN**		

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8:00	**Unresolved Issues from the Previous Day**	**Discussion**	**Dr. J. Modlin (Dartmouth Med. School)**
8:30	**Computerization of ACIP Recommendations** **Adequacy of numeric tables as a representation of recommendations** **Time units and dosing intervals** **Definition of "late" for operational (recall/reminder) purposes** **Related topics**	**Information** **Discussion** **Decision**	**Mr. L. Blumen (NIP, DMD)** **Ms. S. Feikema (NIP, DMD)** **Dr. E. Kilbourne (NIP,DMD)**
10:00	**BREAK**		
10:30	**Pneumococcal Conjugate Vaccine** **Pneumococcal disease surveillance** **Conjugate vaccine information** **Vaccine efficacy study results in infants**	**Information**	**Dr. S. Black (Kaiser-Permanente)** **Dr. P. Paradiso (Wyeth-Lederle)** **Dr. C. Whitney (NCID, DBMD)**
11:00	**Update on the ACIP Influenza Working Group** **Update on U.S. influenza activity** **Update on ACIP Prevention and Control Guidelines** **Influenza outbreak aboard a cruise ship 1997** **Influenza outbreak among tour group passengers in Alaska, 1998** **1997-98 Aviron live attenuated influenza vaccine trial** **1997-98 Vaccine cost effectiveness study of healthy adults workers**	**Information** **Discussion**	**Dr. P. Mendelman (Aviron)** **Dr. C. Bridges (NCID, DVRD)** **Dr. K. Fukuda (NCID, DVRD)** **Dr. J. Miller (NCID,QD)** **Dr. S. Zane (NCID,QD)**
12:30	**LUNCH**		

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1:30 Public Comment

1:45 Polio Update, Overview, and Future Issues	**Information**	**Dr. S. Cochi (NIP, VPDED)**
Polio surveillance update	**Discussion**	**Dr. N. Halsey (Johns Hopkins University)**
Global eradication update		**Dr. N. Khetsuriani (NIP, ESD)**
Vaccine distribution and coverage monitoring		**Dr. M. Kolasa (NIP, ESD)**
Parental compliance with sequential schedule: Immunization delivery evaluation project and the Georgia Demonstration Project		**Dr. S. Melman (St. Christopher's Hospital for Children)**
		Dr. G. Mootrey (NIP, ESD)
Evaluation of adverse events related to IPV		**Dr. R. Prevots (NIP, ESD)**
AAP/AAFP update		**Dr. J. Stevenson (NIP, DMD)**
		Dr. R. Zimmerman (Univ. of Pittsburgh)

4:00 ADJOURN

ATTENDEES:

Committee Members
Dr. John Modlin (Chair)
Dr. Richard Clover
Dr. David Fleming
Dr. Mary Glode
Dr. Marie Griffin
Dr. Fernando Guerra
Dr. David Johnson
Dr. Chinh Le
Dr. Paul Offit
Dr. Bonnie Word

Ex Officio Members
Dr. Robert Breiman (NVPO)
Dr. Geoffrey Evans (HRSA)
Dr. Karen Goldenthal, FDA
Mr. T. Randolph Graydon (HCFA)
Dr. Kristin Nichol (VA)
Dr. Gina Rabinovich (NIAID)
Dr. David Trump (DOD)

Liaison Representatives
Dr. Stanley Gall (ACOG)
Dr. Pierce Gardner (ACP)
Dr. Gregory Gilmet (AAHP)
Dr. William Glezen (IDSA)
Dr. Neal Halsey (AAP)
Dr. Victor Marchessault (NACI)
Dr. Yvonne McHugh (BIO)
Dr. Paul McKinney (ATPM)
Dr. George Peter (AAP)
Dr. Larry Pickering (AAP)
Dr. William Schaffner (AHA)
Dr. Jane Siegel (HICPAC)
Dr. Thomas Vernon (PhARMA)
Dr. David Wilson (AMA)
Dr. Richard Zimmerman (AAFP)

Executive Secretary
Dr. Dixie Snider

Office of the General Counsel
Mr. Kevin Malone

National Center for Infectious Diseases
Dr. Beth Bell
Dr. Carolyn Bridges
Mr. Richard Conlon
Dr. David Dennis
Dr. Keiji Fukuda
Dr. Richard Garfein
Dr. Ned Hayes
Dr. Rima Khabbaz
Dr. William Martone
Dr. Eric Mast
Dr. Craig Shapiro

National Vaccine Program Office
Dr. Martin Myers
Ms. Alicia Posteman

National Immunization Program
Dr. William Atkinson
Ms. Angie Bauer
Ms. Pam Berman
Dr. Bob Chen
Dr. Jose Cordeo
Dr. Steve Cochi
Dr. Sue Chu
Dr. Jen Danielson
Ms. Roz Dewart
Dr. Don Ekwueme
Dr. Suzy Feikeman
Dr. Patrick Flaherty
Ms. Edith Gary
Dr. John Glasser
Dr. Karin Gaul
Dr. S. Humiston
Dr. Sonja Hutchins
Dr. Nino Khetsurain
Ms. Tamara Kicera
Dr. Duane Kilgos
Dr. Kim Lane
Dr. Charles Lebard
Dr. John Livengood
Dr. Hugh Mainzer

National Immunization Program - Continued
Dr. Mary McCauley
Dr. Gina Mootry
Dr. Trudy Murphy
Dr. Setia Sabeena
Dr. Walt Orenstein
Dr. Jane Seward
Dr. John Singleton
Dr. Ray Strikas
Dr. Fran Walker
Dr. Bruce Weniger
Dr. Melinda Wharton

Other Government Attendees
Dr. N. W. Baylor, FDA
Dr. Karen Elkins, FDA
Dr. Karen Midthun, FDA

Others Present
Lynn Bahta, IAC
Douglas Bell, Wyeth Lederle
Thomas Brown, IDF
Jillian Carleton, Conn & Wolfe
Jill Chamberlain, Vaccine Bulletin
Courtois Christian, Smith Kline
Kevin Connolly, Merck
Dack Dalrymple, Bailey & Dalrymple
Susan DeCaro, Pasteur Merieux Connaught
Ruth Dunn, Michigan State University
Frank Dzvonik, Smith Kline Beecham
David Fedson, Pasteur Merieux
Dennis Foley, Wyeth-Lederle
Eddie Gray, Smith Kline Beecham
Ruth Gilmme, Georgia Immunization Program
Elizabeth Goss, Fox, Bennet & Turner
Ken Guito, Pasteur Merieux Connaught
Jeff Hackman, Pasteur, Merieux, Connaught
Claire Hannan, ASTHO
Jennifer Harvey, ASTHO
Terry Harville, IDF
Phil Hosbach, Pasteur Merieux Connaught
John Hollister, Aviron
Barbara Howe, Smith Kline Beecham
Margaret Keane, Merck
Aihim Kaufhold, Smith Kline Beecham
Samuel Katz, Duke University Medical
Aihim Kaufhold, Smith Kline Beecham
Stephen Keith, North American Vaccine
A. N. Krishney
Barb Kuter, Merck Research Labs.
Scott Litherland, Parallax Communication
Shoshana Melman, St. Christopher's Hospital
Paul Mendelman, Aviron
Peggy Monkus, GA Immunization Program
Carleton Meschievitz, PMC

Others Present

Peter Paradiso, Weyeth-Lederle
Dennis Parewth, Smith Kline Beechman
Mara Piasecki, Torre Lazys
Eileen Plante, Merck
Stanley Plotkin, Pasteur Merieux Connaught
Robert Pietrusko, Smith Kline Beecham
Sioshion Quinn, Smith Kline Beecham
Margaret Rennels, University of Maryland Hospital
Cassandra Richardson, Infectious Diseases in Children
Fred Ruben, Pasteur Merieux Connaught
Zeil Rosenberg
Ann Roger, Weyeth-Lederle
A. Schnerderman, Smith Kline Beecham
Florian Schodel, Merck
Connie Scotese, Wyeth Lederle
Kristine Severyn, Vaccine Policy Institute
Frederic Shaw, Washington D.C.
Natalie Smith, CDHS
Dale Spriggs, VRI
Stacy Stuerke, Merck Vaccine Division
Richard F. Thompson, Camino Medical Group
Miriam E. Tucker, Pediatric News
Peter Vigliarlo, Cooney-Waters
Fred Wallace, Merck Vaccine Division
Jo White, Aviron
Deborah Wexler, Immunization Action Coalition
Pam Weinberg, Smith Kline Beecham
John Zahradik, Pasteur Merieux

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Advisory Committee on Immunization Practices
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The Centers for Disease Control and Prevention convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on October 21-22, 1998 at the Atlanta Marriott North Central hotel in Atlanta, Georgia. Dr. Dixie Snider, CDC's Assistant Director for Science and Executive Secretary of the ACIP, called the meeting to order at 8:36 a.m. The ACIP members, ex-officio representatives, and liaison members introduced themselves and stated any potential conflicts of interest. This is compulsory for ACIP members and voluntary for others.

The members introduced themselves and stated their potential conflicts of interest.

- John Modlin, M.D., Chair, owns stock in Merck & Company.
- Fernando Guerra, M.D.: Director of Health, City of San Antonio. His department did an acellular pertussis field trial for North American Vaccine and a demonstration project with hepatitis A vaccine for SmithKline Beecham. They consult to Merck Vaccine Company and are presently working with Metamune Company in a monoclonal antibody vaccine population trial among prematurely born infants.
- David Johnson, M.D., Michigan Department of Community Health, reported no conflicts.
- Chin Le, M.D., Chief of Infectious Disease Division for Northern California Kaiser Permanente, which conducts research studies with Merck, Wyeth Lederle and Smith Kline; he also owns stock in Merck.
- Paul Offit, M.D., Chief of Infectious Disease at Children's Hospital, Philadelphia. He co-holds a patent pertaining to the rotavirus vaccine in development by Merck, and he consults in that development.
- Bonnie Word, M.D., pediatric infectious disease physician in central New Jersey; reported no conflicts.
- William Heyward, M.D., CDC, no conflicts.
- John Livengood, M.D., Epidemiology and Surveillance Division, National Immunization Program (NIP), CDC, no conflicts.
- Walter Orenstein, M.D., NIP, no conflicts.
- Alison Mawle, M.D., National Center for Infectious Disease (NCID), CDC, no conflicts.
- Marie Griffin, M.D., Vanderbilt University Department of Preventive Medicine. She is Chair of Merck's Endpoint Monitoring Committee, which is not vaccine-related.
- Mimi Glode, M.D., pediatric infectious disease physician, University of Colorado, reported no conflicts.
- David Fleming, M.D., State Epidemiologist of Oregon; reported not conflicts.
- Richard Clover; M.D., University of Louisville. He and his department have received honoraria and/or grants from Merck, Connaught, and SmithKline Beecham.

The ex-officio and liaison members in attendance were:
- Rob Breiman, M.D., National Vaccine Program Office (NVPO)
- Geoffrey Evans, M.D., Health Resources and Services Administration (HRSA), National Vaccine Injury Compensation Program
- Stan Gall, M.D., American College of Obstetricians and Gynecologists (ACOG)
- Pierce Gardner, M.D., American College of Physicians (ACP)
- Gregory Gilmet, M.D., American Association of Health Plans (AAHP)
- Paul Glezen, M.D., Infectious Disease Society of America (IDSA)

- Karen Goldenthal, M.D., Food and Drug Administration (FDA)
- Randy Graydon, M.D., Health Care Financing Administration (HCFA)
- Neal Halsey. M.D., American Academy of Pediatrics (AAP)
- Larry Pickering, M.D., American Academy of Pediatrics
- Victor Marchessault, M.D., Canadian National Advisory Committee on Immunization
- Yvonne McHugh, M.D., Biotechnology Industry Organization
- Paul McKinney, M.D., Association of Teachers of Preventive Medicine (ATPM)
- George Peter, M.D., National Vaccine Advisory Committee (NVAC)
- Larry Pickering, M.D., American Academy of Pediatrics (AAP)
- Gina Rabinovich, M.D., National Institutes of Health (NIH), National Institute for Allergies and Infectious Diseases (NIAID)
- William Schaffner, M.D., American Hospital Association (AHA)
- Jane Siegel, M.D., Hospital Infection Control Practices Advisory Committee (HICPAC)
- David Trump, M.D., Department of Defense (DoD)
- Richard Zimmerman, M.D., American Academy of Family Physicians (AAFP)

Opening Comments

Dr. Snider announced that Dr. Fernando Guerra had agreed to serve an additional two-year term, and that Dr. Marie Griffin will serve until another member is appointed. Dr. Gina Rabinovich is now the official NIAID ex-officio representative. On behalf of ACIP and CDC, he thanked Dr. Paul Glezen for his contributions over the years, this being his last ACIP meeting. He is to be replaced by Dr. Sam Katz. He welcomed new members Dr. Yvonne McHugh of the Chiron Corporation as liaison for the Biotechnology Industry Organization; Dr. George Peter as liaison for the National Vaccine Advisory Committee (NVAC); and Dr. David Wilson for the American Medical Association (AMA). Dr. Wilson will begin attending at the February meeting. Dr. Karen Goldenthal was present for FDA liaison Dr. Carolyn Hardegree, and Dr. Jose Luis Diaz Ortega represented Dr. Jose Ignacio Santos, of the National Immunization Council and Child Health Program of Mexico. Dr. Modlin particularly welcome new members Drs. Word, Offit and Johnson.

Welcome by CDC Director

Dr. Modlin then welcomed Dr. Jeffrey Koplan, the newly appointed Director of the Centers for Disease Control and Prevention. He thanked Dr. Snider and Dr. Modlin for their excellent work on the committee. In his 22-year career in the Public Health Service, Dr. Koplan also served as an ACIP Executive Secretary. He noted the essential nature of the ACIP's work to the nation's public health. His work both in public health and in the private sector (health services research with Prudential) involved immunization issues. He noted that this meeting's agenda explores both old issues (e.g., polio) and new ones (e.g., new vaccines such as for Lyme disease). He was struck at how easily some vaccines entered the armory of immunization, such as those for rubella, hepatitis A and B, hemophilus influenza, etc., and applauded the extraordinary advances made in immunizations for children and adults.

Dr. Koplan outlined for the first time publicly his priorities as CDC Director. All of them relate to the ACIP's mission:

1. Strengthen the scientific basis for public health policy and action.
2. Increase collaboration of public health and healthcare delivery (private sector, HCFA, and other agencies involved in health care delivery). Immunization offers an excellent example of such collaboration in policies and delivery systems.
3. Improve attention to health and quality of life as much as to issues of longevity, particularly

focusing on the elderly without losing focus on youth. This includes attention to the growing battery of adult immunizations.

4. Strengthen CDC's role in global health issues such as polio, tobacco use, etc.

Interwoven with all of these priorities is CDC's traditional value of eliminating disparities in disease rates within the population. He noted that the increasing complexity of making immunization policy involves social, ethical, legal, and economic issues. His experience in the private sector demonstrated the extent to which policies are based on ACIP recommendations, clear evidence of the respect the ACIP holds. He hoped to be able to attend future ACIP meetings as his schedule would allow.

Announcements

Dr. Snider announced that the renovation of CDC's Building 1 will require the ACIP meetings to be held off-site for perhaps two years. He requested that the members' waiver letter be signed and turned in before leaving. The 1999 meeting dates were announced: February 17-18, June 16-17, and October. 20-21.

He reminded the members that the ACIP charter now allows the Executive Secretary to temporarily designate the ex-officio members as voting members. This will not be done unless less than seven ACIP members are qualified to vote due to conflict of interest. He noted that the ACIP welcomes open comment, but in its limited agenda time, formal comment periods are scheduled. They must be requested in advance, and a sign-up sheet is available at the meeting. Informal comments will be accepted during open discussion if possible, but must be restricted to stay on time.

Dr. Modlin announced the publication of the ACIP recommendation for MMR in *MMWR* on May 22; a copy was provided. The rotavirus statement is in an advanced form. The vaccine was licensed since the last ACIP meeting. A few package insert conflicts were resolved and are included in the updated version distributed. He encouraged the members to review the statement and to return final comments within 2-3 weeks of this meeting.

Agency Updates

Food and Drug Administration (FDA)

Dr. Goldenthal announced FDA approval for licensure on August 3, 1998 of Rotashield, the live, oral, tetravalent rotavirus vaccine for infants by Wyeth Laboratories. Also approved was the adsorbed DTaP named Certiva, for infants and children, on July 29, 1998. The acellular pertussis component is manufactured by North American Vaccine; the diphtheria and tetanus component by Statens Seruminstitut.

She reported an important policy change on September 8, 1998, to upgrade the FDA's CJD plasma derivative policy. It now advises recall if in-date manufactured products came from a donor who develops a *new variant* of CJD. Previously, only sporadic, familial, or iatrogenic CJD, or development of specific risk factors, advised recall. This policy should improve immunoglobulin availability and decrease the likelihood of recall of albumin-containing products. She noted that new variants have not been observed in U.S. Work is in process to

upgrade FDA's December 11, 1996 guidance and to clarify the September 8, 1998 notice of precautionary measures to reduce the risk of transmission of CJD by blood/blood products. The

FDA lead is Dorothy Scott, M.D.

National Immunization Program (NIP)
Dr. Walter Orenstein announced all-time highs in immunization coverage in pre-school children and adults aged ≥65 years.

Childhood immunizations: The 1997 survey of children born February 1994 to May 1996 revealed that 95% of children aged 19-35 months received ≥3 DTP vaccines; 91% received ≥3 polio vaccines; 91% received a measles-containing vaccine; and 93% received ≥3 doses of Hib. Hepatitis B (HB) coverage rose 47% in the last four years, but only 2% in the last two, implying difficulty in meeting the 1998 goal of 90% antigen coverage. DTP4 coverage is 81% (but up 5% since 1994); varicella is lowest at 26%. A varicella death occurred as recently as week 39 of 1998, in a healthy woman exposed to an ill child. *Adult immunization:* The 1997 Behavioral Risk Factor Surveillance Survey (BRFSS) reported 66% of adults aged ≥65 years were immunized against influenza that year, 6% over the Year 2000 goal; and 45% had received pneumococcal vaccine.

In comparing the maximum and current morbidity for eight vaccine preventable diseases (VPD), 1997 provisional data showed almost universal (≥97%) reduction, 100% for some. Only 138 cases of measles were reported in 1997, down from >27,000 cases in 1990. The data available for the first 39 weeks of 1998 show measles declining to 62 cases compared to 116 in the same period in 1997. The largest single outbreak was in Alaska, with 22 confirmed cases, due to a delay in implementing the two-dose schedule which is now aggressively being pursued. Rubella rose to 324 cases in the first quarter of 1998, from 140 in the same period 1997, about 84% of cases in Hispanics. It is hoped that work with Latin American control programs will decrease this.

Budget: Cuts of 30% are expected in the federal immunization grants to states for infrastructure due to reduced carryover in FY99 compared to FY98. The cuts are due to reductions in the base immunization budgets designed to reduce large state carryover balances of unexpended funds that had accumulated during major budget increases during the mid-1990s as part of the Childhood Immunization Initiative (CII). Now that the carryover is almost eliminated, states may have to cut their base programs to stay within the new reduced base funding.

Concerns have been raised about whether the funding will be sufficient to meet state needs. The core functions supported by the infrastructure funds are disease surveillance, outbreak response, immunization coverage assessment, public outreach/education, program management/evaluation, ensuring service delivery and quality, training health care professionals, health care research, and ensuring vaccine provision to delivery sites. NIP is exploring the states' expenditures and realistic needs.

Vaccine purchase issues: The 1997 biologics data indicate that 60% of U.S. vaccine purchases are governmental in origin, 60% of that by the VFC, 25% by the S.317 grant program to serve children not covered by VFC, and 15% by states. S.317 is expected to have available $137 million in FY99, down from $140 million actually spent in FY98 prior to the ACIP recommendation for universal vaccination against rotavirus and recommendations for enhanced catch-up for other vaccines. Whether the $137 million appropriated in FY99 is sufficient depends on the aggressiveness of state catch-up programs. Those costs for varicella, HB, and MMR2 could raise the total FY99 S.317 vaccine purchase estimate to as much as $195 million. Supplemental House appropriations are possible.

Dr. Orenstein reported a Congressional request that NIP contract the Institute of Medicine (IOM) to assess five questions:

1. To what extent has increased federal spending during the 1994-1998 period affected the immunization coverage rates?
2. How were the new funds spent by the states and to what extent did states maintain their own level of effort over the past 5 years?
3. What are the current and future funding requirements for childhood immunization activities and how can those requirements be met through a combination of state funding, federal immunization funding, and through CHIP?
4. How should federal grant funds be distributed among the states?
5. How should funds be targeted within states to reach high-risk populations without diminishing high levels of coverage in the overall population?

NIP also is assessing the role of the S.317 program for adult immunizations. A provisional IOM report is expected in May 1999; the final report in 2000 could impact FY2001 budget deliberations.

Discussion:: Dr. Guerra asked how the NIP estimated the second dose catch up costs for children eligible for S.317. Dr. Orenstein explained that they assumed coverage for 10% of each of two additional cohorts for MMR2, and estimated the 25% public sector cost for the S.317 program. But the MMR2 cost is minor ($1.8 million) compared to that of HB ($47 of a $51 million estimate). However, he acknowledged that these estimates are imprecise. The $137 million could be adequate or short.

Dr. Fleming asked what warning time the states would have if the funding is short. Dr. Orenstein thought that possible by the first or second quarter of 1999; the states will be polled for their best estimates of need, and their spending patterns will be reviewed. Dr. William Nichols of NIP reported their monthly comparison of CDC contract expenditures for catchup vaccines (especially HB) to those of past quarters, to gauge increased use and project future use. The states also have estimated their needs for S.317 grants at $230 million, but these estimates are usually high and less reliable than monitoring data.

National Vaccine Injury Compensation Program (NVICP)

Dr. Geoffrey Evans was pleased to announce that October 1 marked the tenth anniversary of the VICP. He began with a review of program statistics. To date 4247 petitions have been filed for vaccine administered before 1988, 1057 since 1988. Of the 5304 total, 4577 have been adjudicated, and 1356 found compensable. The program still gets about ten claims a month; up slightly due to the addition of HB, Hib, and varicella vaccine as of August 1997. About 100-200 hepatitis B vaccine claims are expected in the next two years. The program has paid $946.7 million to date, $135.1 million of that in FY98. The trust fund holds $1.3 billion, with FY98 annual income increased by the 3 new vaccines added to the VICP and the $0.75 flat tax instituted in August 1997.

Dr. Evans commented that as the program enters its second decade, it is important to examine how well the VICP is meeting the public policy goals set by Congress.

Compensation: eligibility determinations and compensation have been streamlined and simplified in the current no-fault system, resulting in awards to >1300 families or claimants. The average time from the filing of a post-1988 claim to payment is 2.5 years. *Marketplace*

stabilization: vaccine supply shortages have ended; annual investigational new drug (IND) requests to FDA nearly doubled since 1986. Pricing reflects purchase trends and inflation rather than liability concerns. *Civil litigation*: DTP lawsuits against manufacturers, and presumably against providers, are at the lowest point in the past 15 years. Only four claims were filed against U.S. DTP manufacturers in 1997. A survey of petitioner's attorneys conducted by the Department of Health and Human Services' Office of General Counsel showed most choosing not to pursue civil litigation once an NVICP claim has been adjudicated.

Legislation: The NVICP was unsuccessful in changing the $0.75 surtax to $0.25 per disease prevented, but such legislation has strong bipartisan support. Furthermore, other legislation pending in Congress contains a provision to tax any vaccine licensed for use against rotavirus gastroenteritis. *Media Coverage:* Dr. Evans described a Gannett News Service series critical of the NVICP, citing associations between vaccine reactions and "shaken baby syndrome," SIDS, and OPV-related Vaccine-Associated Paralytic Polio (VAPP); process delays; changes to the Vaccine Injury Table; and excess monies in the trust fund. Other topics included concerns over immunization registries and compulsory immunization.

Dr. Evans noted that an extensive scientific process surrounded the Table changes and these changes affect only claims after March 10, 1995 (about 7% of all claims). Moreover, potential legislative amendements reviewed by the Advisory Commission on Childhood Vaccines (AACV) and presented at the last ACIP meeting address many of these process issues. Finally, legislation pending in Congress will decrease revenues coming into the Trust Fund.

Future NVICP directions possibly include adding influenza vaccine as part of the Pandemic Influenza Preparedness Plan, adding vaccines given routinely to adults (e.g., pneumococcal vaccine), and adding vaccines in clinical trials (a related workshop with NVAC planned). The AACV is also considering whether hepatitis A should be covered by the VICP, sinceit recently became mandated for kindergarten and middle school entry in Oklahoma. Congressional legislation is needed for any of these changes.

National Vaccine Program Office (NVPO)

Dr. Rob Breiman defined the NVPO's role to help coordinate a coherent approach to vaccine issues by federal agencies and organizations. The NVPO's interagency workgroup meets monthly and as-needed to facilitate coordination of relevant federal agencies (DHHS, USAID, DoD) and organizations in achieving the goals of the national vaccine plan. Coordination with external partners (vaccine companies; consumer groups; professional, academic, and nonprofit organizations; international bodies) is emphasized to achieve a national rather than federal program. NVPO will develop better partnerships with these groups, all of which can help greatly if allowed to be involved and contribute.

The key areas of NVPO focus include:

- *National Vaccine Safety Action Plan*. Buy-in is being sought. Its components include research and development towards safe vaccines and decreased potential contamination; improved surveillance for vaccine-associated adverse events and describing their causality; research in risk and health communication about vaccines and in methods to inform the public.
- *Pandemic Influenza Preparedness Plan*: Great progress has been made, and although it is quite a bit larger, it will be a well-documented usable reference volume.

- *National Vaccine Plan:* The NVPO is updating the plan, last published in 1994, which should be completed in 1999.
- *TB Vaccine Development/Evaluation:* In the absence of a TB vaccine for use in immunosuppressed populations or beyond the pediatric years, NVPO/National Vaccine Advisory Committee (NVAC) sponsored an international symposium in August. They also jointly commissioned a TB Vaccine Development/Evaluation Action Plan under an NIH/NIAID lead, with academic, federal agency, and vaccine company involvement. That strategy will be presented to the Surgeon General in the next few months.
- *Adult Immunization Plan* implementation is ongoing, with one area to explore the use of nontraditional settings to boost immunization coverage levels.
- *NVAC:* Dr. Mimi Glode is the ACIP liaison to the NVAC, and Dr. Georges Peter chairs it. It complements the ACIP as a policy arm for vaccine advice. Its working group for pandemic preparedness will discuss policy on the priorities for vaccination needed to maintain social order (e.g. for essential services such as air traffic control) during the initial stages of a pandemic when vaccine is limited. This will be done in collaboration with the ACIP's consideration of clinical indications for vaccination based on the epidemiology of the pandemic strain. The NVAC Immunization Registries working group held hearings this past summer and will develop a report which will be presented to the Surgeon General and DHHS Secretary this winter. Current NVAC products include a 15-step strategy to sustain childhood immunization coverage rates, which will lead to development of a nongovernmental panel on implementation; case studies in vaccine research and development about barriers and opportunities for expediting development, evaluation, and use of safe/effective vaccines; nontraditional sites for adult immunizations and associated guidelines; and the plans for immunization registries and TB vaccine plan.

Accreditation of MMWR

Dr. John Ward, editor of *MMWR*, reported the establishment of a continuing education component in the *MMWR*'s Report and Recommendation series which would grant Continuing Medical Education (CME) or Continuing Nursing Education (CNE) credits. CDC is accredited to do so for its programs. Adding the *MMWR* credits fits the overall CDC mission of providing training opportunities in public health; would highlight the recommendations' major points (helpful in their occasionally dense text); and could extend the reach of *MMWR* to healthcare professionals who might not now read it. An examination would be prepared on the recommendation's information, practice setting, etc. by subject matter experts. It will be published in paper and online versions. A certificate is supplied on completion.

A large initial demand is not expected, but discussions with the *New England Journal of Medicine (NEJM)*, the *Journal of the American Medicine Association (JAMA)*, etc., indicate CME/CNE participation by 1-30% of readership. With an estimated 500,000 public health nurses alone in the U.S., demand could be large. *MMWR* expects to work with the NIP to develop CME/CNE components for ACIP recommendations. Discussions of CE credits for the rotovirus vaccine and harmonized schedule are underway. A small charge will help to offsite this program's administrative expenses. The ACIP members welcomed this idea.

Infectious Disease Society of America (IDSA)

Dr. William Schaffner presented for Dr. Bruce Gellen, Director of the Vaccine Initiative undertaken by IDSA and the Pediatric Infectious Diseases Society to communicate about vaccines. He cited two examples to highlight the need for such an effort. In France, routine Hepatitis B immunizations of adolescents were suspended due to fear of demyelinating diseases, particularly multiple sclerosis. This decision was made without any scientific study to

identify such a risk, and despite strong statements by the U.S. National Multiple Sclerosis Society and a WHO Viral Hepatitis Prevention Board expert panel of no evidence of such a causal link.

In the second case, as opposed to its welcome by public health, media suspicion greeted the release of a Kaiser Permanente study (October 1995-July 1998) proving the efficacy of heptavalent conjugate pneumococcal vaccines. Although its benefit against such diseases as bacterial meningitis, pneumonia, and perhaps inner ear infections was reported, so were questions of whether its benefits outweighed the risks. Opinion was reported that vaccines should be for deadly or contagious vaccines or for those at higher risk, and fear expressed that the unknown side effects might mirror a similar Finnish vaccine's case where immunized children seemed at risk to develop diabetes.

Dr. Schaffner summarized that these two events underscored the need to educate about vaccines' real benefits and putative adverse events. The Vaccine Initiative activity includes 1) audience research (including parent focus groups and a national survey of beliefs about vaccines) to help design interventions; 2) proactive media outreach including an assembly of a national faculty for media consultation on stories; and 3) alliance building to ensure clear and reinforced information to health care professional societies, the pharmaceutical industry, and health insurers, at the national and local level. The ACIP will be kept informed of the Initiative's activities.

Discussion: Dr. Modlin voiced the ACIP's support for this effort. Dr. Stan Plotkin noted some reason for the French response in that three studies had reported odds ratios of 1.4-1.7 favoring an association, although the differences in risk were not statistically significant. But importantly, there was no effective medical/expert voice (including the WHO) to counteract the political pressure to stop vaccination in adolescents.

Revised Rabies Recommendation

Dr. Peter Arguin of NCID provided an overview of the changes made by the Rabies Working Group to the ACIP recommendation since the last meeting. The purpose of the document is to provide primary health care practitioners and public health officials with straightforward guidelines about pre- and post-exposure management of those at risk of rabies virus infection. The new statement, proposed for acceptance by the working group, added information about an additional rabies vaccine prepared from purified chick embryo cells, added a recommendation about exposure to bats, revised the recommendation for post-exposure prophylaxis (PEP) for international travelers, reclassified ferrets as domesticated rather than wild animals, and revised instructions on the local administration of rabies immune globulin.

Additional references were added, and a statement in the introduction that rabies PEP was a "medical urgency not a medical emergency." An additional section describes (but also states the rarity of) human-to-human transmission; it emphasizes that routine healthcare delivery does not constitute exposures, and that exposures can be minimized with standard precautions. A statement was included to clarify that bat associated cases within the same household never have been reported.

The evidence tables compiled to identify research gaps were not included because the working group judged them not to clarify or enhance the guidelines. To address lacking randomized controlled trials that might infer insufficient evidence and spur inappropriate decisions, a

statement was added to the introduction that "Although controlled human trials have not been performed, extensive field experience from many areas of the world indicates that PEP combining local wound treatment, passive immunization, and vaccination, is uniformly effective when appropriately applied." However, there are plans to use the evidence tables in a review article.

Discussion: Two late-arriving related letters to the ACIP were raised for discussion. One was from Dr. Leonard Marcus of Newton, MA, a consultant in Lyme and other insect-borne diseases, and the other was from Dr. Stuart J. Updike, Professor of Medicine at the University of Wisconsin Medical School. Dr. Modlin thought it a little late in the process to consider an apparently major change in the guideline. However, Dr. Johnson felt that since state and local levels are challenged to deal with inapparent exposures, these issues should be reviewed before an ACIP decision. An ad-hoc working group met with the Rabies Working Group members and reviewed the issues over lunch. Their discussions and the committee's conclusion are reported hereafter, rather than in the agenda's consecutive order which continues with the Lyme vaccine presentation.

Dr. Marcus suggested that those living in houses "infested" with bats be considered in the frequent or continuous exposure category. This requires PEP, serologic testing every two years, and booster shots given in the absence of neutralizing antibodies. However, the workgroup noted that studies of healthy, free-ranging bats rarely find rabies; it is more common in those sick, dieing, or found in unusual circumstances (e.g., found on a pillow). Personal contact with bats in such houses is also rare, but if it occurred, the bat could be tested and PEP provided if rabies is found. Exposure to apparently normal bats does not justify pre-exposure vaccination, tests, or boosters.

On the other hand, Dr. Updike expressed concern that the guideline's wording could encourage excessive PEP. He suggested language emphasizing that low-risk situations should be individually considered by trained personnel. Again, the workgroup concluded that the CDC's and ACIP's extensive discussions had already addressed most of Dr. Updike's points and addressed them in the guideline's text. Dr. Updike's other suggested phrase in connection with a bat encounter, "other worrisome circumstance," was considered too vague and potentially risking unnecessary PEP.

In both cases, the ad-hoc group concluded that the recommendations as currently worded accomplish the same purposes as raised in the letters. However, it also was agreed that additional information to physicians and the public may be needed about the risk from such exposures. It was reported that CDC has published a brochure on bats and rabies, and the

CDC Website is developing specific information on bats. Work is underway to evaluate how best to present the statement's information in user-friendly formats.

Regarding the evidence tables, some ACIP members agreed that they were not useful for rabies, but others felt that the reviewed evidence base should be available. Dr. Snider said that while the ACIP policies and procedures default to generating evidence tables, they can also be decided on a case-by-case basis. For example, there could be either little evidence or conflicting evidence for rabies or anthrax. Perhaps the initial position for guidelines in development should be to include evidence tables and only exclude them with good reason. Dr. Griffin called for policies and procedures to gain more uniformity on how to interpret these data. Dr. Modlin summarized consensus to not specifically include this set of evidence tables in this

document, to no objection.

The working group recommended that the guidelines be passed in their present form, to no objection. Dr. Modlin called for a vote, and solicited statements from those with any conflict of interest.

VOTE: To accept the draft rabies guidelines in their present form with the specific comments raised this morning to be addressed. Moved by Dr. Guerra and seconded by Dr. Griffin. Applicable conflicts related to Pasteur-Merieux Connaught and Chiron Corporation.

In Favor: Griffin, Glode, Fleming, Word, Offit, Le, Johnson, Guerra, and Modlin.
Opposed: None
Abstained: Clover
Outcome: Passed

Lyme Vaccine Statement

Public Comment
Dr. Modlin called for public comment on Lyme vaccine, requesting comments to be limited to three minutes and only clarifying questions asked by the committee.

David Weld, Executive Director of the American Lyme Disease Foundation, reported funding received from SmithKline Beecham and Pasteur-Merieux Connaught. He commended the ACIP for the major challenge in addressing a new vaccine based on ecological and geographical foundations, but also expressed concern over the U.S. areas assigned to high, medium, and low risk. Lyme disease has been identified in New York state, as well as in highly endemic areas such as Maryland and Pennsylvania. The costs to society and the assessment of risk must be considered in developing vaccine recommendations, but consideration is also due to the psychological benefit of vaccine availability to those even at low risk. Last year in Westchester county, the foundation received >85,000 calls about fear of Lyme disease from tick bites. The related costs to society of this fear may be difficult to quantify, but must be assessed. He also called for further exploration of how the spread of *I. scapularis* and *B. burgdorferi* would be monitored and necessary information conveyed to local physicians assessing the risk.

William Bethancourt, M.D., of the Lyme Disease Foundation, is an internist in New Jersey, a hyperendemic area. He stated that Lyme is a devastating disease for which many await a safe and effective vaccine. Some scientists have urged that the recommendations be changed. No test is 100% accurate to prove infection and elimination of bacteria. The current two-tiered antibody tests are flawed, not useful early in disease for early diagnosis. In the absence of an effective test, some “cured” patients are later diagnosed with other diseases and syndromes when they downspiral. The cost of Lyme disease has been estimated by Irwin Vanderhoof at $60,000/patient and $1 billion/year. He agreed that grouping risk by states is inappropriate. Case reports from 1995-1997 include counties reporting more cases than hyperendemic states. He urged that vaccine availability be extended to other states than hyperendemic areas in view of increasing reports elsewhere and the movement of people between risk areas.

Recommendation On Lyme Disease Vaccine
Dr. David Fleming reported a conference call and other communications by the Lyme Disease

Working Group. They were now seeking ACIP consensus on the core recommendations on the draft statements pages 14-16.

ACIP consensus was reached at the last meeting on the statement's overall direction, including three categories of risk. The working group added an overarching statement discussing the considerations of patient-provider interaction about getting the vaccine; and more discussion of the geographic and personal risk factors involved in assessing overall risk. Specific issues were raised on the package insert's language about the vaccine's use in pregnancy and children, its timing/dosing administration, booster shots, simultaneous administration with other vaccines, and vaccination at age >70. All oral or written ACIP feedback was welcomed.

Dr. David Dennis of NCID presented background information. The agent causing Lyme disease was characterized 15 years ago, the vaccine development began 10 years ago, and safety/efficacy field trial data of the quickly developed recombinant vaccine was recently published in the *NEJM*. There have been 15 iterations of this ACIP draft recommendation. Its introduction reviews the clinical features of Lyme disease, its epidemiology, the current tools to prevent/control it, description of the vaccine's mechanism of action and performance (safety, efficacy, immunogenicity), and effect of vaccination on serologic diagnosis of Lyme disease. The working group developed a cost-benefit model, the data of which were presented in the past. One sensitivity table is in the draft document.

With no comments offered on the background information, Dr. Dennis defined assessment of Lyme disease risk as the basis of the recommendations: 1) persons at three levels of risk (high, moderate, little/none). Other important issues to be addressed include 2) vaccine use in children and pregnant women, and 3) vaccine scheduling/boosters .

Risk is the most important factor in determining if a vaccine can be usefully applied in a population. For Lyme disease, the workgroup concluded that the decision to vaccinate should follow an individual risk assessment based on *geographical risk* (high, moderate, or low based on reported Lyme disease to the National Disease Reporting System; identified distribution of ticks carrying the disease; and vector competency based on infection rates, as well as ecological parameters); the *individual's activities* around their residence or neighborhood; and

intensity of risk related to frequency/duration of exposure. Persons at high risk typically have prolonged frequent exposure; those at low risk have episodic exposure in infective tick areas.

The Lyme disease risk by state was demonstrated on a U.S. map defining the states in the four risk categories (high, moderate, low, none). There are two highly endemic areas in the northeast and north central U.S., with a small clustering of high risk counties in northern California, which is a low-risk state. The eight states at high risk in 1993-1997 had reported rates equal to or greater than the national average ($\geq$5 cases/year; and contributed 90% of all Lyme disease cases reported). The five moderate risk states range from the 50% to 100% of the national average; the low risk areas have reported still lower rates; and the "no risk" areas had inconsequential reports. Other maps demonstrated national Lyme disease risk by showing counties with levels of risk based on human case rates and tick correlates of risk, and those counties contributing $\geq$90 percentile of reported cases in the five-year period 1993-1997.
A chart was shared of the cost-benefit effectiveness of the vaccine. The analysis, estimating the cost-benefit of vaccine use versus probability of Lyme disease, indicated a threshold level of benefit at a risk of 0.01 (one case per 100 population per year) with a vaccine cost of $100/person/year and vaccine efficacy of 85%. In high risk areas of 0.03/year (highly epidemic

circumstances), the benefits outweigh the costs; but at a prevalence of 0.005/year (still high) the costs exceed the benefits on a population level. As a result, the workgroup did not perceive the vaccine as a mass distribution intervention. A preamble to the recommendation was suggested.

> "Note: Lyme disease vaccine does not protect all recipients against infection with *B. Burgdorferi* and offers no protection against other tick-borne diseases. The vaccine should be considered an adjunct or supplement to the practice of basic personal protective measures against ticks and to the early diagnosis and treatment of suspected tick-borne infections. Decisions regarding the use of vaccine should be based on discussions between potential vaccine recipients and their care-providers that include assessment of tick exposures, relative merits of protective measures other than vaccination, and the potential risks, costs, and benefits of vaccine use."

Core Recommendations

Recommendation for persons at high risk: Lyme disease vaccine **should be considered** for persons aged ≥15 years who reside in or otherwise spend time in geographic areas of high or moderate risk and who engage in activities resulting in frequent or prolonged exposure to tick-infested habitat. Rationale: Vaccine safety (although there are some long-term concerns) and efficacy: 50% from 2 doses, 80% from 3 doses. It is 100% efficacious in preventing asymptomatic infection and may reduce incidence of late-stage disease. However, most Lyme disease is mild, readily diagnosed and easily treated even in its late stages, although there are exceptions making this highly controversial. However, the late stage cases/complications are increasingly rare, probably due to more diagnosis and treatment. It is not fatal. The public health benefits of vaccine over early diagnosis/treatment are unclear, and the vaccine does not follow the usual vaccine paradigm. It only provides individual protection and provides no herd immunity in the community or reduction in infection reservoir.

Recommendation for persons at moderate risk: Lyme disease vaccine **may be considered** for those who reside in/visit geographic areas of high/moderate risk, with neither frequent nor prolonged exposure. The benefit of vaccination is uncertain beyond personal protection and early diagnosis/treatment. Rationale: The evidence is insufficient to recommend for/against vaccination. Those considering vaccination may be sensitized to the issue, obviating potential vaccine benefit; the need for 3 doses/year is awkward and advance planning could be difficult; vaccination could lead to complacency even though the vaccine offers only partial protection against Lyme disease and none against other tick borne diseases; cost effectiveness models indicate high costs per case prevented.

Recommendation for persons at low or no risk: Lyme disease vaccine **is not recommended** for those who live in and remain in geographic areas of low/no risk or who travel to areas of high or moderate risk but conduct activities of low/no risk of exposure to vector ticks. Rationale: This is based on the unlikelihood of Lyme disease infection. There is no public health benefit to vaccination in this category, and cost is expected to be exorbitant.
Discussion: Dr. Breiman asked why the vaccine performance section's details about serological Western blot detection was absent in the discussed randomized control trial. Dr. Dennis traced this difference to what was available in published data from Phase III trials. Only SmithKline Beecham addressed that issue. Dr. Breiman then asked if the high-risk recommendation's term "spending time" would be better defined. Dr. Dennis agreed this is subjective. Dr. Fleming added that "spending time" referred to being in the geographic area, doing activities with

frequent or prolonged exposure.

Recalling the hepatitis B experience, Dr. Offit thought that targeting high-risk individuals would be unlikely to impact incidence. Like hepatitis A, Lyme disease is in a discrete geographical distribution, so those high risk states should be targeted. He asked why such a state-wide recommendation was not made. Dr. Fleming reported a number of reasons raised from the different perspectives of the working group. A strategy of targeting everyone is practical, but offset by issues of long-term safety, cost effectiveness even in endemic areas, and the inability of the vaccine to provide community benefit beyond that to the individual.

Dr. Modlin, who lives in a moderate risk area, suggested removing "or moderate risk." But Dr. Dennis noted the value of this phrase to public health in selected communities within a moderate-risk state (e.g., those high-risk due to ecology, geology, etc.) to reduce incidence, complications, and sequelae of Lyme disease. The state epidemiologist should determine the response to those areas.

Dr. Snider asked to what degree the uncertainty about the duration of protection and need for booster doses supported a weaker recommendation. Dr. Fleming responded that this relates to the issue of cost effectiveness; if recurrent boosters are needed, that would be an important issue of how aggressive to be in a high-risk category.

Dr. Zimmerman raised the differences in implementation if high-risk is defined by county or state data. Dr. Dennis clarified that the recommendation will use the state delineations, but specify that the variable risk within a state should be determined by the state authorities. Dr. Ned Hayes, of the Ft. Collins Lyme disease program, noted that the recommendation's consideration of activities related to exposure to tick habitat allows flexibility for the local practitioner or public health authority to determine the actual risk of any given individual. Nonetheless, Dr. Zimmerman expected a real challenge to implement the recommendation as stated, and encouraged use of county data for greater specificity and to clarify the standard of care.

Dr. Halsey agreed. The Red Book committee advised separate recommendations for people living in high, moderate, and low risk areas, versus those traveling to them. He also advised including the concept of seasonality in the statement. Dr. Guerra also raised the needs of the special population of itinerant or seasonal/migrant farm workers who are not connected to a system of care. Their considerations would have to be incorporated into migrant health centers to begin immunizations before leaving their home base. Dr. Dennis reported the possibility of doing such related risk studies under a special medical care provision for migrant workers in the northeast.

Vaccine Use in Children Aged <15 Years

The vaccine trials to date only addressed those aged ≥15; therefore, rOspA vaccine use **is not recommended** in children <15 pending institutional review of results of safety/efficacy trials. Rationale: there is a lack of supporting demonstrated safety/efficacy or adequate correlates for this age group, and Lyme disease is clinically mild in nature, with high responsiveness to treatment and an excellent prognosis.

Data were presented by SmithKline Beecham on two large reactogenicity and immunogenicity studies among persons aged <15 years. One (LY015) was a pilot trial conducted among 250 Czech children aged 5-15 who received 15 μg or 30 μg of rOspA vaccine on a 0,1,2 schedule. After 2 months, the 15 μg group achieved a titer of 1345 and the 30 μg group achieved 4289;

after three months, the 15 μg group had a titer of 5957 and the 30 μg group, 10,267. A comparison of the 15 μg and 30 μg schedules in children revealed a better immune response than those achieved in adults. This safety trial showed no difference between the two doses, no increase in incidence with subsequent doses, only local injection site reactions, no serious adverse events, and no hypersensitivity reactions.

SKB believes it has found that a serocorrelate of protection, in a titer of 500-1500 which predicts with 95% sensitivity protection provided for one season). However, as of late May, the FDA advisory committee had no consensus that the serological correlate had been demonstrated in children aged <15 years.

Following up on the Czech study, SKB initiated a double blind, randomized, placebo controlled U.S. trial (LY022) involving 4000 subjects (3:1 vaccine:placebo) aged 4-18. It includes an immunogenicity subset of 250 children and safety follow-up to 36 months (2 doses). After two doses, this trial shows no vaccine-related serious adverse events, no unusual patterns, and no reason to defer dose 3.

Discussion: Dr. Gardner suggested text that "indications for Lyme disease vaccine do not include persons at low risk," to reinforce that only lack of data led to that soft recommendation. Dr. Halsey reported Red Book's debate over this. The AAP will not support/encourage vaccine use until the data are widely available. He also recommended clarifying to whom the "institutional use" referenced in the recommendation indicates. Dr. Dennis agreed; it means FDA and CDC. Dr. Fleming also noted the working group's discussion of the fine lines of interpretation between "indicated" or "recommended."

Dr. Glode supported the language used for rotavirus, that "data are insufficient to recommend at this time." Dr. Modlin expected that permissive language will lead to widespread use, and asked if that was the committee's intent. He preferred the current "not recommended" text. Dr. Fleming took that as consensus and requested that any further comments be forwarded.

Vaccine Schedule, Including Spacing and Timing of Administration
The work group recommended that, until further information on spacing and timing of doses is institutionally reviewed, dosage schedules other than 30 μg at 0,1,12 month intervals, timed to provide maximum protection in advance of the tick transmission season, should not be used.

The committee discussed whether or not to reference the as-yet unpublished related vaccine trials, and whether the language on the 0,1,12 schedule should be strong or permissive.

Dr. Dennis Parenti of SmithKline Beecham noted SKB's agreement that the unusual 0,1,12 schedule is somewhat awkward and does not provide optimal protection. To accelerate that schedule, they studied alternate schedules in two large reactogenicity and immunogenicity studies among persons aged ≥15 years. The pivotal efficacy study (LY-008) administered vaccine administered at 0,1,12 months, achieved a GMT of 5704. Study LY-014 administered at 0,1,6 resulted in GMT of 7161, and 0,1,12 achieved titers of almost 11,000. Study LY-016 compared schedules of 0,1,2 and 0,1,2,12. After two doses, the 0,1,12 had titers approaching 1700, after dose 3, titers <10,000; the 0,1,2,12 groups had titers of 1700 after dose 2 and 4900 after dose 3. The 0,1,6 and 0,1,2 schedules were well tolerated and had immunogenic equivalency with the 0,1,12.

Discussion: Dr. Livengood noted that a marked drop off of the shorter schedules by the next

year's season posed implications to booster doses. Those on the 0,1,2 schedule would require a fourth dose to carry high levels to the second season. Dr. Parenti reported an ongoing booster study that should produce data and a strategy by the end of 1998. Dr. Pickering hoped for studies on the shorter intervals, particularly in light of the practicality of the vaccine's use for travelers.

Dr. Goldenthal suggested that ACIP advise the 0,1,12 schedule until FDA reviews data on correlates of protection, and that the last sentence of the recommendation be altered to say "until FDA approval is granted, it is recommended that dose schedules other than 0,1, and 12 months not be used." Dr. Word was concerned that by giving the schedule, some physicians will think they can do it faster. She proposed to general agreement that only the FDA-approved schedule be shared, with a statement that it may be altered in future.

Dr. Fleming summarized ACIP consensus to reference ongoing trials, but minimizing the language such that until further information is available, alternate schedules should not be used. Dr. Johnson advocated some reference without emphasis to the shorter schedules, while retaining the strong ending statement.

Boosters
The workgroup recommended language to indicate that boosters may be necessary and that further data are needed to recommend on more than three doses of rOspA vaccine. Rationale: The purpose for this statement was to alert providers that boosters may be necessary.

Discussion: Dr. Griffin advised elaboration in this section to explain the 50% protection in year one and good efficacy in year 2, but still unknown efficacy in year 3.

Vaccine Use in Pregnancy
The working groups's recommendation was that vaccination of women who are pregnant or who are planning pregnancy in the immediate future is not recommended. Rationale: This was based upon the absence of data that pregnancy itself causes any alteration of risk of Lyme disease, nor of any convincing evidence of a congenital Lyme disease syndrome. However, more data is needed on potential fetal effects and on vaccine safety among pregnant women.

Discussion. Dr. Gardner suggested eliminating the recommendation's statement about lipidated proteins, and only stating that there is no evidence of fetal effects. Dr. Griffin asked what "immediate future" meant. Dr. Fleming acknowledged that this is a problem, given the current vaccine dose of 0,1,12 months. He welcomed comments if more specificity is desired in this ambiguous area.

Dr. Peter recommended, for issues both of pregnancy and children aged <15, that the difference be clarified between "contraindicated" and "not recommended." Dr. Zimmerman agreed, and called further for a clear, consistent use of terminology between recommendations.

Dr. Johnson asked what FDA's statement on vaccine use in pregnant women would be. Dr. Goldenthal said that pregnant women were excluded from the trials, and animal reproductive toxicology studies were not done. As with many vaccines, this one's use in pregnancy will fall into the FDA's pregnancy Category C (data is not available). Dr. Breiman stated the importance that the recommendations for new vaccines must credibly demonstrate that the evidence is driven by safety as well as efficacy.

Dr. Orenstein suggested deleting the "planning to become pregnant" text because this is a killed vaccine. There may be issues molecular mimicry, but that is not known now. He proposed instead saying simply "women known to be pregnant." Dr. Fleming agreed; with the 12 month vaccine schedule, a woman planning to become pregnant might not be able to complete the protocol, but at least would have half the dose.

Simultaneous Administration with Other Vaccines
The working group recommended text that the safety and efficacy of simultaneous administration of rOspA vaccines with other vaccines is not established. Pending additional data, rOspA should not be given within one month of the administration of other vaccines.

Discussion: Dr. Halsey found this statement wording too strong and inconsistent with ACIP's general immunization guidelines. He expressed concern that the greater fear of Lyme disease could undercut uptake if it were offered with other vaccines such as pneumococcal and influenza. To some agreement, he suggested text acknowledging the absence of data but also noting that two different antigens have not been shown to be problematic.

Dr. Livengood asked that "one month" be revised to "28 days." Although he agreed that this vaccine might involve seasonality, he was unsure that vaccine given on the same seasonal schedule would induce sufficiently high antibody for 20 months (e.g., administered in November with influenza vaccine). He proposed the statement's inclusion of the trial's strategy to provide maximum protection in advance of the risk season: vaccination in mid-late winter and the other two doses in mid-late summer. Dr. Modlin asked the working group to consider that and other opportunities to enhance uptake, particularly with influenza vaccine. Dr. Ned Hayes commented that the immunization timed appropriately for the season may obviate some concern about simultaneous administration (e.g. influenza administered in November/December and Lyme in February/March).

Dr. Halsey suspected that the vaccine schedules will be approved before another Lyme disease statement is written. He urged the working group to not lose the opportunity of uptake enhancement by seasonality, as applicable here as to other underutilized booster opportunities such as for DTP and pneumococcal vaccines.

Dr. Modlin requested that specific comments about the recommendation on *vaccine use in persons aged 70 years* be sent to Dr. Fleming. With that, the committee adjourned for lunch.

Report on Progress in Task Force Development of the *Guide to Community Preventive Services*; Vaccine-Preventable Disease Chapter

Dr. Peter Briss and Dr. Jeffrey Harris, of EPO, and Dr. Lance Rodewald of NIP, updated the ACIP members on the progress made by the Task Force on Community Preventive Services in developing the *Guide to Community Preventive Services*, focusing on the chapter on vaccine-preventable disease.

Background: Dr. Harris explained that this Guide was intended to help public health, HMOs, etc. select interventions in the context of community health. The Guide was launched by DHHS in August 1996 as an interdepartmental effort building on the *Guide to Clinical Preventive Services*. A 15-member independent non-federal Task Force on Community Preventive Services is developing the Guide, supported by DHHS agencies and partner organizations and

coordinated by CDC.

The Guide develops each area through four activities: 1) summarize what is known about the effectiveness of population-based interventions for disease prevention and control; 2) summarize information on cost effectiveness for these interventions based on data; 3) provide recommendations on population-based interventions and methods for delivery; and 4) identify and prioritize a research agenda to address the research gaps found.

Methods: Dr. Briss stated that evidence based guidelines require 1) a systematic review of evidence that is appropriate for answering particular public health questions, and 2) an explicit process to translate that evidence into recommendations. The Guide chapters are developed in depth by multi-disciplinary chapter development teams (CDT) representing diverse backgrounds.

After deciding their conceptual approach, they consider the outcomes to be influenced, the strategic points for prevention strategies, and potential strategies. This chapter's outcome of interest is vaccine coverage to prevent disease, with the efficacy of vaccine unquestioned. The focus is on population based interventions to improve coverage with universally recognized vaccines for children, adolescents, and adults. The interventions addressed are

increasing community demand, enhancing access to immunization services, mandating immunizations, and provider-based strategies.

After research questions are crafted for each intervention, the CDT then conducts a search and abstraction. The search attempts to limit selection and publication biases, systematically searching multiple databases, reference lists, and in consultations with experts. The abstraction is done by two independent reviewers using a standardized instrument. Any differences are resolved by consensus. The resulting body of evidence is categorized as strong, sufficient, or insufficient based on the number of studies, the suitability of design and quality of the study, and the consistency of the findings and effect sizes.

Dr. Briss outlined the criteria with which the CDT judges suitability of study design for assessing effectiveness. Greatest suitability resides in prospective measurement of exposure and outcome and/or concurrent comparison groups; moderate suitability is retrospective designs or time series with multiple pre-/post measurement but no concurrent comparison group. Least suitable are before/after studies with no concurrent comparison group or exposure/outcome studies of a single group at one point in time.

In translating a body of evidence into recommendations, in which a strong evidence base generally leads to a strong recommendation; insufficient evidence leads to no recommendation, and sufficient evidence of ineffectiveness or harm leads to discouraging the intervention. Other considerations in translation include the intervention's generalizability. Interventions are recommended broadly unless theoretical or empirical reasons restrict recommendations to particular settings, populations, or intervention subtypes. Large harms relative to benefits can lead to negative recommendations, and information on cost effectiveness and barriers are summarized for users but not incorporated into the recommendation itself.

Vaccine Preventable Disease Chapter: Dr. Rodewald described how this strategy was incorporated into the chapter on vaccine-preventable disease. The intervention of performance measurement with feedback has been recommended by ACIP. Aside from feedback to

immunization providers, other peer-provider strategies reviewed are reminder-recall systems, standing orders, and education to providers.

Operationalized, this intervention provides standardized unbiased measurement of performance of coverage at practice level, which is fed back to providers, which provides data for action. It is an important intervention that can overcome provider complacency and stimulate them to action. Assessment of services delivered is a public health function, and through HEDIS, MCOs are using performance measurement. A study of California counties compared estimated and measured immunization performance rates. The median estimated was 95%, the median measured was 68%, and the mean error was 32%.

The Task Force literature review covered 28 assessment feedback studies. For the eight best studies, all increased coverage (1% to 32%, with a 17% median improvement) and showed a positive impact regardless of baseline coverage. Similarly, a line graph of effect size by study setting demonstrated improvement in coverage.

Based on the evidence, the Task Force concluded that this intervention should be strongly recommended. It is generalizable to a variety of practice sites and has no identified harms, although barriers to implementation include the multitude of immunization providers, the expense of such assessments, technical measurement issues, and non-optimized feedback techniques and sampling strategies for private practice. Also of concern is immunization information overload.

The current research in process includes the Core Functions Project, which is implementing provider assessment feedback applied to public and private settings; a study counting immunization providers, gaining access to them, and optimizing their feedback; reducing the cost of assessments (e.g., pursuing quality assurance sampling, or a smaller, simpler sample than a random sample); linking coverage performance with VFC accountability (e.g., among the 50,000 VFC-enrolled U.S. physicians); and another large project on harmonizing HEDIS and the National Immunization Surveillance's measurement.

Discussion: The committee welcomed the Task Force's effort. If this Guide is used similarly to the frequently-consulted Clinical Guide, the benefits will be substantial. When asked to what extent it was informed by the similar Canadian process published five years earlier, Dr. Briss reported collaboration with those authors and attempts to move beyond that high bar. Regret was expressed that the field must wait to late 2000 for the publication of such good data. Dr. Snider noted that resources prevent such labor intensive work at this level of detail, and hoped for future support to allow more.

Harmonized Immunization Schedule

The issues regarding the harmonized immunization schedule were: 1) proposed changes to the graphical representation of each vaccine on the schedule and 2) proposed changes to footnotes to each scheduled vaccine.

Hepatitis B
Dr. Paul Kilgore of NIP presented the hepatitis B recommendation.

- No graphical changes were proposed. The new footnote (#2) reflects the merger of two 1998 schedule footnotes (#2, #3) into one proposed 1999 footnote. This resulted from changes in the manufacturer dosage and input from the working group and others in the

process.

- Footnote changes:
  a. "... second dose of hep B vaccine should be administered at least one month after the first dose; the third dose should be administered at least four months after the first dose and at least two months after the second dose, but not before six months of age, for infants."
  b. Paragraphs regarding infants born to hepatitis B surface antigen positive mothers, and to those whose antigen status in unknown, were streamlined; the content did not change.

Discussion: Text changes: 1) In deference to physicians using the hep B/Hib combination Comvax but unwilling to drop the newborn dose, alter the second sentence to recommend the "last dose of hepatitis B vaccine series should be administered at least 6 months... " 2) Begin the first paragraph with "For infants, the second dose of hepatitis B vaccine should be administered..." In other matters, the only potential impediment cited to dropping the numbering of the recommended hepatitis B vaccine doses was the risk of causing confusion. However, the consensus was to drop that numbering from the 1999 schedule.
Decision: Agreed.

DTP, DTaP Vaccine

- The graphical representation was changed to remove DTP from all doses in 1999. Only DTaP is shown at 2,4,6,15-18 months and 4-6 years. The Td booster remains at 11-12 years. No changes were made in the DTP or DTaP footnotes.

Discussion: There was discussion to drop the symbol for DTP because DTaP is the preferred vaccine formulation. This was the recommendation of the ACIP members and AAP liaison members in attendence. The AAFP commission's unanimous agreement was also reported to switch their recommendation to DTaP. Based on those recommendations, the DTP symbol will be dropped in the 1999 schedule; DTaP will be the symbol and the recommended vaccine in the 1999 schedule."
Decision: Agreed.

H. Influenzae type b (Hib) Vaccine

- There was no change to the graphical representation. The footnote number moved up to #4 with the hep B footnote merge, and text was added to advise against using DTaP/Hib combination products for primary immunization in infants at 2,4,6 months unless FDA approved, due to suboptimal immune response to the Hib component in some combination products. Dr. Modlin noted that this addition was strongly supported by all participants in the conference call.

Discussion: Text changes: 1) add "for these agents" to "FDA approved;" 2) use "lower level of antibody response" rather than "suboptimal." It was left to Dr. Livengood's judgement whether to mention Comvax since it also contains the PRP-OMP Hib component; the text should be consistent.
Decision: Agreed as noted.

Polio Vaccine

- The graphic could remained unchanged from 1998, or the first two doses could be marked as IPV. The footnote will be #5 in 1999, and adds "and AAP" to the final bullet indicating their agreement to change the first two doses to IPV.

Discussion: Deferred to next day's discussion of polio issues.

Rotavirus Vaccine
This newly licensed vaccine is recommended for routine infant immunization at 2,4, and 6 months. The proposed abbreviation is "Rv."

- The proposed footnote acknowledges that time/resources may be needed to incorporate this new vaccine into practice. The first dose should not be administered at <6 weeks of age, and the minimum interval between doses is 3 weeks. Rotavirus vaccine should not be initiated after 6 months of age, and all doses should be completed by age one.

Discussion: Graphic representation to highlight the vaccine as new was discussed. AAP and AAFP were content to shade only from 2-12 months, the age at which vaccine is administered. But the committee's consensus was to not bar or shade across the width of the schedule, but rather to shade and change font only on the vaccine name. Text changes: 1) indicate no administration ≥7 months after an infant is born (i.e., six months plus 4 weeks of age); 2) replace "This new vaccine" with "Rv vaccine"; 3) mention Rv vaccine in the first sentence; 4) drop "The ACIP anticipates"; 5) state "physicians and other healthcare providers" and 6) "complete by the age of 12 months" to ensure providers don't think that immunization by age two is acceptable; 7) state that "no dose should begin on or after the first birthday."
Decision: Agreed as noted.

MMR Vaccine
- No changes to graphical representation; footnote number remains #7 due to Rv inclusion.

Discussion: Text changes: 1) "no later than 11-12 years" to "by 12 years"; 2) specify weeks rather than months in intervals. Voiced opinions both supported and opposed delineating doses as MMR1 and MMR2. CDC will take this under advisement.
Decision: Agreed as noted.

Varicella
- Graphical representation changed only to note "acceptable ages of immunization" rather than "recommended age of immunization." The footnote would only change "susceptible children" to "susceptible persons."

Discussion: Dr. Orenstein noted that children with histories of varicella rarely develop varicella disease, so parents' recollection is accepted; but this may be reconsidered as prevalence drops. Dr. Guerra described great confusion at the local level, suggested at the next meeting defining "reliable" history. Inexperienced parents or child care workers may not be able to distinguish varicella from scabies, which relates to school entry and child care issues. Dr. Halsey proposed that CDC and NIP address this with a newsletter or other release, as this is more of an implementation issue less well addressed in this schedule.

Text changes: 1) define "susceptibility;" 2) change "during 11-12 year old visit" to "at or before the 11- or 12-year old visit." 3) The second part of the footnote may be redundant; state "at any visit after the first birthday, and no later than the 11 or 12-year old visit;" 4) insert "children who lack a reliable history of chicken pox may receive varicella vaccine at any visit after the first birthday (...appropriate text...) and by 11-12 years." 5) The schedule's ovals may not clearly define this as the time to redress missed prior vaccinations; define susceptibility as "unvaccinated children or those without a reliable history of chicken pox disease."

After further discussion of numbered doses, there was general ACIP agreement to drop the numbering protocol for all the vaccines.

Decision: Deferred to further discussion on the following day.

VOTE: on ACIP acceptance of harmonized schedule, except for polio and the varicella footnote. Moved by Dr. Guerra, seconded by Dr. Fleming. All members were eligible to vote.

In Favor: Griffin, Glode, Fleming, Clover, Modlin, Guerra, Johnson, Le, Offit, and Word.
Opposed: None
Abstained: None
Outcome: Passed

Update on Hepatitis B and DTaP Vaccine

Dr . John Livengood requested approval of two *Notice to Readers* for Hepatitis B and DTaP vaccines.

1. FDA Approval of a Fourth Acellular Pertussis Vaccine for Use Among Infants and Young Children" In its wish to move aggressively when DTaP was licensed for children, the ACIP approved it for the VFC program before it was licensed, contingent on a publication of a Notice to Readers and a CDC vaccine purchase contract. That set a precedent for acellular pertussis products, with four products now licensed.

Issues: At question was whether the ACIP wished to express any opinion on the products to guide state purchasing decisions and to clarify the absence of differences among products. A statement was added to the Notice that "the ACIP (AAP and/or AAFP) have not expressed a preference between different acellular pertussis vaccine formulations." CDC and FDA found no definitive data to indicate safety or efficacy differences in the products. FDA had written a letter to that effect noting that differences in studies made uninterpretable any conclusions about differing points efficacy.

Discussion: Dr. Clover thought there was an inference in the last statement inferred that ACIP had addressed this, but it had not and should. However, Dr. Orenstein thought that no stated ACIP preference in the DTaP statement had been interpreted as a defacto opinion of the products' essential equivalence. Dr. Griffin suggested a statement that the data are insufficient. Dr. Johnson noted the Notice's reference to a fourth dose 15-20 months of age, while the harmonized schedule indicates it as acceptable at 12 months. He advocated text mentioning the 12 months of age and explaining that allowance for providers fearing the child would not return at the right age for dose 4.

VOTE: To accept the Notice to Readers on pertussis with the changes suggested by the committee. Conflicts involved North American Vaccine for the fourth dose of acellular pertussis.

In Favor: Griffin, Glode, Fleming, Clover, Modlin, Johnson, Le, Offit, Word.
Opposed: None
Abstained: Guerra
Outcome: Passed

2. *Recombivax HB® formulation change*. On August 27, 1998, Merck replaced the 2.5 μg dose of RECOMBIVAX HB®, administered to infants of surface antigen-negative mothers and other children to 11 years of age, with a single 5 μg dose. The ACIP recommended one combined 5 μg dose for all children and adolescents 0-19 years of age. Either dose can be used to complete any vaccine series already begun for children aged $\leq$10 years. The change is FDA approved; AAFP endorsed; and ACIP recommendation was recommended.

Discussion: Dr. Halsey suggested specifying "To simplify the vaccination schedule for all children... receiving the Merck product." This would avoid any perceived product endorsement, and draw attention to the antigen since other products calls for different doses.

VOTE: To accept the Notice to Readers on hepatitis B with the changes suggested by the committee. There was no member conflict for the Merck product, since there were no commercial consequences involved.

In Favor: Unanimous: Griffin, Glode, Fleming, Clover, Modlin, Guerra, Johnson, Offit, Le, Word.
Abstained: None
Outcome: Passed

Revised Recommendation for Vaccination of Children Against Hepatitis A

Workgroup Chair Dr. Mimi Glode recalled the formation at the June meeting of a working group to review possible revisions to the hepatitis A statements. The members were Bill Schaffner, Geoffrey Evans, Fernando Guerra, Paul Offit, Natalie Smith (California), David Fleming (Oregon), Bob England (Arizona), Chin Le, Hal Margolis, Francisco Everhoff, Beth Bell, Craig Shapiro, Jose Santos, and Martin Meltzer.

Dr. Beth Bell of NCID reviewed the information presented at the last ACIP meeting. Communities that experience Hepatitis A outbreaks can be divided into high or intermediate rate communities. In the high rate communities outbreaks are periodic and most cases occur among children; these communities tend to be small and geographically well-defined. The intermediate rate communities, toward which the proposed recommendations are directed, tend to be larger (e.g., Memphis, St. Louis). Cases also occur among children, adolescents, and young adults; the outbreaks may be periodic, but some communities experience sustained elevations in hepatitis A rates.

Dr. Bell reviewed the December 1996 ACIP recommendations for use of hepatitis A vaccine in high rate communities. These recommended that children be routinely vaccinated against hepatitis A beginning at 2 years of age, and recommended catch-up vaccination of older children within 5 years, or sooner if an outbreak was ongoing. In intermediate rate communities, groups with the highest rates of disease were recommended for vaccination to control outbreaks, with routine childhood vaccination to prevent future outbreaks.

Since the publication of these recommendations, the effectiveness of controlling and preventing hepatitis A outbreaks in both types of communities has been evaluated. In high rate communities, relatively high (50-80%) first-dose vaccination coverage of pre-school and school-age children has been achieved, and rapidly implemented vaccination programs have been successful in interrupting ongoing outbreaks. In intermediate rate communites, the effectiveness of vaccination programs has been more variable. In general, first-dose coverage

of preschool and school-aged children has been relatively low (20-60%). The impact of vaccination on ongoing outbreaks has been modest and generally limited to reducing reported disease rates in the targeted age groups, which may not represent the majority of cases.

The working group proposed an updated strategy of focusing on sustained vaccination of at least one age cohort to prevent outbreaks and eventually lower incidence in areas with elevated rates. Although ultimately, hepatitis A vaccine should be incorporated into the routine vaccination schedule for all children, as an interim measure routine childhood vaccination would be limited to certain states and counties with consistently elevated hepatitis A rates. Analysis of long-term epidemiologic trends indicates that a well-defined number of states have accounted for the majority of cases over the past decade(s) and include most communties that can be classified as intermediate rate. Ongoing routine childhood vaciantion in these areas would be expected to ultimately result in a sustained reduction in hepatitis A incidence.

The updated draft recommendation would indicate that: in states with an average 1987-1997 annual hepatitis A rate of $\geq$20/100,000 (double the national average, involving 50% of reported cases nationwide in this time period), routine hepatitis A vaccination of children would be done statewide. In states with a lower average not implementing routine vaccination, routine vaccination of children would be done in communities/counties with average annual rates during 1987-97 of >20/100,000.

The preliminary results of an economic analysis of routine vaccination implemented in 7 states with elevated rates were shared. The model assumed a linear decline in hepatitis A cases over 30 years. Successive single age cohorts would be vaccinated. The baseline number of cases were derived from average reported cases during 1992-97 in the 7 states with an adjustment for under-reporting. The cost data (direct/indirect) was taken from a 1991 study of 287 reported Sentinel County cases, adjusted to 1996 dollars, and do not include the costs of liver transplantation. At a vaccination cost of $30/person, the analysis showed cost savings to society with 65%-75% coverage. At $60/person cost, the costs were estimated at about $50-170 million. The model indicated that the direct medical costs per case prevented for hepatitis A vaccine was of the same order of magnitude as that for rotavirus and varicella vaccine.

Areas of further research relevant to hepatitis A vaccination include 1) determining the optimum dose and schedule for hepatitis A vaccine in infants. The vaccine is safe in infants and they respond to vaccination with protective antibody levels, but the final GMT is lower in infants with passively acquired maternal antibody; 2) determining the efficacy of one dose of vaccine over time. One dose was 94%-100% efficacious in the prelicensure studies, but few data exist regarding longer term efficacy of one dose of vaccine. No disease was reported among a cohort in Alaska followed for 19-30 months after receiving one dose; 3) combination vaccines that include hepatitis A vaccine, none of which are expected to be available for use in infancy in the near future.

Dr. Bell indicated that the working group discussed measures to promote routine vaccination, such as integrating hepatitis A vaccine into routine health care, and vaccination of single age cohorts (e.g., 2-5 years old, school entry laws) Some of the working group members, particularly those from state health departments, are concerned about the financial burden to states and competing priorities with other recently-recommended routine vaccinations.

Dr. Bell summarized that the current strategy is unlikely to produce a sustained reduction of the incidence of hepatitis A, and that routine vaccination is the most effectigve strategy. As an interim strategy until routine hepatitis A vaccination can be recommended nationwide, routine

vaccination of children in areas with elevated rates is likely to reduce hepatitis A incidence over time. When an infant formulation is available, it should be integrated into the routine immunization schedule in all states.

Discussion

1. Does the ACIP favor revision of the current hepatitis A statement, moving away from outbreak control toward more routine vaccination?

Dr. Livengood commented that the states' ability to assess their own situations and select their own strategies is consistent with the current recommendation, and asked to what extent they should be assisted. Dr. Glode responded that the approach is to be a little more proactive, since the current strategy is less effective than hoped. Dr. Bell agreed, and noted that the states proceeding on their own also reflects frustration, and the ACIP's guidance is sought.

Dr. Fleming cautioned, though, that some states wishing to promote more immunization for hepatitis A may not be ready to implement a school entry law. He wondered if the ACIP recommendation for the VFC program would need to be altered to help such states. Dr. Livengood thought that any county designated as high- or intermediate rate that implemented routine vaccination would already be covered by VFC.

Dr. Guerra supported a more specific recommendation to help attract support for further resources to help address children still at risk. Dr. Orenstein also noted the greater ability of an ACIP statement rather than state health department consultation or a provider group's recommendation to better impel a policy to implementation in a community. Drs. Natalie Smith and Dr. Hal Margolis urged the ACIP to move forward toward prevention, since outbreak control hasn't worked.

2. Is it appropriate to target states and communities with rates >20/100,000?

Dr. Johnson asked when infant vaccination might be feasible. Both Merck and SmithKline Beecham representatives estimated 3-5 years. On Dr. Johnson's further question, Dr. Bell affirmed that the economic model was based on communities with a rate of at least 20/100,000. Alterations for states such as Texas and smaller states probably would not change the bottom line.

Dr. Le urged the ACIP to not be held back from recommending by the lack of an infant formulation. He expected good acceptance by parents for immunization even from 2 years of age for children in day care centers. When the infant vaccine is available, the statement can be revised.

Dr. Snider asked the states' input on whether they could find the resources to take action to vaccinate against hepatitis A if they had a case baseline lower than the 20/100,000 rate. Dr. Guerra reported Texas' limited success in getting funding from the legislature to target the high-rate border counties, and San Antonio's use of the general fund to support school districts with high rates.

However, Dr. Clover raised the arbitrariness of 20/100,000, favoring more flexibility for states, and expressed his unease with an interim strategy to make this a routine vaccine. He suggested that the cost effectiveness data be revisited for a routine program. He also asked about data indicating that children aged >1 year have good response to vaccination, avoiding the maternal antibody interference of ages <10 months. Dr. Bell termed said this question is still under investigation. It is likely that some children, but perhaps only a small proportion, have

passively acquired maternal antibody at 12 months.

Dr. Zimmerman did a quick calculation that, with 100% vaccine efficacy, 500 children would have to the treated to prevent one case over 10 years. This differs greatly from most of the other routine vaccines. From that perspective, he wondered if a stronger "should be vaccinated" recommendation should be used for a 40/100,000 rate, and more permissive language at 20/100,000.

Dr. Fleming cautioned that the analysis used reported cases; the actual incidence of the disease could be greater. He favored the overall goal of routine hepatitis vaccination, with some flexibility (e.g., >20 cases versus <20 cases). He also noted that it higher cutoffs (e.g., 40/100,000) can be counterproductive because this makes it harder to mobilize counties emerging from an outbreak, or disqualifies counties without that rate to prepare before an outbreak.

When asked the AAP's position, Dr. Halsey reported their support of states to protect their children against hepatitis A with this vaccine, although they didn't have the cost effectiveness data at the time of their meeting. He supported its administration in the second year of life if possible, to include it in routine visits and avoid extra costs. He encouraged exploration of how soon before travel the vaccine can be given. The AAP and ACIP statements differ; the AAP indicates that the vaccine should be given at least 2 weeks before departure while the ACIP recommends that the vaccine be given at least 4 weeks before departure. The ACIP should revisit this issue becuase providing vaccine 4 weeks before departure often is not practical.

Dr. Le agreed thought that parents would be receptive to immunizations at a 2 year visit, and expected this to be even more true for hepatitis than for measles.

Dr. Snider saw the need to change to a more proactive stance; the challenge is to define the cut-point rationale to target communities. He would avoid language that precludes low-rate areas with hot spots of higher rates. There is a value to being specific to impel action, but not to the degree that it prevents action. Dr. Modlin agreed; as Dr. Fleming suggested, the wording should allow as much flexibility as possible at the local level, while still providing direction.

3. How do we balance disease burden potentially controllable with more widespread vaccine use, with the strength and flexibility of recommendations and the burden of implementation (e.g., prioritizing among competing priorities)?

Dr. Fleming noted that for vaccines addressing a potential cohort of children, the approach has been through school entry laws, but this would not work in all cases. A single-age cohort exclusively eligible for vaccine is often counter-productive (e.g., precluding immunizing a sibling at the same visit). Dr. Natalie Smith also advocated implementation flexibility in light of such competing priorities as the hepatitis B catch-up program.

Dr. Bell requested that the members fax her any further comments by October 31. Dr. Modlin assumed there would be some revision made to the hepatitis A statement, with related discussion at the February 1999 meeting. He requested that the working group circulate a draft to the committee members within 6-12 weeks to get more feedback before February.

Dr. Evans commented that states approving mandated vaccination involves implications to the liability coverage for vaccine injuries. By law, the compensation program covers any vaccine designated by CDC for routine administration to children. Dr. Guerra urged future discussion of

giving hepatitis A vaccine to children with hepatitis C infection. Dr. Modlin appreciated that point. The validity of the data regarding hepatitis A following on hepatitis C is unclear; a review might be in order. Dr. Bell said that this would be considered.

Vaccines for Children Program

Dr. John Livengood, NIP, presented a resolution to include rotavirus vaccine in the VFC program and to consolidate resolutions for vaccines.

Varicella

- **Resolution 10/98-1:** repeals VFC resolutions 6/95-4, 6/95-5, 6/97-1 and 6/98-2. The purpose of this resolution is to consolidate all previous recommendations pertaining to varicella vaccine into a single resolution. It clarifies contraindications and precautions, which are not separated in the varicella statement. Separation could be discussed at the next meeting. It also expands the eligible age groups through 18 years of age. Previously, only those who were at least 12 months of age and who were born after January 1983 were covered.

Discussion: Dr. Orenstein encouraged deletion of the 1983 date, and using text similar to that of MMR about "all susceptible children who are at least 12 months of age through 18 years of age." Covering all children would also allow deletion of the text regarding household contact with high risk persons.

Dr. Pickering asked if, in the absence of much data for varicella, the time periods for measles and varicella vaccine administration could be harmonized or clarified. Dr. Halsey explained that the Red Book would try to do so while stating the lack of data, and supported Dr. Orenstein's suggestion. Procedurally, he suggested simply indicating that the precautions/indications are concurrent with ACIP policies, because addressing all precautions and contraindications would require constant new VFC votes.

Dr. Livengood explained that the VFC is legally required to review all precautions and contraindications. The Office of General Counsel also prefers them to be freestanding documents on the Internet. However, he also preferred simplicity and harmonization. In the absence of data, a footnoted table such as used with MMR is possible, and the same guidelines seem reasonable for two live virus vaccines such as varicella and measles. Dr. Snider noted, though, that absent a pressing need, such significant changes should be accomplished in a statement revision rather than a VFC vote. It was generally agreed to defer this topic until the next meeting. However, it was also noted that extending the age distinctions would be consistent with the varicella recommendation.

VOTE: **Resolution 10/98-1 to approve the varicella recommendation**, with two modifications: to define the eligible groups as "all susceptible children aged at least 12 months old," and to revise on page 1 the text about catchup vaccination to recommend varicella vaccine "for all susceptible children who are at least 12 months of age through 18 years of age." The resolution will be effective as of this day. Moved by Dr. Glode. Conflicts involving Merck's varicella vaccine affected Drs. Clover, Griffin, Le, Modlin and Offit, leaving only five members eligible to vote. With 7 needed, the ex-officios were asked to vote.

In Favor: Glode, Fleming, Guerra, Johnson, Word, Trump, Graydon, Breiman, Rabinovich and Evans
Opposed: None
Abstained: Goldenthal, Offit, Le, Modlin, Griffin and Nichol
Outcome: Passed

Polio

- **Resolution 10/98-2:** repeals VFC resolutions 2/94-10, 6-94-8 and 10/96-1. The purpose of this resolution is to clarify the timing of the third dose of IPV to reflect current ACIP recommendations, to clarify the eligible groups, and to make the contraindications and precautions consistent with the ACIP statement. This is part of a continuing ACIP trend to specificity in all vaccine statements regarding immunodeficiency.

Discussion: focused on no contraindication to a child with cancer on chemotherapy and steroids. A strong statement was favored that any child on immunosuppressive agents should not get OPV. A suggestion to add solid organ and hematopoietic transplantation as contraindicated to OPV was altered to instead use the varicella and MMR text regarding immunosuppression for the OPV section. Recent data on polio vaccine regarding pregnancy was discussed, resulting in the conclusion that precautions for pregnancy will state that both OPV and IPV "may be given if immediate protection is needed."

VOTE: Resolution 10/98-2 as stated, with modifications to make IPV and OPV paragraphs regarding immunosuppression identical to those in varicella; and stating under IPV use in pregnancy "if immediate protection is needed, IPV can be administered"; and to change "bone marrow transplantation" to "hematopoietic cell transplantation". There were no conflicts with Wyeth Lederle or Pasteur Merieux Connaught, allowing a quorum of member to vote.

In Favor: Griffin, Glode, Fleming, Modlin, Guerra, Johnson, Word
Opposed: Offit
Abstained: Clover, Le
Outcome: Passed

Measles, Mumps, Rubella

- **Resolution 10/98-3:** Repeals VFC resolutions 2/94-12, 2/94-13, 6/94-7 and 6/97-3. The purpose of this resolution is to clarify the contraindications and precautions and clarify MMR vaccine use during outbreaks (i.e., before the recommended age).

Discussion: There were no revisions offered except to state 28 days rather than 1 month for the administration of MMR or component vaccines. Mr. Kevin Malone clarified that the statute involving employees of a federal agency which has interests with a private entity does not constitute a conflict of interest; the ex-officio representatives could vote. If an individual receives a research grant in their official capacity, there is no conflict, but the same does not apply to work as a private individual, including those who may operate in dual capacities. Dr. Snider asked anyone uncertain of their status to consult with Mr. Malone.

VOTE: Resolution 10/98-3: As stated, with one modification to state 28 days rather than 1 month. The ex-officio members were required to vote.

In Favor: Glode, Fleming, Word, Johnson, Guerra, Evans, Rabinovich, Breiman, Graydon, Trump

Opposed: None
Abstained: Offit, Le, Modlin, Griffin, Goldenthal, Clover
Outcome: Passed

Influenza

Resolution 10/98-4: Repeals VFC resolutions 6/94-4 and 2/95-1. The purpose of this recommendation is to consolidate all previous resolutions pertaining to influenza vaccine into a single resolution. It clarifies the recommended influenza vaccine schedule and dosage intervals, the influenza vaccine contraindications, and adds additional eligible groups.

Discussion: Again, month should be changed to 28 days for dosage intervals. Inclusion was suggested of inadvertently excluded text to add to the eligible groups children or adolescents who are household contacts of persons with chronic and other high-risk conditions, which would include pregnant non-adolescents. This could be addressed further in February or June. If the statement becomes more permissive, coverage for children traveling to flu-endemic areas, for children in the U.S. endemic season, and for outbreaks could be considered. The text under contraindications could also clarify that the vaccine does not increase risk of adverse events. There was discussion of specifying a history of Guillain-Barré Syndrome "after previous influenza vaccination and influenza disease," but with insufficient evidence, the consensus was to not alter the text.

VOTE: **Resolution 10/98-4:** As stated, with modifications to state 28 days rather than 1 month; and to add to the eligible groups 1) children and adolescents who are residents of nursing homes or other chronic-care facilities that house persons at any age who have chronic medical conditions, 2) adolescent females who will be in the second or third trimester of pregnancy during influenza season, and 3) children and adolescents and household members of persons in high-risk groups. Conflicts with Connaught, Wyeth Lederle, Parke-Davis, and Evans did not involve enough members to require ex-officio votes.

In Favor: Griffin, Glode, Fleming, Modlin, Guerra, Johnson, Offit, Word
Opposed: None
Abstained: Clover, Le
Outcome: Passed

Rotavirus

Resolution 10/98-5: The purpose of this resolution is to include rotavirus vaccine in the Vaccines for Children program.

Eligible groups: All infants who are at least 6 weeks old and under the age of 12 months.

Schedule: The routine schedule recommended for rotavirus vaccination for an infant is dose 1 at 2 months; dose 2 at 4 months; dose 3 at 6 months. The ACIP recommends the first dose of rotavirus vaccine for all full-term infants ($\geq$37 weeks of gestation) by 6 months of age. The first dose of vaccine is not recommended for infants $\geq$7 months of age and older.

Catch-Up Vaccination: Children $\geq$7 months of age should not begin the vaccine series due to the increased rate of febrile reactions after the first dose in older infants.

Accelerated Schedule: An accelerated seasonal schedule, starting at 6 weeks of age, with a minimum dosing interval of 3 weeks, may be used to assure protection prior to the onset of

rotavirus season.

Dosage Intervals: Minimum age for first dose: 6 weeks; minimum interval from dose 1 to 2: 3 weeks; minimum interval from dose 2 to 3: 3 weeks. The first dose should not be administered at ≥7 months of age. Doses 2 and 3 should not be administered after 12 months of age.

Contraindications: 1) Allergy to vaccine components; 2) moderate or severe illnesses with- or without fever; 3) known or suspected immunodeficiency; 4) infants born to mothers with HIV infection until tests for HIV infection in the infant are negative at 2 months or older.

Precautions: 1) Premature Infants (< 37 weeks); 2) infants living in households with an immunocompromised person; 3) infants with pre-existing chronic gastrointestinal tract disease; 4) infants with on-going diarrhea.

Effective date: This resolution is not effective until the publication in the *MMWR* of the ACIP general recommendations for use of rotavirus vaccine. A footnote will explain that vaccines approved by the ACIP for inclusion in the VFC program are not available for use in the program until after the CDC has established a contract for the purchase of the vaccines.

Discussion: The committee suggested using the same text as page 21 of the rotavirus draft statement, to advise against administration to infants of mothers with HIV infection unless it is established that the infant is not HIV-infected. Also suggested was flexibility in implementation, as done in the harmonized statement, to allow the practitioner time to incorporate this into practice. Tailoring is also needed to the revised statement about immunosuppressive therapy. Text suggested to general agreement was "immunosuppressive therapies to include..."

Reassessment of Economic Analysis of Rotavirus Vaccine

Mr. Andrew Tucker reviewed the information provided at the last ACIP meetings on outcomes preventable with a rotavirus vaccine program. The annual cost of rotavirus to the U.S. is $1 billion ($264 million direct cost, mostly from hospitalization; and $736 million indirect cost, mostly loss of caregiver income). At $20/dose, the program would costs $107 million, but allow a 30% net overall savings to society of $296 million. However, the effect of adverse events could eliminate almost all the cost benefit.

Mr. Tucker then presented a reassessment of the economic analysis of rotavirus vaccine conducted after the FDA's licensure of the vaccine and Wyeth-Lederle's announcement of its list price of $38/dose. The break-even price per dose of $9 for the healthcare system and $51 for society (direct and indirect cost) was altered to $8 and $41, respectively. Again, the cost increase essentially eliminated the $200 million cost benefit of a vaccine program.

A program/no program analysis of outcomes prevented was presented. The estimate assumed a 60% federal and 40% private purchase of vaccine. The negotiated federal price was estimated at $19 and $30/dose. The population was stratified into two socioeconomic status (SES) groups: 75% "higher" and 25% "low" (having one-third the income of the high SES group). Since the Newman et al (1998) study presented previously indicated that Medicaid coverage for low-SES infants presented a significant risk factor (1.5 odds ratio) for viral gastroenteritis hospitalizations. a higher morbidity risk was assigned to the lower SES group. It was lowered slightly for the high-SES group, therefore averaging an overall stable morbidity. The lost earnings per day for this group were also stratified at three times that of the lower SES group.

The results were presented for the overall population as well as the two SES groups. For the

VFC analysis, it was assumed that the 60% federal purchases would cover all the low SES persons (25% of the population), with the 35% balance covering some of the higher SES group. Costs of $19 federal and $38 private sector resulted in $154 million saved. The savings at a $30 federal price was lower.

A negotiated VFC price of $19/dose would result in a $55 million decrease in health care costs, and for the 60% of the population covered by VFC, a gain of $114 million. The break-even prices are $9 from a healthcare perspective and $39 from a societal perspective. The analyses' have consistently concluded that a national routine vaccination campaign would be cost effective, with the exact results subject to the vaccine price. Charted, the several analyses done were as follows:

CDC Cost Effectiveness Analyses Comparisons: Net Savings/(Losses)				
Analysis	**Medical (millions)**	**Medical (per $1 saved/spent)**	**Societal (millions)**	**Societal (per $1 saved/spent)**
Old (*JAMA* 1998,279)	(107)	0.63	296	1.39
Old with Adverse Events	(115)	0.60	200	1.69
New (SES/morbidity @$38/$19/dose) "High" SES "Low" SES	 (179) (167) (11)	 0.49 0.41 0.84	 154 139 14	 1.44 1.49 1.21
VFC @ $19/dose VFC @ $30/dose	(55) (119)	0.67 0.49	114 50	1.68 1.22

Discussion: In response to Dr. Halsey's question, Mr. Tucker confirmed that administrative costs were included in the calculation at $10/visit, comparable to OPV. The analyses done for the public sector were also done for the private sector; for example, the $0.41 and $1.49 for each dollar spent was the same ratio at the private sector's $30 dose as the federal sector's $38/dose.

Dr. Livengood pointed out that public sector cost is not yet known, so the median and lowest potential discount were modeled for a range of likely value. He asked if the VFC analysis, which required a good deal of work, was helpful to the committee in the decision making process. He expected more concern about the vaccine's cost than its cost effectiveness, and reminded the committee of the expected shortfall in all the S.317 program categories next year. He also suspected the 1.5 disease burden odds ratio to be underestimated in lower SES groups, since it used birth certificate data to predict outcome in only the first year of life. Even so, a higher relative risk will be necessary to show medical cost savings in the VFC program, even though it is close in the lower SES groups.

Dr. Fleming was also concerned that not knowing the vaccine cost undercuts justification for an ACIP decision. He stated for the record that the federal government must exercise its power of discretion in negotiating the contract, to decide if the price is warranted. Dr. Florian Shödel, of Germany's EVAX, wondered since a VFC statement requires a definitive date how the flexible introduction to practice already agreed upon could be done with a VFC vote.

Dr. Livengood explained that the VFC vote is not effective until the contract is signed. Many states also worry about having the resources to reach additional populations not covered by the

VFC program. The VFC program intends in the next year to subsidize the states for vaccine expansion beyond the S.317-eligible population. The suggested language for flexibility reads that "The ACIP anticipates that due to logistical constraints, health departments, individual physicians, and other health care providers, may require time to incorporate this new vaccine into practice." This simply acknowledges the reality that the vaccine's adoption will be variable over time, in part because a physician may be uncomfortable at not being able to provide it for a non-VFC child. Such a tolerance is consistent with the AAP, AAFP, and ACIP recommendations.

Mr. Malone stated that the law is utilized to determine what risk groups are entitled to vaccine. But this concept is a different twist on that, allowing provider discretion on whether to implement the vaccine. He felt that if narrowly drawn, the statute does allow the ACIP to confer that discretion to providers, but was concerned that the proposed language may be overly broad. A standard of reasonableness is needed, such as an end date by which a VFC provider must provide the vaccine.

Dr. Fleming suggested, alternatively, that the ACIP set a date to revisit that allowance of flexibility, for example, a year hence. Dr. Johnson supported issuing the current statement text, then dropping it upon evidence that the vaccine is in wide use. Mr. Malone encouraged that because upon any legal challenge, a court would apply a reasonableness standard to how ACIP interpreted its powers under this law. ACIP has the right to change its recommendations, but a standard is still required of how much discretion is conferred to the physicians. As currently written, it could be interpreted to mandate practice implementation within six months. Absent the knowledge to establish a firm end date, a stated ACIP commitment to address such criteria would be favored by the court.

Dr. Le noted that this rotavirus recommendation will be widely used (e.g., by public health clinic nurses, or others without much supervision). He expressed concern that using the word "precaution" would raise questions in the field, and asked to whom ACIP would assign the responsibility to decide whether or not to give the vaccine. He suggested greater specificity in this text. Dr. Modlin appreciated those issues, but thought them more pertinent to the statement than the VFC recommendation. Dr. Shödel suggested wording of "precautions in the absence of clinical data," both here and in the statement. Dr. Modlin asked Dr. Livengood to incorporate these suggestions overnight, to be revisited the next morning.

Dr. Snider summarized the suggestions: make the statements and VFC resolution consistent regarding immunodeficiency; change the age to $\geq$7 months; expand the conditions under known or suspected immunodeficiency to parallel the statement; modify #4 of the contraindications to bar vaccine until infants born of HIV-infected mothers are known to be uninfected; add language regarding delayed implementation until the ACIP revisits the issue at (a defined point in time); and cite precautions due to lack of data. With that, the committee adjourned at 7:00 p.m.

Unresolved Issues

On reconvening at 8:00 a.m. on the following day, October 22, 1998, the committee addressed unresolved issues from the previous day's agenda.

Should a Working Group Be Formed to Revise the Present ACIP General Recommendations on Immunization?

Dr. Jay Watson summarized the purpose of the present ACIP general recommendations, which

were last updated in June 1994. Their purpose is 1) to provide practical standard guidelines and recommendations for vaccine administration; 2) summarize issues which apply to multiple vaccines; 3) provide guidance for development of vaccination policies by the public and private sectors; and 4) provide background information and references which support current vaccination practice.

The present general recommendations include definitions of terms used in vaccination and a description of the storage and handling of the available immunobiologics. They also address vaccine administration, age at vaccination, vaccination schedules (which are often rapidly obsolescent); the spacing of immunobiologics; hypersensitivity; vaccination of special groups; misconceptions about true contraindications and precautions; reporting of adverse events; vaccine injury compensation program contacts; patient information; issues regarding immunization records; vaccine programs; VPD reporting; and sources of vaccine information.

Several proposed additions/deletions/other changes for ACIP consideration are:

- Immunobiologics: adding 1) a list of manufacturers; 2) a table of recommended storage conditions; 3) guidelines for determining disposition of expired or improperly stored vaccine.
- Administration of vaccines: adding 1) recommendations for a post-vaccination waiting/observation period; 2) discussion of techniques for alleviating pain/discomfort; 3) withdrawing current recommendations for use of multi-dose nozzle jet injectors.
- Vaccination scheduling: adding 1) discussion of principles used to develop vaccination schedules; 2) a table of vaccines recommended for specific age groups; 3) deleting routine and catch-up vaccination schedules.
- Spacing of immunobiologics: reconsider the 4-week interval between doses of live-virus vaccines.
- Vaccination of special groups: adding a section addressing vaccination of bone marrow recipients, adding a table of vaccines for specific risk groups, adding a table of vaccines indicated/contraindicated for pregnancy.
- Hypersensitivity to vaccine components: adding 1) a table listing vaccine composition; 2) guidelines for initial identification and initial treatment of anaphylaxis.
- Vaccine safety: adding contraindications/precautions for varicella, influenza, pneumococcal, and hepatitis A vaccines to the existing table.
- Update/expand, add Website addresses for sources of vaccine information.

Some potential issues related to the general recommendations which may require major discussion are:

- Should the recommendations continue to undergo the ACIP approval process? If not an ACIP document, would they have less influence/dissemination?
- Should they be expanded past the focus on children to include adult immunization issues?
- Should harmonized national standards for vaccine administration be developed? If so, to include what, and coordinated with whom?
- Should current guidelines for accepting foreign vaccination records be changed?
- Should ACIP provide explicit guidance for deciding when to accept or not accept vaccine doses not conforming strictly to minimum ages/intervals between doses?
- Should the ACIP publish guidelines for vaccinating marrow transplant patients?
- Are current guidelines adequate for vaccinating persons using corticosteroids?
- Should ACIP reconsider the current recommendation of a 4-week interval between doses of live virus vaccines?

Possible alternatives to ACIP general recommendations include: 1) publication of a CDC “technical manual” on general vaccination practices; 2) establishment of a Website easily and

regularly updated; 3) referral to other publications addressing general immunization practices (Red Book, Green Book, etc.); and 4) harmonized national standards for vaccine administration.

Discussion: Dr. Modlin reported correspondence from Dr. Wexler and others that the current recommendations are out of date. Dr. Word called for inclusion of adults for better-utilized recommendations. Pediatricians use the Red Book and physicians treating adults seldom raise immunization issues.

Dr. Guerra asked the recommendation document's potential and/or historical audience. In Houston, it is an important reference for public health departments dealing with such historical issues as outbreak preparedness and new issues such as practical cost benefit modeling, particularly for new products. He also wished for a section addressing registries, tracking systems, etc.

Dr. Pickering suggested folding the issues of computerized ACIP statements and harmonized national standards into the general recommendations' revision. Dr. Modlin noted the time needed for such harmonization. Dr. Halsey expressed AAP's desire for a standardized review of computerizing medical records.

Dr. Le favored ACIP input to the guidelines over a simple CDC staff revision. This pertains particularly to policy issues such as the intervals between vaccination, for which there are few data to support immunological differences. He also suggested consideration of immunization as a quality determinant in the utilization of managed care.

Dr. Snider commented that this process of developing/revising general recommendations parallels the challenge of maintaining consistency over time between VFC resolutions and vaccine statements, as well as keeping the released information up to date. He supported the formation of a workgroup not just to revise the general recommendations but to address all the issues raised about them. For example, if there should be general recommendations, how best should they be disseminated and utilized? How could ACIP avoid, for example, addressing contraindications to combination vaccines three times (for general recommendations, VFC, and the combination vaccine statement).

Dr. Gardner urged an active role by the IDSA. Dr. Halsey urged the workgroup's consideration of a standardized target date for general recommendations revision. A workgroup on the ACIP general recommendations was formed, with Drs. Zimmerman, Pickering, Gardner, Marchessault, Peter, Clover, Word, Le, Guerra, Evans, Trump, Vernon, Gilmet, and Rubin volunteering to participate.

Rotavirus VFC Resolution

Dr. Livengood presented the rotavirus resolution, revised according to the previous evening's discussion. The amendments were:

- Page 1: edited to recommend vaccine *"...before* ≥7 months...," and to delete the second sentence not recommending the first dose to infants ≥6 months.
- Page 2: Added to contraindication #3, of known or suspected immunodeficiency: "Because the safety and efficacy of rotavirus vaccine is not established in these populations, rotavirus vaccine should not be given to infants with compromised immune status because of

immunosuppressive disease or therapies, leukemia, lymphoma, or other malignancies. The safety of rotavirus vaccine has not been established in children with chronic granulomatous disease and other primary disorders of neutrophil function, but no evidence of increased severity of rotavirus infection has been observed in these children."

- Page 3: a second note would state that "The ACIP recommends immediate implementation of this recommendation upon availability of vaccine under federal contract. However, due to logistical constraints, some health departments, individual physicians, and other VFC providers may phase rotavirus vaccine into their practice by no later than [July, 1999] [six months after a contract is established]."

Dr. Livengood expressed the opinion that the Page 3 note is unneeded, as well as being unclear whether it targets individual physicians or state health departments. CDC has never taken enforcement action to VFC providers who do not offer the full range of vaccines. Some states are still implementing varicella vaccine. The last survey of state health departments indicated that 72% would implement the rotavirus vaccine by April 1999; the last response estimated July 1999. State implementations have frequently been phased, and he expected no problem in this case. Finally, he thought the ACIP position would be consistent with that of the AAFP, to have the vaccine available, discussed with the parent, and then chosen if it will be administered. However, he felt that a state should not be allowed to decline a VFC vaccine for poor children just because it cannot afford to also provide it to those not covered by VFC.

Discussion: There was general agreement to delete the second footnote on page 3, and that the point of the previous day's discussion was to set a date for the committee to revisit the resolution, not to force compliance by July 1. Dr. Guerra asked whether the VFC could replenish new vaccines purchased in areas before VFC program phase-in. Dr. Dean Mason, Chief of the VFC Contracting and Distribution Support Branch, stated that upon a standing recommendation, ordering patterns consistent with the proportion of the physician's VFC-eligible patient population are accepted.

VOTE: **Resolution 10/98-5:** To adopt the VFC Rotavirus resolution as stated, with modifications to remove the second footnote; to delete the second sentence on page 1 about not recommending the first dose of vaccine in infants ages ≥6 months, and replacing the "≥" to "before" 7 months. All were eligible to vote but for those with conflicts involving Wyeth-Lederle.

In Favor: Griffin, Glode, Clover, Fleming, Modlin, Guerra, Johnson, Offit, Word
Opposed: None
Abstained: Le
Outcome: Passed

Computerization of ACIP Recommendations

Dr. Edwin Kilbourne reported the near-completion of work on the computerization of the ACIP's recommendations for immunization. Under workgroup Chair Dr. Guerra, the membership includes Drs. Pickering, Clover, and Fleming. First, Dr. Kilbourne reviewed the basic elements of a computer algorithm to determine if a child needs an immunization: recommended age or age range; minimum age; recommended interval between doses; and minimum interval between doses.

Eight issues were submitted for ACIP feedback:

1. *Time units and precision of the immunization recommendations.* Current recommendation time units are generally weeks and multiples of 4, used interchangeably with months. Proposed: retain days and weeks, but one month = 4 weeks (28 days); two months = 8 weeks (56 days); ≥3 months equates to calendar months. Years equate to calendar years.

Discussion: Coordinate with the Year 2000 Project.
Decision: Proposal accepted.

2. *Violations of minimum ages and intervals*. Occurs if age or interval between doses is below that recommended. Proposed: not count that dose. Two options for valid revaccination: count time from last doses (valid or invalid) or count time from last valid dose.

Discussion: No consensus was reached. A decision weighing the risks of under-immunization (i.e., doses given too early) versus the possible adverse effects of extra-immunization (more than required in a series) will have to be developed by the next meeting. NIP staff will collaborate with the work group on this. Dr. Halsey reference David Fraser's study of sensitivity to tetanus two decades earlier, and Roland Sutter's review, were suggested to inform the little data on whether hypersensitive reaction comes from interval violation or total number of doses.

Decision: Deferred.

3. *Clinician overrides.* To allow for the inevitable exceptions, the program would flag an otherwise invalid dose as valid "by clinical judgement." Challenges are multiple options, different clinician judgements if providers are changed, and assessment purposes (e.g., HEDIS) which hold to standards. Alternatives are unattractive; allowing a "fudge factor" changes the recommended minimum.

Discussion:
- *Pro:* In absence of evidence base, a consensus-based guideline is appropriate. However, unique individual situations may call for an override; in clinical practice, decisions are made on SES and other data as well as clinical data. Using intervals gives clinicians guidelines of reasonable boundaries, and firms up measurement to allow progress in the vaccine arena. Define intervals per current ACIP recommendations and allow override, while providing text on what is a rational clinical override. Disallowing override could artificially lower immunization rates and cause over-immunization. Where required, don't count as valid vaccine given at inappropriate intervals to avoid interference with school, daycare, etc. policies.
- *Con:* Regulatory issues include school, daycare, etc. rule; and a question of FDA acceptance of 28 days if package insert indicates one month (FDA found that acceptable at this meeting). However, allowing override essentially codifies off-label vaccine use.

Decision: Allow overrides.

4. *Spacing of live-virus vaccines:* (e.g., MMR, varicella). Proposed: space at least 28 days apart. Challenge: do the same rules apply for all such vaccines?

Discussion: The risks and benefits of over-vaccination versus missed opportunities may have to be evaluated on an antigen-specific basis. Potential was noted for interference with OPV, MMR, and perhaps varicella if administered <4 weeks apart. Over-immunization is done mostly in seasonal migrant laborers, and unusual reactions not seen in those children. One

suggestion: to avoid interference, program the standard for live viral vaccine as the interval from the last dose (option #1). But for inactivated antigens, the need to repeat doses may be evaluated differently.

Regarding parenteral versus live-virus vaccine: There are no data on rotavirus minimum intervals, but they won't be administered with other live parenteral vaccine. The 28 day interval does not apply to parenteral versus oral vaccines (e.g., MMR/OPV), where any interval is acceptable. OPV studies indicate a minimum interval of 3 weeks; less invites interference; 8 weeks presented a slight advantage, but 4 weeks was satisfactory. However, oral vaccines are not to be mixed (e.g., OPV and salmonella typhi 21A), only program the algorithm to allow oral/parenteral. Note was taken that the 28-day interval between two live vaccines needs to be reexamined and guidelines applied.

Decision: Referred back to the working group for a recommendation.

5. *Accelerated schedules; definitions and rules for use*: Proposed: program the underlying concept in the ACIP general recommendations' table of accelerated schedules that vaccines are given at minimum intervals until the child is caught up. However, if a catch-up schedule is ever developed with a schedule differing from the minimum intervals, entirely different program parameters will be needed, an undesirable event.

Discussion: General Recommendations base the accelerated schedule on minimum intervals.
Decision: Proceed with programming on that basis, leaving the acceleration decision to the practitioner.

6,7 *6: Process for maintaining consistency in recommendation updates; and 7: codifying inferences.* Inconsistencies in the ACIP documents are rare, but arise if respecification of age/interval in a new recommendation is incomplete (e.g., when the 1998 harmonized schedule for an all-IPV dose 3 was changed from 12-18 months to 6-18 months, the recommended interval was not changed). Proposed: Modify the recommendations as necessary for the revised recommendation to make sense (e.g., in the example above, the recommended interval between doses 2 and 3 in all-IPV schedule should be 2-14 months). In future recommendations, inconsistencies with previous recommendations will be explicitly stated and resolved.

More common are incomplete specifications (e.g., that the minimum age for Hib dose 1 is 6 weeks and the minimum interval is 4 weeks. One can infer that the Hib dose 2 minimum age is 10 weeks, dose 3 is 14 weeks, etc.). Proposed: using the most recent recommendations, infer minimum and recommended intervals and ages where necessary. These inferences will remain valid until they are superseded by future recommendations explicitly specifying the parameters in question.

Decision: Proceed as proposed.

8. *Overdue immunizations*. Challenge is to define "overdue." The ACIP recommendation to initiate recall when child is one month or more behind implies one month as the defining "overdue" for an algorithm. Option: do not address this at all; allow local decisions based on local variables.

Discussion: Recall should allow local option. One month could trigger recall for infants, with potential for override to stretch this to 6-8 weeks (e.g., failed appointment, then recall); and

adolescent immunizations could be age specific.

Decision: Consider vaccination "overdue" if more than one month past upper end of recommended vaccination age.

Dr. Modlin commended the working group's progress in the last three months, and looked forward to its specific recommendations on spacing live and inactivated vaccines. Dr. Breiman also asked the workgroup to consider extremes beyond which overrides would not be allowed.

Dr. Atkinson of NIP commented that there is no guidance on what to do if the 28-day interval is infracted, a question repeatedly asked about varicella and MMR. Dr. Modlin thought this might have to be addressed vaccine by vaccine, and referred it to Dr. Jay Watson.

Pneumococcal Conjugate Vaccine

Pneumococcal Disease Surveillance
Dr. Cindy Whitney of NCID presented recent surveillance data of invasive pneumococcal disease by age. In children aged <2 years, the attack rates are high, affecting 140-150 per 100,000 children per year.

Active population based surveillance collected in 8 areas covers a total population of 420,000 children aged <2 years. A case is defined as invasive pneumococcal disease when pneumococci are isolated from a normally sterile site, so the data are probably an underestimate of the disease burden.

The 1997 U.S. estimate of culture-confirmed pneumococcal disease is 11,200 cases in children aged <2 years. Most were bacteremia (70%), 14.8% were pneumonia, and 7% were meningitis. The overall case fatality rate is only 1.6% overall in this age group, and about 8% for meningitis. But children aged <2 have the highest overall drug resistance of any age group; 40.2% of children have reduced susceptibility to penicillin. Many isolates are also resistant to other agents. The 7-valent vaccine covered about 80% of cases when examined by serotype, and about 83% of the drug-resistant strains.

Conjugate Vaccine Information
Dr. Peter Paradiso of Wyeth-Lederle presented their data from an efficacy trial in northern California on a pneumococcal vaccine in development since 1986. Since the control of hemophilus influenza, pneumococcal disease has caused a variety of illnesses from meningitis, bacteremia/sepsis, pneumonia, otitis media, and group B streptococcus in neonates. Therefore, pneumococcal disease presents a large portion of invasive disease in children. The rationale for pneumococcal vaccine rises from the burden of disease in the developed and developing countries, the applicability of conjugate technology, and increasing antibiotic resistance.

Among the challenges to vaccine development was the many serotypes of pneumococcus (>90, each with distinct polysaccharide capsules). However, most disease stems from 7-11 serotypes, varying geographically. The vaccine serotypes cover 80-85% of disease in the U.S., perhaps more if there is cross-reactivity with pneumococcus types 6A and 19A.

Among several generations of vaccines, Wyeth-Lederle developed a 7-valent vaccine, a liquid formulation now in Phase III trials. The 9-valent lyophilized vaccine adds pneumococcal types 1

and 5, prevalent outside the U.S., including much of Europe. They plan to add other serotypes to the vaccine to cover most of the world's pneumococcal serotypes.

The vaccine was tested in several settings. The U.S. schedule was at 2,4,6 months; the European trial is also examining 2,3,4 and 3,4,5 months; the South African/Gambia trial is 6,10, and 14 weeks with a booster in the second year of life.

The antibody responses to different serotypes varied. Some antigens produced a good response after two doses, many not until after three, but all showed a response with a GMT >1 μg/ml. The South African tests of the 9-valent vaccine demonstrated that adding serotypes 3 and 5 added response for the other two, and did not negatively impact efficacy for the 7 original serotypes. A significant drop of antibody occurred after the third dose and at the time of the booster dose. However, a boost occurs with both the conjugate and the polysaccharide vaccine, showing that the children are primed for a boost fr om either. Importantly, there is a good correlation between the ELISA antibody titer and the opsonophagocytic antibody titer, the functional assay for the pneumococcus.

The 7-valent testing is being tested in three efficacy trials: northern California (systemic disease), Finland (otitis media), and among American Indians (systemic invasive disease, a different design by cachement area). The 9-valent in Phase III efficacy trial in South Africa enrolled 5000 children. With WHO, they will study pneumonia, and pneumonia and death in Gambia.

Dr. Paradiso then presented the pneumococcal conjugate vaccine data. The safety base will be extensive, documented in 16,400 children with 40,000 doses. They are also working in catchup programs (primary dose/booster), testing in children aged 7-11 months (2/1 dose), 12-24 months (1-1) , and >24 months (1/0). They expect these regimens to be the most applicable and produce data similar to that of the hemophilus vaccine, except that in this age group, a booster will be required. One dose should be sufficient for immune response and memory in those aged $\geq$24 months.

The northern California Kaiser Permanente trial will supply some data on otitis media. More definitive data on children aged to 9 years, the age to which recurrent otitis media has been demonstrated, is expected from the Finnish trial and should be available in mid-1999. Incorporated into many trials in the U.S. and Europe is the simultaneous administration of the pneumococcal vaccine with other pediatric vaccines. At licensure, compatibility data is expected with Tetramune, DTaP, Hib, hepatitis B, etc. vaccines.

Dr. Paradiso concluded that this is an important vaccine disease prevention tool for children globally. It has a proven conjugate technology and could serve as an anchor for a family of vaccine products.

Northern California Kaiser Permanente Vaccine Efficacy Study Results in Infants
Dr. Steven Black of Kaiser-Permanente reported the initial data results of the northern California efficacy trial of the 7-valent pneumococcal vaccine. The trial involved about 38,000 children. The study components included safety analysis assessed by telephone interviews at 48 hours and 7 days after dose, in two subsets of children (receiving concurrently whole-cell pertussis and acellular pertussis vaccines, respectively). Surveillance for rare events also was done in their automated datasets, and serology on another subset of children receiving the whole cell and acellular vaccines.

The efficacy study objectives were to determine the vaccine efficacy against invasive disease as defined by culture for vaccine serotype pneumococcus from a normally sterile site. They also examined effectiveness against otitis media (identified from automated clinic encounter sheets) and clinical pneumonia (identified through hospital, outpatient, and emergency room records). The x-rays of a subset of the children with abnormal chest x-rays will be examined for consolidation on the film, which will be compared between the two groups.

The study involved infants randomized at 2 months to receive either pneumococcal disease vaccine or meningitis CRM conjugate vaccine with concurrent childhood immunizations at 2,4, and 6 months and with a booster at 12-15 months. This was a sequential study design with an initial look at 17 fully-vaccinated cases of invasive disease due to vaccine serotype. A cost effectiveness study is also underway. Both direct (program) and indirect costs (caregivers' time lost from work) will be examined. The children involved are a subset of the total Kaiser 1997 population. The cost of pneumococcal disease, otitis media, pneumonia, and invasive bacterial disease and meningitis will be assessed using a decision cost effectiveness analytic model.

Dr. Black then presented the Phase III trial results. In four doses, they delivered 18,900 pneumococcal vaccine doses and 18,930 meningococcal vaccine doses to children aged 2.1 to 13.7 years. The vaccine was administered at 2,4, and 6 months with a booster at 15 months. Safety data percentages from a prior preliminary study were almost identical to that reported by Dr. Margart Rennels in a separate cohort. The local reactions were infrequent, especially for significant swelling and redness. Fever data also were similar.

Regarding immunogenicity, a significant boost for all serotypes was shown, but the antibody declines fairly quickly before the booster dose. Dr. Black shared data of the vaccine given alone and with DTaP and Hib. There was some interference in the pneumococcal response, but not of any clinical significance. The GMTs of the post-booster dose showed that when the vaccine was given with DTP/HbOCm, the antibody titer for diphtheria and PRP was slightly lower but still remained quite high.

The results on invasive disease were then presented. The first analysis was of 17 cases of vaccine-serotype disease in fully vaccinated children (3 doses in the first year of life; 4 doses in those children aged >12 months). Ten of the 17 cases were in children who had received 3 doses; 5 additional cases were partially vaccinated, and 8 other cases had a non-vaccine serotype.

The disease diagnoses of the partially vaccinated versus fully vaccinated children were shared, most commonly bacteremia alone. No fully vaccinated children had meningitis, but two in the partially vaccinated group did. The fully vaccinated group had 2 cases of sepsis, 1 of cellulitis, and 1 of pneumonia.

The vaccine's point efficacy was 100% within a lower bound of the 95% confidence interval of 75.7% for the total vaccinated population. All 17 cases in fully vaccinated children were in the control group. None of the partially-vaccinated cases were in the vaccine group; again, effectiveness was 100% with a lower bound of the 95% confidence interval of 81.4%. Regardless of the vaccine serotype and number of doses received, the overall effectiveness was 88.9%. Regarding nonvaccine serotype disease, 5 cases occurred in the fully vaccinated children, and 3 in partially vaccinated children. Of the 8 cases, 3 occurred in vaccinated children (2 fully vaccinated and 1 partially vaccinated) and 5 occurred in placebo children (3 fully vaccinated and 1 partially

vaccinated.

Dr. Black then outlined the data set for the otitis media study. It includes >49,300 visits and 35,000 episodes in children. A subset of 3600 had frequent otitis, defined as 3 episodes within 6 months or 4 episodes within one year. The results of that analysis are expected in November. In additional pneumococcal cases since the code was broken, the study has found 7 cases in the control group, 6 in fully vaccinated children and one in a partially vaccinated child. There were no cases in vaccinated children.

He summarized that the data indicate that this vaccine is safe, immunogenic, and highly effective in preventing invasive disease caused by the 7 vaccine strains when given at 2,4, and 6 months of age with a booster in the second year of life. The otitis, pneumonia, and cost effectiveness studies' results are awaited, but it seems fair to conclude that the use of this vaccine should have a significant impact on invasive disease.

Discussion: Dr. Offit expressed concern that other serotypes could rise. He asked if the data indicated the vaccine's capacity to decrease colonization of its serotypes, or if there are any data on those vaccinated as having increased colonization of non-vaccine serotypes. Dr. Black reported no colonization studies done, although another study has shown reduced colonization. But it is difficult to distinguish between replacement and unmasked previously existing organisms not previously detectable. At least in this study, the non-vaccine serotype disease was in the same amount as would occur in the absence of vaccine. To answer this question of colonization would require a significant study population and ongoing surveillance. Dr. Le wondered if the colonization is linked with the serotypes' virulence, but Dr. Black suspected that more might be involved.

Dr. Guerra asked if any children in the study group had febrile illnesses for which they were prescribed antibiotics, and whether children were included with risk factors such as sickle cell anemia. Dr. Black reported that known immunodeficiency disease such as sickle cell were excluded in this study, but not other studies. The cases were also tested to ensure they were not immunodeficient. Regarding the first question, the study did not attempt to change the physicians' diagnostic practices (i.e., increase use of cultures or antibiotic treatment). Some of the children could have had bacteremia and been treated presumptively and not included, but he thought the only effect of that would have been to lower the study power.

Dr. Fleming asked if there were any data on the result of primary hemophilus series among the children who showed a potential blunting of response to the Hib booster. Dr. Black said no, but results from the initial study showed that after dose 3 the antibody with PRP was in the same range as Hib given without pneumococcal vaccine. In fact, the booster ranges seemed higher than seen in recent days with Hib, but the data analysis on the subset of children with acellular vaccine is not yet complete.

Dr. Paradiso reported that in Finland and South Africa, where Hib vaccine was given, the Hib response was higher after three doses when pneumococcal vaccine was given in the other arm. The same response was seen in the U.K. when meningococcal vaccine was given in the other arm, but why is still unknown. On Dr. Glode's question, Dr. Black stated that during the five-injection visits, the pneumococcal vaccine was given with IPV and the others were administered in the lower extremities. While the doctors and nurses were upset about the number of shots, the parents were satisfied that the vaccines were safer and did not object.

Dr. Gardner noted that the mortality of pneumococcal disease is much greater in adults. Based on these spectacular data, he asked what research was planned for an adult vaccine. Dr. Paradiso reported limited studies done in adults, who responded to the conjugate better than to the polysaccharide, but not to the ten-fold-plus antibody titer increases the Hib conjugate achieved over that polysaccharide. However, the quality of antibody seemed better. Studies are needed to see if efficacy is improved over the polysaccharide, whether more than one dose will boost in adults as occurs in children, etc. But the disease serotype distribution also differs in adults, so the 7-valent vaccine would probably only cover 60-65% of adult disease. They will add another 3-4 conjugates to the adult vaccine.

Dr. Glezen asked if the partially vaccinated children were aged <6 months. Dr. Black was not sure, but confirmed that they were all very young children but for one. Dr. Fedson emphasized that there are few data on a multidose schedule of pneumococcal conjugate or polysaccharide vaccine in adults. But recently published data on adolescents indicate excellent results even after one dose. NIH plans to study various schedules of conjugate vaccination in older adults within the next few months. Dr. Paradiso expressed his appreciation to NIH/NIAID for their funding to the early research.

Dr. Modlin congratulated the researchers on their work and thanked them for sharing their data. He suggested forming a working group on pneumococcal vaccine by the next meeting. The volunteers include Drs. Glode, Fleming, Halsey, Zimmerman, Gardner, Schaffner, Guerra, Johnson, Offit, Word, Breiman, and Nichols. Others in the audience were advised to inform Ms. Kovach of their interest.

Update on Influenza Working Group

Dr. Keiji Fukuda summarized the summer/fall influenza activity, reporting outbreaks in Alaska and the Yukon territory, Montana, Florida, Tennessee, California, and New York. Sporadic cases were reported in Texas, Idaho, Washington, and Louisiana. Except for the B-isolates, all the viruses antigenically characterized were A/Sydney, identified last year and in this year's vaccine. No antigenic drift has yet been seen.

The ACIP Influenza Working Group met May 11-12, and addressed 1) whether ACIP should recommend routine vaccination of healthy children against influenza, and 2) what recommendation ACIP should make regarding the use of a live attenuated influenza vaccine. A presentation on the latter was to follow. At the more recent September 1-2 meeting, the workgroup considered 1) ACIP recommendation of routine influenza vaccination of healthy adults aged <65 years, and 2) the role of antiviral drugs regarding ACIP's viral guidelines document.

The points discussed regarding vaccination of healthy adults were:

- There is low influenza-related mortality and severe morbidity in this group.
- Vaccination coverage of those <65 years but in high risk groups is unacceptably low and should be the first priority for vaccination efforts in that group.
- The Behavioral Risk Factor Surveillance Survey has indicated that 65% of the elderly are vaccinated for influenza, but an NIP study also showed that <10% of asthmatic children are immunized. Therefore, increasing coverage of high risk groups <65 years is the top priority.
- There was no overall consensus as to whether vaccinating healthy young adults against influenza is cost effective. CE in this group depends on several factors such as attack rate in season, vaccine match to circulating strains, vaccine effectiveness, study design, etc.

- It was agreed that ACIP recommendations must not outpace the fragile national vaccine supply.
- Dr. Nichol suggested emphasizing the benefits of vaccinating healthy young adults in the guidelines text, without a formal recommendation.
- Dr. Gardner proposed that ACIP consider decreasing the recommended age for routine influenza vaccination to ≥50 years from the current 65. The prevalence of high-risk conditions increases at age 50, but research is needed of the likely impact of such a recommendation, which also would have to be coordinated with pneumococcal vaccine recommendations.

Also discussed was the role of anti-viral drugs in the ACIP document:
- They play an important role in ACIP guidelines.
- Newer antivirals (neuraminidase inhibitors) are in progress (estimated licensed product in 1 year).
- A suggestion was made that ACIP indicate rimantadine as preferred over amantadine. Both are equally clinically efficacious, but rimantadine has fewer side effects.
- Proposed changes to the text on antiviral medications were to 1) decrease the overall text; 2) indicate the sparsity of studies on the use of antivirals in institutional settings outside of nursing homes, especially to control influenza outbreaks in institutions such as hospitals; and 3) emphasize the need for better viral diagnostics such as rapid antigen tests.

Dr. Paul Mendelman of Aviron Corp outlined the research of their 2-year pediatric study (year 1 was published in the May 14, 1998 *NEJM*). He first shared a photo of a spray device for nasal injection to deliver large particle aerosols. With an adaptor, 1.25 mL is sprayed in each nostril. He provided some history of the development since 1960 of the cold-adapted influenza

vaccines. NIH has conducted multiple studies, including efficacy trials which led to Aviron's involvement. In 1996-97, NIH/Aviron conducted the pediatric Phase III efficacy trial.

The objectives of the pediatric trials in year 1 were to 1) evaluate the safety, immunogenicity, and efficacy of the live attenuated cold-adapted influenza vaccine in children (Phase III pivotal trial). One and two doses administered about 60 days apart were tested. Another cohort received a single dose and was compared to a placebo group. The year 2 objective was to evaluate an annual revaccination dose. The only vaccine change in year 2 was to change the H1N1 virus to A/Texas; the other two strains remained the same. This study was of a one-dose vaccine versus one dose of placebo, with subjects randomized at 2 vaccine to 1 placebo. The case definition was culture positive influenza. A total of 1070 were in the vaccine group, 532 in the placebo group, at an average age of 42 months. The demographics of the year 1 children were that most (65%) were in daycare/preschool; households had 2.6 children; and about 50% of the children had a sibling in the trial. In year 2, 917 of the 1070 re-enrolled for vaccination and 441 of the 532 placebo children also returned, an 85% return.

Dr. Mendelman summarized the safety data:
- No serious adverse events were associated with the vaccine; most common was runny nose/nasal congestion on day 2 post-vaccine. The 5% difference between vaccines and placebo was not significantly different, nor was revaccination in year 2 on the second dose. However, a 9% difference after dose 1 was significant.
- The fever documented in 2% of vaccinees versus 1.8% of placebo on revaccination in year 2 was not significant. However, there was a 5% (significant) difference in vaccinees over the placebo group in dose 1 of year 1, but not in dose 2. A bar chart demonstrated serum

antibody by hemagglutination inhibition assay after revaccination in year 2, showing that high antibody responses were elicited in vaccinated children to the three types of virus used. About 200 children of the 1600 were in an immunogenicity study subset in year 2.

A line graph demonstrated the outbreak periods in years 1 and 2. Only one type B isolate appeared in the cohort group in year 2. In year 2, culture-positive influenza occurred in 15 study children for type A (versus 55 in the placebo group); and none for type B (versus 1 in the placebo group). That correlates to a 2% attack rate for the vaccinees and 14% for the placebo group.

The efficacy by antigenic type (A/Sydney) showed 15 vaccine cases and 81 placebo cases, for 86% efficacy. There were four cases isolated for the Wuhan-like influenza illness, all in the placebo group, for 100% efficacy. The overall efficacy was 87%, with a lower confidence bound of 77%.

Bar charts demonstrated efficacy after dose 2 in year one. The children dosed with Wuhan were tested against the drifted variant strain, and appeared to have cross-protection to A/Sydney (over 90% seroconversion). The year 2 efficacy data for type A and type B virus combined for year 1 and year 2 showed high efficacy. A line chart demonstrated an attack rate of <2% for vaccinees in two subsequent influenza seasons.

The study also investigated protection by natural infection with influenza in year one against natural infection in year 2, demonstrating an efficacy of 85%. A chart of demonstrably milder clinical spectrum of disease among influenza culture positive influenza cases was shared. Days of fever were 2-fold higher in the placebo versus vaccine group and similar to year 1, 94% efficacy against influenza acute otitis media (17 in 500 placebo and 2 in 900 vaccinees) was demonstrated. Also evident in year 2 was significant disease burden for A/Sydney all 8 cases in the placebo group versus none in the cohort. The latter also had fewer respiratory diseases diagnosed by practitioners as pneumonia, bronchitis, or significant wheezing episodes.

The conclusions from the year 2 study were:
- Children re-enrolled for annual revaccination at a high rate.
- Annual revaccination was safe and well tolerated.
- Compared to children in a placebo group, a higher proportion of vaccinated children had antibody to each strain in the vaccine.
- Protection against A/Sydney was induced by vaccination with live, attenuate A/Wuhan.
- Vaccine was 86% efficacious against the variant strain A/Sydney.
- The vaccine was 100% efficacious against influenza culture positive lower respiratory disease, and 90% efficacious against influenza culture positive otitis media.

Cost Effectiveness Analysis of Influenza Vaccine in a Health Working Adult Population
Dr. Carolyn Buxton Bridges of NCID described a cost effectiveness analysis of influenza vaccine in a healthy working adult population. Persons aged ≥65 are at increased risk of influenza-related complications. For this group, vaccination is clearly cost effective even though the vaccine is not 100% effective. But healthy persons aged <65 have lower rates of complications, and influenza-related costs are largely due to work absenteeism. Several cost effectiveness studies were done in this population, with inconsistent results. Many of the studies were not randomized or placebo controlled and had problems with vaccine match with the circulating strain. However, Dr. Nichol's study published in *NEJM* in 1995 showed a significant cost benefit for that year. CDC attempted to duplicate that study in a year with a

different virus, different vaccine, and, as it turned out, a different vaccine match.

The study was a double-blinded, randomized, placebo controlled trial of 1184 healthy workers aged 18-64, 95% of whom were included in the CE analysis. Half received a placebo, half were injected with influenza vaccine in October; all were followed through April. The population, aged 18-64, consisted of salaried workers at a large U.S. manufacturer in Michigan.

One follow-up questionnaire (99% response) investigated side effects. The only significant difference between vaccine and placebo groups in the follow-up was arm soreness and injection site redness. Subsequently, bimonthly questionnaires were sent from November-April, asking about respiratory illness. The laboratory components consisted of serology studies among a subset of participants and collection of a virology throat swab from ill participants. ILI was defined as occurring in influenza season, with a temperature of $\geq 100^{\circ}F$ or reported feverishness and the presence of a cough or sore throat. Influenza season was based on the timing of viral swabs isolated from participants, and timing of follow-up questionnaires.

There was no significant difference between the placebo and vaccine groups regarding direct or indirect medical costs. Vaccine recipients bought slightly more over-the-counter medication and had a few more sick days. However, that difference was mostly driven by one person who was hospitalized with pneumonia, but was not cultured for influenza, so its influenza-relatedness is unknown. Similarly, no differences were seen in the mean number of lost work days.

The combined serology and questionnaire results showed no difference in illness rates; 3% of the placebo group and 5% of the placebo group had influenza illness. Of the 274 persons with complete serologic and questionnaire data, 24% reported ILI, but only 4% had influenza. Of the 217 swabs collected, 20 were positive for influenza A, and all characterized isolates were A/Sydney. There was not a good match between the vaccine and A/Sydney strains.

The investigators then modeled the average costs per vaccination and ILI from a societal perspective, pooling the vaccine recipients' data for costs per illness. The vaccine cost was $10; total vaccination cost was $30. Direct medical costs were about $60 per illness. When lost work days were combined (with direct costs), the total cost per illness was almost $280. A sensitivity analysis varied the attack rate and vaccine efficacy for ILI. For this population, vaccine would be cost beneficial at an attack rate of 15%, assuming a vaccine efficacy of 90%.

However, the vaccine was a poor match to the prevailing influenza strain, and ineffective in decreasing influenza-like illness (ILI), physician visits, or absenteeism. Nonetheless, the data were useful for modeling non-match vaccine years. However, the study was unable to determine the overall benefits of influenza vaccine in a good match year. A year 2 study is now being done in the same facility, with over 1000 participants.

Discussion: Dr. Offit asked Dr. Mendelman if the vaccine side effects were compared with the attenuated parent, particularly to see if the vaccine strain is more virulent. He presumed that the genetic molecular base of influenza virulence is a multigenic phenomenon and wondered to what extent those two genes confer that. Dr. Mendelman reported that a recombinant influenza program prior to the cold-adapted vaccine had done such comparisons, and that data could be provided. A historical search also showed that almost all studies were done on a 6-2 vaccine. However, although other vaccines (7-1, 5-3) were also tested and not reported as more or less virulent, they were not directly compared. On Dr. Fedson's question, Dr. Mendelman confirmed a 30% reduction in antibiotic use between the vaccinated and nonvaccinated groups.

Dr. Halsey asked why the attack rates were lower than other studies, and asked the projections of manufactured doses for years 1 and 2 of production. Dr. Mendelman thought the rates might be related to the older children enrolled, but thought the attack rate consistent Dr. Glezen's study's attack rate of 40%. The vaccine is unlikely for the 1999 season, but if the application is approved for 2000, perhaps 10 million doses will be manufactured. Dr. Jo White of Aviron reported a target launch in 2000 of up to 20 million doses.

Dr. Le asked if the cold attenuated live vaccine caused asthma attacks in children with reactive airway disease, as natural influenza has been known to do. Dr. Mendelman reported that investigators allowed enrollment of children with wheezing episodes in year 2, but not moderate to severe asthmatics (NHLBI definition). However, another study did so, enrolling 48 children aged 9-17. There were no statistical differences in the primary measurement point (the FEV1 change), nor in other well-defined endpoints. Two exacerbations of asthma occurred in the vaccine group, and none in the placebo, but this was not statistically significant.

Dr. Bob Chen of NIP reported that the 1991-1992 study of Guillain-Barré Syndrome will be published soon. The paper's conclusion quotes the ACIP current influenza recommendation that the benefits outweigh the risks of influenza for all age groups. He asked that the workgroup be so advised if this meeting's data would change that recommendation.

Dr. Nichols was impressed with CDC's cost effectiveness modeling. She recalled that her study noted significant differences in the cohorts by income, type of work done, gender distribution, etc. She was struck that the CDC study found zero days of work lost in the previous six months, unlike her study. Research needs to attend to how representative the cohort may be to other adult groups. Dr. Bridges agreed; much of the cohort also did not have young children. There may be subpopulations at increased risk such as parents with children in daycare and smokers.

Report of Outbreak Investigations

Dr. Fukuda introduced two reports on summer influenza outbreaks among tourists on the semi-closed environment of cruise ships, which increasingly involve larger organized groups of travelers, many elderly and international travelers. These exposures in the "off" (summer) season, including early exposure to and different strains of influenza strains from the southern hemisphere, may result in increased risk of morbidity. This poses questions with policy implications: 1) are cruise ship populations at higher risk of influenza exposure and to southern hemisphere strains not in northern hemisphere vaccine?; 2) should an ACIP recommendation specifically target cruise ship staff for influenza immunization?; and 3) if so, when and how often?

1997 Cruise Ship Outbreak Report.

Dr. Joy Miller of NCID reported on the influenza outbreak on a New York-Montreal cruise ship with predominantly elderly passengers. This investigation documented the first outbreak of influenza A/Sydney in both the U.S. and Canada in 1997. The North American cruise ship industry serves about 4 million passengers a year, about 33% elderly (>60 years). Multinational passengers and crew live in close contact in semi-closed compartments, on average for about 6 days.

This 1997 outbreak began on the first cruise ship, 75% of whose passengers were aged >65, and 30% had a chronic health condition. Over 100 persons presented to the ship's clinic with acute respiratory illness (ARI) and 6 were hospitalized. It spread to the crew and passengers

on the second cruise.

Health Canada and CDC were invited to investigate. A case patient was defined as person presenting to the ship's clinic from August 30 - September 30 with any two symptoms: fever, sore throat, chills, nasal congestion, myalgia, or arthralgia. Influenza-like illness (ILI) was defined as fever and either sore throat or cough. Onset examined by nationality indicate that the cases may have originated from Australian passengers, who were 35 times more likely to develop symptoms early. The 39 nasopharyngeal specimens collected showed 16 positive for influenza, all but one as A/Sydney (one was A/Wuhan).

The ship company followed the protocols for influenza outbreak in nursing homes: notify passengers; do active surveillance; cohort the ill crew; treat ill crew/passengers with rimantadine; give prophylaxis to non-ill passengers/crew; and vaccinate the crew to eliminate them as a reservoir. Antiviral medications and isolation halted transmission between cruise members by the end of the cruise, with minor transmission to passengers on the third cruise. The compliance of passengers/crew was good: 72% of passengers attended counseling sessions; 81% took the rimantadine prophylaxis; 95% of the crew was vaccinated, and the ill crew was isolated for at least 48 hours.

Alaska/Yukon Territory Outbreaks
Dr. Suzanne Zane of NIP discussed the summer 1998 influenza outbreak in the Alaska/Yukon Territory. Its magnitude was related to the size of the Alaska tour industry. From May-October, about 840,000 visitors, 40,000/week, visit Alaska (1998 population 620,000) and the Yukon (population 32,000) by land and sea. Thirty-three percent of these visitors come on 28 cruise ships, each carrying 1000-2000 passengers with a median age of 62 years.
In July 1998, 3 clusters of febrile respiratory illness were reported to CDC among older travelers on combined land/sea tours in Alaska and Yukon. Health Canada, CDC, and the state of Alaska investigated. The case definitions for ARI, ILI and pneumonia were established, with onset between May 1- September 30. Those with symptom onset >10 days after travel were excluded.

Retrospective surveillance of cruise ship medical records and passive reports from May 1 - August 5 indicates that the outbreak began as early as the start of the tour season. Active prospective surveillance during August showed 80 people a day presenting with ARI. Later reports showed influenza A becoming widespread in large regions of Alaska and the Yukon as well as on cruise ships in the region. Reported cases declined with decreasing ships as the season closed. Over 5500 cases of ARI were documented, 2500 which were of ILI and 146 of pneumonia. Three deaths from ARI were reported. Laboratory analyses identified 66 specimens of influenza A; of 36 subtyped, all were all A/Sydney. Since only the ill persons who presented are included, these data are probably markedly under-reported. Few residents were affected; by far, tourists fell ill, representing 41 countries.

CDC recommended that persons aged >65 or with chronic conditions consult with their physicians before traveling to Alaska or the Yukon. Physicians were advised to consider influenza in the differential diagnosis of summer respiratory illness, and to provide information on symptoms of influenza A and possible uses of antiviral agents for treatment and prophylaxis. Cruise lines were advised to implement surveillance among travelers and employees; to offer the latter the 1998-99 influenza vaccine; and to obtain rimantadine or amantadine and rapid antigen detection kits for influenza A. Compliance with these recommendation has been good by much of the cruise industry, which participates in surveillance.

The public health issues involved include the possible increase of the magnitude/scope of such outbreaks and such pandemic planning as availability of vaccine. Improved surveillance infrastructure is needed. ACIP may wish to consider influenza recommendations for ships sailing in U.S. waters and for high-risk travelers.

Discussion: Dr. Modlin asked if this a truly new phenomenon. Dr. Miller reported that the retrospective medical review noted the markedly different 1997 baseline season, with little influenza activity. But cruise ship physicians have noted peaks and valleys in the past. Aside from that, Dr. Marty Cetron noted the newness of the industry's rapid growth (16-20%/year) and the size/carrying capacity of the vessels (some carry 20,000, with daycare centers, dialysis facilities, etc.; virtual floating cities). The industry is very concerned and seeking guidance on cost effective vaccine recommendations. They will meet with the NCID Division of Quarantine in the coming year to discuss these issues.

Dr. Le asked if choosing the annual influenza strains would be accelerated and consider bihemispheric considerations. He also noted that the nonformulated nature of rimantadine poses implications for managed care. While Dr. Fukuda reported that rimantadine would be a generic drug this year, affecting cost, drug supply is still an issue. The seasonal strains relate to complex vaccine policy issues. Vaccine is manufactured for the northern hemisphere for only a limited period of time. Beginning this year, the WHO will issue biannual northern and southern hemisphere vaccine recommendations. But the FDA may not approve the vaccine for the southern hemisphere, affecting supply, and other questions pertain to when and how often it should be administered.

Dr. Guerra reported working group agreement that ongoing education is needed to increase awareness that this disease can occur year-round and for physicians to consider greater use of antivirals under special circumstances. He asked about the related experience of military ships. Dr. Fukuda reported that influenza outbreaks among troops decreased with the initiation of troop vaccination, but also that recent shipboard outbreaks were reported in the military due to vaccine/strain mismatch.

Dr. Modlin noted that the influenza statement would be reviewed in February and asked the working group to return with comments on the related issues.

Polio Update, Overview, and Future Issues

Dr. Rebecca Prevots of NIP outlined the objectives for this session: 1) to review the issues for future consideration in the transition to all-IPV schedule, and 2) to discuss the experience of the transition to sequential IPV/OPV schedule.

Among the issues for transition to an all-IPV schedule are: 1) current experience with transition to this sequential schedule, including the impact on VAPP, the acceptance of the sequential schedule, and the frequency of potential adverse events as monitored though the VAERS system related to IPV; 2) the progress towards polio eradication; and 3) the status of development of combination vaccines. The key questions raised prior to the change were 1) the impact of the introduction of a sequential schedule on vaccine-associated paralytic poliomyelitis (VAPP); 2) the impact of the revised polio schedule on childhood vaccination coverage; and 3) the potential for adverse events related to the expanded use of IPV.

Polio Surveillance Update
Dr. Nino Khetsuriani of NIP provided an overview of poliomyelitis surveillance in the U.S. since

the introduction of the sequential schedule (1997-1998). Since 1980, 149 polio cases have been reported in the U.S., 141 of which were vaccine-associated paralytic poliomyelitis (VAPP). Four cases of VAPP were confirmed in the U.S. in 1997-1998 due to OPV. No recipients were immune deficient, and no cases were associated with the sequential schedule. Three suspected VAPP cases with onset in 1998 are under investigation.

Global Polio Eradication Update
Dr. Steven Cochi of NIP updated the committee on the global eradication program. Since the 1988 unanimous WHO resolution to eradicate polio by 2000, and even with rapidly improving surveillance, evidence indicates an 85% decline in reported polio (1997 data indicate about 5,106 reported cases worldwide).

This success is largely attributable to a strong global partnership of multilateral and bilateral organizations and donor governments. Wild polio virus transmission is confined to Central Africa, South Asia, and parts of the Middle East. The strategies that accomplished this include the use of medical surveillance officers, the National Immunization Days of 110 countries which often span borders, and the addition of house-to-house visits when virtual elimination is achieved. Sensitive surveillance (identifying non-flaccid paralysis per 100,000 children aged <15 years) exists almost everywhere except those cited above. The Global WHO Polio Laboratory Network was instrumental in strengthening polio surveillance.

The challenges for the final 800 days include accelerated surveillance for acute flaccid paralysis (AFP); special initiatives for areas in conflict; increasing the political/financial support needed; and expansion of national and international field staff to fully implement/strengthen AFP surveillance. America has been free of indigenous polio since 1991. The last world region should be certified by 2003, so global certification is possible by 2005. WHO laboratory containment of polioviruses begins in 1999, with hope for wild polio containment by 2002. The ultimate goal is cessation of immunization after eradication.

Vaccine Distribution and Coverage Monitoring
Dr. John Stevenson of NIP reported on monitored vaccine distribution and coverage. CDC will continue monitoring from these data sources, including introduction of newly recommended vaccines.

- *Are states ordering vaccine?* Yes. Biologics surveillance is voluntary manufacturer report of total dose purchases, and the NIP Vaccine Ordering and Distribution System places state bulk orders off federal contract and maintains the electronic CDC-vaccine manufacturer data interchange. These indicate that IPV doses purchased by nonfederal sources rose from 0.5 million in 1996 to 2.5 million in 1997. Including federal purchases, a total of 5.25 million doses were purchased in 1997. By the third quarter (Q3) 1998, just under a million doses were purchased.

- *Are providers administering IPV?* Yes. The data sources to support this include immunization registries such as Oklahoma's registry system (OSIIS). The advantages to this data source are that it captures the outcome of interest, is timely and easy to use, and has flexible data structures. However, not all states have these data; or where they are available, they do not cover all providers/children. The OSIIS holds the records of 17.5 million children born in 458 facilities from 1996-1998, 70% of the birth cohort in this state's population, and 33% of whom have private providers. Only $\leq$2% in 1996 received an IPV first dose; in the second quarter (Q2) of 1998, 78% did. The same trend emerged for the second dose. Based on the federal contract purchase data in the first 3 quarters of 1998,

the IPV market share was only 32%. The same trend was shown for infants born in Q1 1998, 68% of whose second polio dose at 5 months was IPV.

- *Are children receiving IPV at greater risk of not being up to date?* No, neither presently nor historically. OSIIS indicates that of children born in 1997 Q1, 992 received IPV, and 85% were up to date at 3 months, with a relative risk of tardiness of 0.99. In 1998 Q2, the RR declined to 0.52.

Parental Compliance with Sequential Schedule
Dr. Shoshana Melman of NIP addressed parental compliance with initiation of a sequential schedule for polio immunization. Concerns were raised by the National Medical Association (NMA) and others that the schedule change risked parental noncompliance, increased immunization refusals, increased office visits and costs, and lowered immunizations. A chart review study of infants due to begin polio immunization from November 1996 - August 1997

was done following implementation of this schedule. The parents were educated about the recommended sequential schedule.

The information collected was patient demographics, type and number of immunization injections given, and recorded reasons for delay. Of the 250 eligible patients, 50% were male, and 90% had federally funded medical insurance. Of these, 249/250 children received a first polio vaccine dose with IPV; of the 237 patients who returned, 235 received an IPV second dose. IPV was administered to 452 evaluable children in 237 of 238 visits with 3 injections due and in 210 of 212 visits with four injections due.

The study revealed overwhelming parental compliance and no refusals of IPV. Only one parent requested division of vaccines between two visits and there were no significant increases in number of office visits. The conclusion was that physicians should not assume parental resistance as a serious barrier; healthcare providers should be aware of their critical role in influencing parents' decisions.

The study's limitation is that its applicability may be limited to inner city populations and the subset that seeks medical care. Vaccine compliance also decreases in the second year of life, prompting concern that children not completing the sequential schedule could lower intestinal herd immunity. Research is underway to assess completion of the four-dose schedule.

Public Comment was inserted at this point in the agenda due to the speakers' travel schedules.
Mr. John Salamone, President of Informed Parents Against VAPP, stated that his group is funded by Pasteur-Merieux for educational and organizational activities. He is also Vice Chair of the Advisory Committee on Childhood Vaccines, and father to David, a VAPP patient. He termed VAPP patients as the "sacrificial victims" of an all-OPV policy. Their parents were not told the risk of VAPP from OPV or that a safer injectable vaccine was available. Allegedly 8-10 cases of VAPP occur yearly, but others could be misdiagnosed as Guillain-Barré Syndrome or meningitis. Even one VAPP case is too many.

The ACIP endorsement of an all IPV schedule was welcome, but it is transitional for 2-5 years. Two years later, four new VAPP cases are confirmed. Despite the requirement to use a vaccine information sheet, one couple reported receiving a 3-year old sheet *after* their 3-month old daughter received OPV. A Texas boy developed VAPP after a second dose of OPV. The only way to avoid a clear a gap in communication between physicians and parents is to adopt an all-

IPV schedule and avoid the option of confusion. Mr. Salamone stated that "polio has become an optional disease in the U.S." He urged the ACIP to swiftly recommend to remove all vestiges of polio in America. He hoped not ever to have to return with still more parents whose children have VAPP simply because the ACIP decided to study further, after a decade of studies.

Dr. Terry Harville, of the University of Georgia School of Medicine, represented the Immune Deficiency Foundation (IDF). An immunologist formerly on the Duke faculty, he cited the rarity of early immune deficiency diagnoses. He reported an IDF survey of 2000 respondents from patients with primary immune deficiencies. About 50% were diagnosed by 18 years of age, but only 13% were diagnosed before their first birthday. In cases with a family history, diagnosis may occur at 2½ years or at 3½ years without that background. More than 50% of the patients' recognizable symptoms did not develop until after 9 months of age; another 25% of cases were not recognized until after four years of age. Still another type of immune deficiency associated with VAPP has an even later stage of onset, sometimes in adolescents. There is much physician misperception that immune deficiency is diagnosed shortly after birth. Finally, Dr. Harville cited the mandate to "first, do no harm" as supportive of an all-IPV schedule.

Immunization Delivery Evaluation Project (4x4)
Dr. Maureen Kolasa of NIP presented two projects demonstrating the impact of the sequential schedule on immunization coverage levels. The preliminary findings of the *Immunization Delivery Evaluation Project* (data collection in progress) revealed that most infants are receiving IPV and receiving up to four injections per visit. Infants were up to date for polio and all antigens combined at the 3-month visit both before and after the sequential schedule. The sequential schedule was rapidly implemented in the study sites.
The study followed infants in 30 publicly funded clinic study sites in three urban U.S. areas at risk for under-immunization. The clinic clients were primarily African-American and Latino and the balance were white. All clinics use DTaP and recommend the IPV/OPV schedule. Cohorts were compared, pre- and post-recommendation of the sequential schedule, for immunization coverage rate and number of injections at the 2-month visit. There are 308 infants in each of the 4 cohorts per city.

The percent distribution of the first polio dose was demonstrated on a bar chart, showing OPV used primarily pre-implementation, IPV thereafter, in all 3 cities. Up to four injections at the first visit were administered post-implementation, versus two before. Nonetheless, the sequential schedule was rapidly implemented in study sites. A bar chart demonstrated basically no change in overall coverage rates for the 3-month visit administration of DTaP (or, pre-recommendation, DTP), Hib, polio. and Hep B at 3 months of age.

The limitations of the study include the preliminary nature of the data, some of which is still in collection and analysis, and that it may not be generalizable outside these urban areas.

The NIP's *Georgia Demonstration Project* was conducted in suburban Atlanta's Cobb County, GA. Its objectives were to measure the proportion of infants receiving a first dose of OPV and IPV polio vaccine before and after implementation of the sequential schedule; and to compare immunization coverage rates for subsequent doses of poliovirus vaccine and other vaccines given in the first year of life.

The study was set in 6 Cobb County public health clinics. All offered the three vaccination options and recommended the sequential IPV/OPV schedule. Two cohorts were followed to 6 months of age, one being those born from the baseline of January-June 1995, and the other the evaluation cohort born January-June 1997. They also followed the third dose cohort, those

born August-November 1996, until 18 months of age.

Eligibility stemmed from polio administered in a Cobb County clinic, residence there or in the surrounding catchment areas, and documentation of at least one dose of polio, DTP, or Hib by 6 months of age. The cohort demographics were 30% African-American and 6% Latino; 77% were enrolled in WIC. In the baseline cohort, 99% received a first dose of OPV; in the evaluation cohort, 91% received IPV. A bar chart demonstrated the number of injections at the first visit (2 months) over the course of the study. The 2% receiving one injection in the baseline cohort rose to 27% receiving 2 injections, to 53% receiving 3, and 18% receiving 4.

Another bar chart demonstrated the up-to-date status for dose one of recommended antigens (polio, DTP/DTaP, Hib, HepB), showing no decrease and a slight increase in coverage in the evaluation cohort. Dose 2 also showed no decrease in coverage. For the 185 children for whom information on dose 3 is available, 78% received 2 IPV and 1 OPV; 10% received 3 OPV; 9% received 3 IPV; and 2% received an odd-mixed schedule.

The study findings were that, regarding parental choice and provider recommendation, most parents chose IPV. The need for additional injections at the 2- and 4-month visit was not a barrier to receiving all needed vaccines, and infants receiving IPV were as up to date for other recommended immunizations as those receiving OPV.

Evaluation of Adverse Events Related to IPV
Dr. Gina Mootrey of NIP presented the findings on adverse events related to polio as reported to the Vaccine Adverse Events Reporting System (VAERS), a passive reporting system for adverse events among post-licensure vaccine safety. Data from other countries using IPV before U.S. implementation indicated no serious adverse events. To assess the U.S. experience, VAERS initiated surveillance after implementation of the sequential schedule. The study objective was to evaluate adverse events reported to VAERS following IPV vaccination from January 1991 through December 1997, and compare those to OPV.

VAERS reports from January 1, 1991 to December 31, 1997 were categorized as fatal, nonfatal serious, and non-serious (excluding “no drug effect”). Reporting rates were calculated from CDC’s Biologics Surveillance Report of doses distributed. The age groups for the initial analysis were <1 year, 1 year, 2-6 years, 7-17 years, and ≥18 years; the secondary analysis used the VAERS age groups corresponding to doses 1 and 2 for polio vaccine (i.e., <3 and 3-6 months).

IPV severity profiles were consistently lower than OPV for children aged <3 months in the pre-recommendation period of January 1991- September 1996 and the post-recommendation period of October 1996 - December 1997. Any suspicious increase in severity or safety category for IPV versus OPV was followed up by examining symptoms, reporting source, and vaccination date. In general, the annual rate of fatal events was similar for IPV and OPV, except in 1993 when OPV was higher, but the magnitude of effect was <1/100,000 distributed doses. Similarly, nonfatal serious event rates were higher in 1993 than 1992, but with the same magnitude of effect.

The study noted that since 1997, the number of VAERS reports of vaccine-related adverse events has decreased from reports of infants vaccinated in earlier years, but there are no data as to whether this is due to less adverse events, reporting bias, or reporting delay.

Since the sequential schedule recommendation, 60% of IPV-associated reports were for infants

aged <3 months and 34% were for children aged 3-6 months. The severity profiles for IPV and OPV, examined for children <3 months pre- and post-implementation, were similar for both vaccines. Slightly more (5%) were nonfatal-serious in the pre-recommendation period. The distribution of symptoms was remarkably similar in IPV/OPV fatality reports.

Post-recommendation, the proportion of both fatal and nonfatal serious reports due to IPV was less than for OPV in the 3-6 month-old group. Frequency of symptoms in non-fatal reports among those aged <3 months was similar between the two vaccines compared to the pre-recommendation period.
The VAERS passive surveillance data limitations include under-reporting, biased reporting, and delayed reporting. In addition, multiple changes to the childhood vaccination schedule occurred within a short period time (e.g., introduction of DTaP use in infants shortly after the sequential polio vaccine schedule). Finally, polio virus vaccines are usually administered with other vaccines, confusing attribution of ensuing symptoms.

The study concluded that comparison of biannual rates by severity, severity profiles, and safety profiles in VAERS indicated that the sequential polio vaccine schedule recommended by CDC in October 1996 did not result in any increase of vaccine associated adverse events for IPV compared to OPV.

Discussion: It was noted that the data shared here were greeted with relief by such groups as those initially opposing the schedule, but direct comments from them have not been received by CDC. As of several months ago, the NMA's work with the AAP in a study of office settings revealed that 50% of NMA physicians use IPV as a first dose. No concern was voiced at the recent AAP meeting about decreased acceptance, but some concern was expressed about full vaccination outcomes at 24 months. Nonetheless, on the whole, they are satisfied.

Dr. Modlin asked the likelihood of the suspected cases to be added to the total tally. Dr. Prevots hesitated to say, but in the past only two-thirds to three-quarters of suspected VAPP cases have been confirmed. Dr. Johnson asked if any of the suspected cases used the sequential schedule and if any more clinical information was available. Dr. Khetsuriani reported limited clinical information, but none have yet had poliovirus isolated, and none received IPV as an initial or second dose.

Dr. Peter asked about the U.S. contribution to the global program and the vaccine cost. Dr. Orenstein reported increases of global eradication funding unrelated to global costs. The catalogue price for OPV and IPV have remained constant. OPV lowered in 1996 from $7.95 to $4.95 but since had risen again to $5.46. Dr. Zimmerman reported that a private sector check a few months earlier showed IPV a little cheaper than OPV, but comparable.

AAP Update
Dr. Halsey reported the Committee on Infectious Disease's review of the AAP's polio policy. The AAP board's review of the resulting statement should be completed by November 1, and he was optimistic that the policy will be accepted. It recommends IPV as the first 2 doses of polio vaccine in most circumstances, with the third and fourth doses as IPV or OPV. Where parents refuse all the immunizations recommended or children are delayed (aged >6 months when started), an accelerated catchup schedule is acceptable.

The statement stresses the need for parents to be fully informed of the benefits and risks and provided up to date vaccine statements. (He recommended that the ACIP look into having expiration dates on the vaccine information sheet to help providers determine its timeliness.) If

an outbreak of wild polio occurred in the U.S., OPV would be used, and the federal government should fund CDC to effect that. The statement reaffirms the WHO recommendation to use OPV in the global eradication program, especially in the countries with recent wild polio; and it anticipates that beyond 2001, IPV only will be the recommended schedule. He encouraged the ACIP to decide/recommend based on what is best for children now.

AAFP Update

Dr. Richard Zimmerman reported the AAFP's review of the evidence and issues related to polio. Data indicate that >60% of parents prefer the IPV starting schedule. The AAFP found private sector prices comparable, immunization rates stable, and that international concerns about the U.S. switch were alleviated. He announced that as of this week, the AAFP now prefers a schedule beginning with IPV for the first two doses, and would like that reflected on the 1999 harmonized schedule. However, they still accept all three schedules, and state that OPV should be available to parents who refuse IPV and that OPV should be used in an outbreak.

Committee Discussion

Dr. Modlin concluded that if the AAP board approves the proposal, they would be at variance with the ACIP harmonized schedule. They would prefer to not give OPV first (unless the parent rejects all the recommended immunizations at that visit), and the schedule accepts all three. There is some urgency in addressing this to finalize the 1999 harmonized schedule. He summarized the options, therefore, as 1) to not change the ACIP policy, 2) to adopt the AAP's likely stance, or 3) to proceed to an all-IPV schedule. Dr. Halsey also encouraged a clear ACIP statement, within a time frame, of the intent to pursue an all-IPV schedule.

Dr. Offit strongly supported an all-IPV 4-dose schedule. He termed VAPP an unconscionable side effect not accepted for any other vaccine. Dr. Le had left a statement with Dr. Offit also expressing his support of an all-IPV schedule. Dr. Glode advised, at minimum, providing better information to practitioners about VAPP, the number of documented cases, and how many parents have felt that the choice was not presented. She supported a negative recommendation on OPV, beyond a preference for IPV, and could support all-IPV in the first year.

Dr. Griffin agreed; at the least, advice should be issued against using OPV in the first 2 doses. Dr. Guerra also supported all-IPV schedule. The schedule recommendation was well received; parents now ask for IPV. When he asked if polio importations of polio have been documented, Dr. Orenstein reported the last wild polio virus importation in Canada in 1996, in a child with diarrhea. Dr. Guerra concluded that essentially parents can be reassured of the absence of risk.

Dr. Word felt that realistically, most parents bringing children for immunizations are so engaged that they will do whatever the physician advises, as proven by the uncomplaining schedule switch. She supported the all-IPV schedule, particularly since some immunodeficient children are not diagnosed early.

Dr. Snider reviewed the ACIP's present statement about the criteria/time frame for a schedule change. The "preference for sequential schedule is expected to remain 3-5 years until further progress toward global eradication is achieved." That has been done. "Such progress, along with the development and licensure of combination vaccines that reduce the need for multiple simultaneous vaccine injections, is expected to lead to adoption of an all-IPV schedule." There

are data on the impact of the new combination vaccines. But the statement does not address the concern about reintroduction of polio to a population immunized with only IPV. He wondered if in retrospect that was flawed thinking, or if the decreased likelihood of importation has eliminated that as a concern.

Dr. Offit took some comfort from the Netherlands outbreak limited to Dutch church members who refused 4-dose immunizations. Dr. Marchessault reported that the Canadian contact was in a population immunized by IPV, and the disease did not spread. Dr. Chen reviewed his past studies about spread of vaccine virus in unimmunized children. He had examined seroprevalence in 1-, 2-, and 3 year-old children and the secondary spread. In general, the type 1 spread was greater than type 3, but type 2 was the highest. However, the spread was <30% in those unvaccinated, a small degree.

Dr. Modlin asked for opinion as to whether the situation had changed, to avoid overlooking an issue. Dr. Livengood recalled that the number of unimmunized children found in Dr. Chen's study was quite small. Coverage for polio then by age 2 was probably less than the current 90%, but still high. He also commented that an infant now beginning a sequential schedule in the U.S. probably will not complete it, because by its age 4 OPV may not be used. He was unsure if one dose of OPV would provide intestinal immunity.

Dr. Orenstein expressed concern that the same degree of input for this decision was not possible at the end of an ACIP meeting with limited membership present. Dr. Snider also raised the difficulty CDC had in gaining the buy-in to the sequential schedule. The next change to IPV will require that as well to ensure that all understand and approve. However, CDC could try to do that rapidly. He also observed that making OPV essentially unavailable is in itself a defacto decision. He wondered about the availability of OPV in Canada and the Netherlands for those who want it. Dr. Stan Plotkin reported several manufacturers of OPV distributing in Europe, and advised that whatever ACIP does, it should be clear and not vacillate.

Dr. Snider added that CDC cannot accept any recommendation until ACIP writes it down and submits it. He sensed that the committee members desired as rapid movement as possible, and distilled the discussion as whether to use the AAP approach of expressing a strong preference for IPV for first doses, or an all-IPV approach.

Dr. Halsey requested that ACIP consider a recommendation that OPV be reserved for children whose parents refuse to receive all the immunizations necessary for that age. That is not totally inconsistent with the AAFP, would make the harmonized schedule much easier, and only states ACIP's current preference more strongly. The AAP's draft policy calls for the change by 2001, but they could reconsider that next year.

Dr. Guerra agreed that ACIP must be definitive to resolve this for the long term. He suggested that a working group be convened before the February meeting to frame the discussion and facilitate a resolution that would build on the momentum now providing an opportunity to accelerate the process toward an all-IPV schedule. He asked the immunization requirements for immigrant entry to the U.S. Dr. Orenstein reported that these are only required of those applying for permanent residency. There are none for traveling or entering for other reasons. Dr. Watson cited data that at least some children are arriving from some countries (e.g., orphans) with forged immunization documentation.

Dr. Peter commented that disavowing OPV will require a statement to document why; such a change should not simply be recorded in a footnote. Dr. Orenstein stated that placing IPV in the

schedule's first two doses is a clear message to begin with. He could agree with Dr. Halsey's concept of making OPV less equal than IPV, but still felt that the opportunity must be afforded for input from the same groups as the last schedule change. He found a working group a reasonable way to proceed. Dr. Modlin disagreed that no change could be done without a statement; an *MMWR* article could be published. But this, and the discussion of potential conflicts between more timely VFC statements and statements, call for a way to do such things more efficiently.

Dr. Snider summarized that CDC could develop an *MMWR* statement expressing a much stronger preference for the sequential approach, or restricting only OPV; another option is to form a workgroup to discuss the an all-IPV approach.

Dr. Johnson thought that strengthening the language for the harmonized schedule would not require an immediate statement change, since it already expresses a preference. But Dr. Modlin wished to go further, publishing an announcement that OPV should not be used for the first two doses, and then including that in the next statement revision endorsing four doses of IPV. Dr. Glode said that the all-IPV issue would require input from all parties, but supported a statement that "..based on report of four cases of VAPP since 1997, ACIP recommends IPV for the first doses or for all four doses. The ACIP recommends that OPV not be used in the first year of life except for the following circumstances..."

However, Dr. Johnson thought this to risk implying a continuing OPV endorsement by supporting parental refusal, the wrong message. It should be strongly conveyed to physicians that IPV is a better vaccine and should be used. Dr. Peter suggested stating that AAP, ACIP, and AAFP recommended IPV for the first 2 doses in most circumstances.

However, Dr. Orenstein reiterated that the all-IPV issue is a new topic of discussion requiring broad input. ACIP has been upset before at not have good advance notice of significant issues to be decided. He also noted that the ACIP didn't actually prefer a sequential schedule, it was recommended, and therefore the limitations on the first two doses are not that different; but making IPV and OPV equal for the last two doses is a more significant change.

Rather than set an arbitrary date for a changeover, Dr. Snider referred to set criteria for an all-IPV schedule to define what needs to happen before changing over. When met, the ACIP could move forward with the involvement of all involved.

But Dr. Halsey demurred that those criteria have been met, and strongly discouraged the same lengthy (2 year) process taken by the last schedule change. He cited more information available and more consensus on the committee. The reason to set a date is to facilitate the necessary planning. He reiterated his request for a resolution recommending OPV for the first two doses only when the parents refuse all injections needed for that age.

With that, Dr. Livengood shared the proposed preamble to the harmonized schedule:

> "The ACIP and the AAP [and AAFP] now recommend that the first two doses of poliovirus vaccine should be IPV. The ACIP continues to recommend a sequential schedule of two doses of IPV administered at ages 2 and 4 months, followed by two doses of OPV at 12-18 months and 4-6 years. An all-IPV schedule for all doses is also acceptable, and is recommended for: 1) immunocompromised persons and their household contacts for whom OPV is contraindicated, and 2) all infants and children living with persons older than 17 years who are known to be inadequately vaccinated against poliomyelitis because of the increased risk of VAPP in adults.

"An all-OPV schedule is recommended for infants and children in whom routine vaccination is not initiated until after six months of age, and for parents concerned about the number of injections. OPV remains the vaccine of choice for mass vaccination campaigns to control outbreaks of wild poliovirus."

Dr. Modlin liked the language, and encouraged an *MMWR* article to elaborate on the rationale for the change, stating that the issue remains active. Dr. Glode demurred that this text does not withdraw the acceptability of an all-OPV schedule. Dr. Griffin agreed, and suggested changing it to "...an all-OPV schedule is not recommended, except..." to be clear that the ACIP is withdrawing something. Dr. Orenstein suggested saying "OPV is no longer routinely recommended for the first two doses except for special circumstances such as..."

Dr. Word disliked the statement that parents are concerned with the number of injections. Dr. Livengood suggested saying ".. for parents who refuse injections." Dr. Orenstein proposed stating that "an all-OPV schedule is acceptable for infants and children..." rather than "recommended." Dr. Peter commented that the Academy's statement is implicit that an all-OPV schedule is not used, but does not state that. He suggested saying that "An OPV schedule is only acceptable in the following circumstances..."

Dr. Snider agreed that an *MMWR* article to call attention to this change should be done. Dr. Glode stated that providers need to be updated on what is happening and why the ACIP stance changed, including that four documented cases of VAPP occurred in 1997. But Dr. Orenstein noted the large information bases of other information that would have to be quickly assembled for such an article prior to the release of the schedule (e.g., aside from the VAPP cases, the unexpected acceptance of the IPV schedule).

Dr. Cochi commented that everyone will be better served by energy devoted to a truly harmonized policy about transitioning from a sequential to an all-IPV schedule by the end of the decade. He cited the danger of a "leapfrogged" development of policies every six months, with each body differing on how quickly or slowly to proceed.

Dr. Livengood summarized the latest suggested text for the harmonized schedule:

"An all-OPV schedule is no longer recommended for the first two doses of the schedule and is acceptable only for the special circumstances detailed below: 1) infants and children in whom routine vaccination is not initiated until after six months of age, and 2) parents who refuse the number of injections necessary to that age. OPV remains the vaccine of choice for mass vaccination campaigns to control outbreaks of wild poliovirus."

Dr. Glode asked about the considerations of children traveling overseas. Dr. Peter thought they would receive one dose if they are leaving imminently, and Dr. Orenstein noted that ACIP accepts both IPV and OPV. For type 1 seroconversion, both vaccines are identical; OPV is 40% better for seroconversion for type 2, and improves 10-15% for type 3. Therefore, the ACIP would not want to decrease the ability to give OPV in that circumstance. Reference could be made to the statement, which does include specific OPV preferences.

VOTE: Resolution 10/98-6: The purpose of this resolution was to adopt the discussed language for the harmonized schedule, which would have to be approved by all parties. There were no conflicts with Pasteur Merieux Connaught; all members remaining could vote. Dr. Guerra moved to adopt the resolution and Dr. Johnson seconded the motion. Drs. Clover, Fleming, and Le were absent.

In Favor: Griffin, Glode, Modlin, Guerra, Johnson, Offit, Word.
Opposed: None
Abstained: None
Outcome: Passed

Dr. Snider thanked the committee members for the resolution. He will have it reviewed by the programs and circulate any differently-crafted text among the committee. Dr. Modlin also restated the implicit understanding that the NIP staff would craft an *MMWR* article to be circulated to all committee members, liaisons, and ex-officios, to state the rationale behind this resolution. He asked if this could be done in 3-4 weeks.

Dr. Livengood proposed that the three paragraphs addressing the rationale for the changes to the schedule, which would be in the introduction to the harmonized schedule, be circulated among the committee. This is published in the *MMWR*. A longer article will take more time to craft than is possible before the harmonized schedule is published. Dr. Modlin understood, and urged that the article be pursed over time. Dr. Johnson clarified, to assent, that this just-approved text would be not in the schedule footnote but in the schedule's introduction. Dr. Livengood promised to fax the specifics of the footnote, which will be similar to this text and must be complete by November 1.

Dr. Modlin asked for volunteers for the polio work group, and Drs. Offit, Guerra, Zimmerman, Peter, Glode, Word, Mischevitz, and Modlin volunteered. Finally, Dr. Evans announced that the rotavirus text was passed by Congress, and will be in the vaccine compensation program in the next few months.

Dr. Modlin thanked Ms. Kovach and the staff for their excellent work in arranging this meeting. Dr. Snider thanked the members for their patience with the new meeting site, and looked forward to meeting again in February. With no further comment, the meeting adjourned at 4:00 p.m.

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

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John Modlin, M.D., Chairman, ACIP Date