CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICE

Records of the Meeting Held on

June 16-17, 1999

Atlanta Marriott North Central Hotel
Atlanta, Georgia

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Atlanta Marriott North Central - Atlanta, Georgia
June 16-17, 1999

16, 1999

Agenda Item	Purpose/Action	Presider/Presenter(s)
8:45 Welcome		Dr. J. Modlin (Chair, ACIP) Dr. D. Snider (CDC, OD)
9:00 Updates Food and Drug Administration National Center for Infectious Diseases National Immunization Program National Vaccine Program Vaccine Injury Compensation Program	Information	Dr. Wm. Egan (FDA) Dr. A. Mawle (NCID, OD) Dr. W. Orenstein (NIP, OD) Dr. R. Breiman (OD, NVPO) Dr. G. Evans (HRSA)
9:45 Working Group Updates Adult Immunization Plans to address selected topics including TdaP recommendations	Information Discussion	Dr. R. Clover (University of Louisville)
General Recommendations Decision of topics and format	Information Decision	Dr. C. Le (Kaiser-Permanente)
10:15 BREAK		
10:45 Polio Issues related to transition to an all-IPV schedule	Information Decision	Dr. P. Offit (Children's Hospital) Dr. R. Prevots (NIP, ESD)
Revision of Hepatitis B Recommendation	Discussion Decision	Dr. H Margolis (NCID, Hepatitis Br)
12:15 Consolidated VFC Resolution for Hepatitis B	Discussion VFC Vote	Dr. J. Livengood (NIP, ESD)
12:30 LUNCH		
1:30 Pneumococcal Conjugate Vaccine ACIP Recommendations for Use of Pneumococcal Conjugate Vaccine Is there general agreement with the draft table of recommendations? What additional data are needed to finalize the statement at the October ACIP meeting?	Information Discussion	Dr. C. van Beneden (NCID, DMBD) Dr. D. Johnson (Mi. Dept. of Comm. Hlth.)
2:15 Revaccination with pneumococcal polysaccharide	Information	Dr. L Jackson (Group Health Cooperative)
2:45 Pneumococcal polysaccharide vaccine in adults with HIV infection: Results of a CDC case control study	Information Discussion	Dr. A. Schuchat (NCID, DMBD)

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3 BREAK		
3:45 Coccidioidomycosis vaccine	Information	Dr. R Hajjeh (NCID, DBMD) Dr. G Rutherford (UC Berkeley)
4:15 Update on Influenza Neuraminadase Inhibitor Live attenuated vaccine Influenza A(H9N2) Infections in Hong Kong	Information Discussion	Dr. K. Fukuda (NCID, DVRD) Dr. N. Cox (NCID, DVRD)
4:45 AAFP Recommendation for Universal Influenza Vaccination starting at age 50 years	Information Discussion	Dr. R. Zimmerman (AAFP)
5:15 Status of Immunization of Bone Marrow Transplant (BMT) Recipients Publication	Information	Dr. J. Modlin (Dartmouth Medical School)
5:30 Adjourn		

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8:00 Unresolved Issues from the Previous Day	Discussion	Dr. J. Modlin (Dartmouth Medical School)
8:30 Bioterrorism	Information Discussion	Dr. S. Lillibridge (NCID, OD) ?? (ACIP?)
Teaching Immunization for Medical Education (TIME) Project	Information Discussion	Dr. R. Zimmerman (Univ. of Pitts.)
10:30 BREAK		
11:00 Use of Standing Orders for Nursing Home Immunization: A HCFA/CDC Collaboration Will the ACIP endorse a nursing home standard to require standing orders for immunization?	Information Discussion Decision	Dr. L. Rodewald (NIP, ISD) Dr. R. Strikas (NIP, ESD)
12:00 Update on comments received on Decision Rules for Immunization	Information	Dr. R. Bernier (NIP, OD)
12:30 LUNCH		
1:30 Electronic updating of ACIP recommendaitons	Discussion	Dr. J. Ward (EPO, MMWR)
1:45 Cost-Effectiveness and Economic Analysis How does immunization compare to other health interventions?	Discussion	TBA
2:15 IOM Report on Priorities for vaccine development	Information	D. K Stratton (IOM)
3:00 ADJOURN		

ATTENDEES:

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

Ex Officio Members
Dr. Robert Breiman (NVPO)
Dr. William Egan (FDA)
Dr. Geoffrey Evans (HRSA)
Mr. Randolph Graydon (HCFA)
Dr. Kristin Nichol (VA)
Dr. Regina Rabinovich (NIAID)
Dr. David Trump (DOD)

Executive Secretary
Dr. Dixie Snider

Liaison Representatives
Dr. Eric France (AAHP)
Dr. Stanley (ACOG)
Dr. Pierce Gardner (ACP)
Dr. Neal Halsey (AAP)
Dr. Barbara Howe (PhARMA)
Dr. Rudolph Jackson (NMA)
Dr. Samuel Katz (IDSA)
Dr. Victor Marchessault (NACI)
Dr. Georges Peter (NVAC)
Dr. Larry Pickering (AAP)
Dr. William Schaffner (AHA)
Dr. Jose Santos-Preciado (NICCHP)
Dr. Jane Siegel (HICPAC)
Dr. Richard Zimmerman (AAFP)

Office of the General Counsel
Mr. Kevin Malone

National Immunization Program
Ms. Pamela Berman
Dr. Roger Bernier
Dr. Kris Bisgard
Dr. Susan Chu
Dr. Jose Cordero
Dr. Jennifer Danielson
Dr. Don Ekwueme
Dr. Gary Euler
Dr. Suzy Feikenia
Mr. Bill Gallo
Ms. Edith Gary
Dr. John Glasser
Mr. Michelle Groux
Dr. Sharon Humiston
Dr. Sonja Hutchins
Dr. Nino Khetsuriani
Dr. Duane Kilgos
Ms. Carla Lee
Dr. John Livengood
Dr. Hugh Mainzer
Dr. Mary McCauley
Ms. Jennifer Millen
Dr. Trudy Murphy
Dr. Bill Nichols
Dr. Walt Orenstein
Ms. Bette Pollard
Dr. Rebecca Prevot
Dr. Ben Schwartz
Dr. Jim Singleton
Dr. Vishnu-Priya Sneller
Mr. Robert Snyder
Dr. Ray Strikas
Dr. Fran Walker
Dr. John Watson
Dr. Melinda Wharton
Mr. Jessie Wing
Mr. Ed Yacovone
Ms. Lynn Zanardi

Office of the Director
Mr. Sam Gerber
Ms. Martha Katz

National Center for Infectious Diseases
Dr. Joseph Bresee
Dr. Carolyn Bridges
Mr. Scott Damon
Ms. Roz Dewart
Dr. Rana Hajjeh
Ms. Rita Helfand
Dr. Keiji Fukuda
Dr. Alison Mawle
Dr. Martin Meltzer
Mr. Errol Reiss
Dr. David Shay
Moutse Soriano-Gabarro
Dr. Kanta Subbarao

AAP
Dr. Jon Abramson

ASTHO
Dr. Claire Hannan

AVIRON
Iksung Cho
Julie Cordova
John Hollister
Paul Mendelman
Carol Olson
Rhoda Sjoberg
Camela Stuby

Bailey & Dalrymple
Dack Dalrymple

Biochem PhARMA, Inc
Dr. James Veazey

Childrens' Vaccine Institute
Roy Widdus

Cooney-Waters
Sherri Michelstein
Peter Vigliarolo
Beth Waters

Evax Technologies
Florian Schodel

Food and Drug Administration
Leslie Ball
Douglas Pratt

Georgia Immunization Program
Ruth Gilmore

Group Health
Lisa Jackson

IDSA
Bruce Gellin

Immunization Action Coalition
Lynn Bahta
Deborah Wexler

Infectious Disease in Children
Cassandra Richardson

International Medical News Group
Bita Honarvar

IOM
Kathleen Stratton

IPAV
Michelle Ceballos
Carolyn Kress
Lani Lipking
Lisa Moreno
Nancy Perrone
John Salamone
Alicia Thompson
Tom Vaughn

Johns Hopkin School of Medicine
Dr. Dennis Brooks

Kaiser Permanente
Steve Blake

Merck
Brant Bichon
Daniel Casto
Hillel Cohen
Stanley Music
Jane Quinn
Brett Saunders

Merck-Continued
Michael Severino
Stacy Stuerke
Ling Su
Thomas Vernon

National Immunizaton Hotline
Mary Stuart

National Institute of Health
Albert Kapikia

National Vaccine Program Office
Martin Myers
Alicia Postema
Larry Sparks

NIAID/JHU
Filip Dubovsky

North American Vaccine
David Zielinski

OSASPE
Lynn Cates

Parallax Communication
Scott Litherland
Ann Rogers

Pasteur Merieux
Sean Campbell
David Fedson
Mary Gadek
Philip Hosbach
Len Lavenda
Stanley Plotkin
Fred Rutsen
Judith Shindman
Jaco Smit
David Webster

The Press
Sheeren Ahranjani-CNN
Diana Davis-WSB-TV
Mark Deutchman-CNN
Karan Klaus-CNN
Rhoda Rowland-CNN
Steve Sorg-CNN
Miriam Tucker-Pediatric News

PTV
Adeline Beth'

Refugee Health Program
Alice Long

SmithKline Beecham
Hugoes Bogaerts
Christian Courtois
Scott Harward
John Jabara
Charlotte Kroft
Schuerman Lode
Amy Scott

South Carolina Department of Health
Jesse Greene

Stanford University
Dr. Lucy Tompkins

University of California
George Rutherford

University of Maryland
Dr. Margaret Rennels

Vaccine Policy Institute
Kristine Severyn

WLV
Connie Scotese

Wyeth-Lederle
Liz Anderson
Troy Couch
Craig Engesser
Bill Hausdorff
Lisa Ohlandt
Peter Paradiso
Lois Privor-Dumm
Roland Rodriguez
Peter Tobar
Laura York

Wyeth-Ayerst
Werten Bellamy
Michael Blum
Pat Cannon
Nancy Fix-Bloeser

Others Present
Gary Cochran
Marie Murray

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Centers for Disease Control and Prevention
Advisory Committee on Immunization Practice
June 16-17, 1999

JUNE 16, 1999

The Centers for Disease Control and Prevention convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on June 16-17, 1999 at the Atlanta Marriott North Central Hotel in Atlanta, Georgia. Chair Dr. John Modlin called the meeting to order at 8:50 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.

Opening Comments
ACIP Executive Secretary Dr. Dixie Snider welcomed two new liaisons, Dr. Barbara Howe of the Pharmaceutical Research and Manufacturers of America (PHARMA), and Dr. Eric France, of the American Association of Health Plans (AAHP). He reported that Dr. Yvonne McHugh, the Biotechnology Industry Organization representative, would be absent for this meeting but present in October. Three ACIP members' terms were to expire this month, Dr. Jessie Sherrod (not present), Dr. Mimi Glode, and Dr. John Modlin. Dr. Snider anticipated Dr. Modlin's reappointment and resumption as Chair to maintain the committee's continuity. A letter and certificate of appreciation was presented to Dr. Glode from CDC Director Dr. Jeffrey Koplan, who attributed the committee's success to the members' contributions.

In other announcements, Dr. Snider reported an e-mail address for the ACIP (acip@cdc.gov), and work underway to develop a ListServ for the members' use. And, in a change in committee management specialist support, he announced the departure of long-time ACIP coordinator Ms. Gloria Kovach. The next committee coordinator will be within the National Immunization Program and is hoped to be in place by the October meeting. ACIP meetings in the year 2000 will be on February 16-17; June 21-22; and October 18-19. Finally, Dr. Snider reminded all the attenders that the ACIP charter allows the committee Secretary to designate ex-officios to vote when the majority of ACIP members have conflicts of interest.

Dr. Modlin requested introductions of those present and statements of financial conflicts of interest. Members with such must abstain from making a motion, seconding a motion, or voting on resolutions pertaining to the Vaccines for Children program.

Those members present reporting no conflicts of interest were:
- David Fleming, M.D.
- David R. Johnson, M.D.
- Marie R. Glode, M.D.
- Charles M. Helms, M.D.
- John F. Modlin, M.D.
- Bonnie Word, M.D.

Those members present reporting conflicts were:
- Richard D. Clover, M.D.: has a grant with SmithKline Beecham, and has received honoraria from Wyeth Lederle. His department has received funding from Connaught and Merck in the past, but no longer has those conflicts.
- Marie Griffin, M.D.: is a consultant to Merck for non-vaccine issues.
- Fernando Guerra, M.D. : contracts for vaccine studies with Merck, Metamune, and SmithKline Beecham, and occasionally consults with SmithKline Beecham, Merck, and Pasteur Merieux Connaught

- Chinh Le, M.D. : holds stock in Merck. He also is on the staff of Kaiser Permanente, which has research interests with Merck, SmithKline Beecham, Wyeth Lederle, and North American Vaccine.
- Paul Offit, M.D. : is a consultant with Merck on the development of rotavirus vaccine.

CDC staff present on the committee, also with no conflicts to state, included:
- John Livengood, M.D., Epidemiology and Surveillance Division, National Immunization Program (NIP)
- Alison Mawle, M.D., National Center for Infectious Diseases (NCID)
- Walter Orenstein, M.D., NIP

The ex-officio and liaison members in attendance were:
- Rob Breiman, M.D., National Vaccine Program Office (NVPO)
- William Egan, M.D., Food and Drug Administration (FDA)
- Geoffrey Evans, M.D., Health Resources and Services Administration (HRSA), National Vaccine Injury Compensation Program
- Eric K. France, M.D., American Association of Health Plans (AAHP)
- Stanley A. Gall, M.D., American College of Obstetricians and Gynecologists (ACOG)
- Pierce Gardner, M.D., American College of Physicians (ACP)
- T. Randolph Graydon, Health Care Financing Administration (HCFA)
- Neal Halsey. M.D., American Academy of Pediatrics (AAP)
- Barbara J. Howe, M.D., Pharmaceutical Research and Manufacturers of America (PHARMA)
- Rudolph Jackson, M.D., National Medical Association (NMA)
- Sam Katz, M.D., Infectious Disease Society of America (IDSA)
- Victor Marchessault, M.D., Canadian National Advisory Committee on Immunization
- Kristin Lee Nichol, M.D., Department of Veterans Administration (DVA). She announced a conflict of funding received from Pasteur Merieux Connaught, Merck and Aviron.
- George Peter, M.D., National Vaccine Advisory Committee (NVAC)
- Larry Pickering, M.D., Red Book, American Academy of Pediatrics (AAP)
- Regina Rabinovich, M.D., National Institutes of Health (NIH), National Institute for Allergies and Infectious Diseases (NIAID)
- Jose Santos-Preciado, M.D., National Vaccination Council of Mexico
- 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)

Dr. Modlin noted the publication of six recommendations since the last meeting, which were inserted in the members' meeting books. They addressed the Prevention and Control of Influenza, statements on Varicella, on Combination, Rabies, and Rotavirus vaccines, and on Lyme Disease. In other areas, he announced that a photographer and camera crew may be present over the course of the meeting.

He noted recent attention to the issue of meningococcal disease among college students, which may be addressed in detail in October, and asked those interested in participating in a Workgroup on Meningococcal Issues. Volunteers were Drs. Clover, Fleming, Gardner, Guerra, Helms, Jackson, Katz, Le, Peter, Rubin, Schaffner, Trump, and Zimmerman. A conference call is probable before the next meeting. He also hoped for a small workgroup to discuss the electronic update of ACIP statements, and would explore this with the members privately.

Agency Updates

Food and Drug Administration (FDA)
Dr. William Egan announced the closing of the vacancy for the Director of Office of Vaccine Research and Review. A Permanent Director is hoped to be in place by fall. Pneumococcal vaccine is currently under discussion; Wyeth Lederle has a pending polysaccharide conjugate vaccine application. A September 7-10 workshop is planned on vaccine substrates, cosponsored by FDA, NIAID, NIH, the NVPO, WHO, and the International Association for Biologics Standardization (IABS). It will focus on the introduction and use of tumorgenic cell lines and the use of continuous cell lines for live viral vaccines. None are yet licensed in the U.S. New members on the Vaccine-Related Biologics Advisory Committee (to meet September 16 and chaired by Harry Greenberg of Stanford are Diane Griffin, Walter Faggot, and Barbara Fisher (consumer representative). Finally, NIH's Vaccine Research Center is under development, headed by Gary Navel. FDA will anticipates continuing to participate in vaccine development discussions with NIH, particularly with the AIDS focus of the new NIH Vaccine Research Center headed by Gary Navel.

National Center for Infectious Disease (NCID)
Dr. Allison Mawle updated the committee on the Influenza A/H9N2 outbreak in Hong Kong. Two apparently unrelated cases, in children hospitalized in February and March, recovered. Five possible Chinese cases remain unconfirmed. Sporadic cases of this virus, an avian infection distributed by poultry to humans, have occurred in Hong Kong and China. NCID is developing serological detection tools and several studies are underway Hong Kong. A possible relationship to pandemic influenza is being investigated. The frequency of human infection with these viruses is unknown; studies are pending.

Dr. Mawle briefly reviewed recent data on meningococcal surveillance in all states among college students. Out of 60 cases that could be typed of 83 occurring in the U.S., 47% were type C, 27% were type B, and 19% were type Y; 49% of them occurred in males and 46% in freshman. Similar observations have been made among new military recruits who are now routinely vaccinated. The reported rates are lower than those for the general population of 18-23 year-olds, but higher for freshman living in dorms. **(Please check with Dr. Mawle. I don't think this is accurate -- [Mawle e-mailed w/high priority 1/18/2000 -- mm])** The latter may be good targets for possible vaccine intervention and an ACIP recommendation. Studies continue.

National Immunization Program (NIP)
Dr. Walter Orenstein stated that vaccination is one of the ten great public health achievements this decade. Surveillance data from 1998 indicate coverage at >95% for smallpox, diphtheria, pertussis, tetanus, wild-type polio, measles, mumps, rubella, and congenital rubella syndrome. ACIP recommendations played a major role in these successes.

Overall vaccination levels in children remain extremely high. In the third quarter of 1998, nearly half the children in three surveillance sites were immunized against varicella, with a noticeable reduction of morbidity. The 1988-1991 measles resurgence produced >55,000 case reports, >11,000 hospitalizations, and >123 deaths. Final 1998 data indicate the interruption of indigenous measles transmission in the U.S. Its elimination in the northern hemisphere by 2000 is a goal, but importations remain a hazard. In 1998, 26 measles importations from 21 countries occurred, 12 among American travelers abroad. However, the 390 importations from 1989-91 declined to 6 during 1996-98. In a cooperative agreement with PAHO, NIP is providing technical assistance to aid in the elimination of measles south of the border.

Dr. Orenstein reported substantial (average >30%) cuts in infrastructure for U.S. immunization programs in 1997-98. An interim IOM report ("Immunization Finance Policies and Practices," on the Web) stated that immunization efforts deserve careful attention; that the Child's Health Insurance Program to address the underinsured will be inadequate; and that further reductions in federal support would threaten provision of immunization services.

Dr. Livengood provided a follow-up report on the low-potency lots of DTaP (Tripedia®) discussed at the last meeting. Serological tests demonstrated that 98% of the infants vaccinated developed adequate protection, but only 43. 5% achieved the optimally protective level (>. 1 IU/ml). Normally, this rate should be 60-80%. But CDC is confident that these children are immunologically primed. If they travel to area of risk, a booster dose would be recommended, but for now, no additional action is planned.

National Vaccine Program Office (NVPO)

Dr. Rob Breiman reported on the NVPO and its National Vaccine Advisory Committee (NVAC), which is Chaired by Dr. George Peter. NVAC recently prepared a manuscript on standards for adult immunization in nontraditional settings. The ACIP members' review and comment on these standards was requested. They recognize the potential of these settings to boost adult immunizations, as well as the challenges of record keeping, liability, the legal implications of administering vaccines, and the potential for fragmentation of care.

NVAC also recently recommended development, upon available resources, of a comprehensive vaccine safety action plan built on 3 components: education and communication, epidemiology and surveillance, and research and development. An important meeting on combination vaccines is planned for February 2-4, to discuss the laboratory and epidemiology "state-of-the-art" needed to develop standards for the rapid development of safe and effective vaccines. A resolution was also passed recommending a supplemental appropriation for immunization infrastructure funds in fiscal year 1999 (FY99), reflecting concern about the impact of reduced funding on immunization delivery.

Dr. Breiman reported ongoing NVAC/DHHS development of a comprehensive pandemic flu preparedness plan. A recent related satellite conference was well received, and four states now have model plans. An NVAC workgroup chaired by Dr. Walter Dowdle will advise on policy and risk assessment issues. Recent NVAC-developed papers addressed strategies to sustain success in childhood immunizations (*JAMA*, in press); and lessons learned from the development of new vaccines (*Pediatrics*).

Dr. Peter reiterated NVAC's concern about the reductions to the 317 Program. The success of disease reduction is linked to the ability to sustain immunization rates, particularly with the constant threat of importation. This was to be further discussed at the National Immunization conference to be held the following week in Dallas.

National Vaccine Injury Compensation Program (NVICP)

Dr. Geoffrey Evans reviewed the NVICP's compiled statistics. Petitions filed have risen with the approach of the 2-year deadline for hepatitis B claims, with 130 claims received. In adjudications, he reported efforts to close out the pre-1988 program, with about 150 claims left. Awards paid total >$1 billion.

In Congressional bills, the Vaccinate America's Children Now Act would reduce the vaccine tax from $0.75 to $0.25 per dose or disease prevented. Companion Senate legislation is expected to pass this year, as is the Senate "Affordable Education Act of 1999." The latter allocated

monies from the tax on the soon-to-be-licensed pneumococcal vaccine to pay for education expenses. Dr. Evans explained that wording in last fall's legislation did not cover vaccines added to the program. The 1998 budget bill added that language but still excluded people injured by licensed but not yet taxed vaccines. A similar necessary adjustment to legislation language pertains to the June 9 resolution by the Advisory Commission on Childhood Vaccines (ACCV) seeking legislation to impose an excise tax for childhood hepatitis A vaccine. The original legislation had no mechanism for adding new vaccines. This was provided under rule making for Hib, hepatitis B, and varicella vaccine. It included a vaccine table (Box 12) which automatically included any new vaccine added by CDC to the VFC program. However, Box 12 requires publication in the *Federal Register* within a month of ACIP recommendation and VFC designation. However, as in the case of a limited (e. g., hepatitis A) recommendation effective for routine use in only a few states, selectively taxation cannot be done. An advisory commission proposed grouping vaccines in two categories, those with a universal use recommendation, and those with limited use, such as for Lyme Disease and (formerly, but changing), hepatitis A. Congress will address this.

National Institutes of Health (NIH)

Dr. Regina Rabinovich reported the appointment of Dr. Carol Heitman as Director of the Division of Microbiology and Infectious Diseases. The cornerstone was laid the previous week for the Dale and Betty Bumpers Vaccine Research Center. The Vaccine Study Section has been in place for a year. She also noted that the NIH/Institute of Medicine (IOM) study on preparing a quantitative model for use in vaccine development would be presented at this meeting. Dr. Orenstein also reported that the Task Force on Community Preventive Services, which had presented its methods to the ACIP, had researched successful immunization strategies. A short version of their report is scheduled to be published in the *Mortality and Morbidity Weekly Report (MMWR)* within the next few months.

Working Group Updates

Adult Immunizations Workgroup

Dr. Richard Clover reported a workgroup conference call which discussed 1) pneumococcal polysaccharide vaccine; 2) the adolescent and adult use of DTaP. This was spurred by recent reports of pertussis in adults and the application by companies in other countries for an adolescent/adult indication for the use of acellular pertussis vaccine (a formal presentation is planned in October); and 3) revising the adult immunization guidelines.

ACIP advice was requested as to the need to revise/update the adult immunization recommendation, or to incorporate this into the update of ACIP General Recommendations by Dr. Le's General Recommendations Workgroup. They have identified three areas of focus: specific vaccine recommendations targeting adults, programmatic issues affecting adult rates, and attention to populations at risk.

Upon Dr. Peter's inquiry about the recent licensure of adolescent TdaP in Canada, Dr. Marchessault reported this was discussed at the June meeting of the Canadian National Advisory Committee on Immunization. No new recommendation has yet been issued on its use. The current Canadian recommendation is a dose at age 14-16 years and another in adulthood.

In discussion, several members supported a recommendation for adults. Dr. Gall appreciated a focus separate from the usual childhood immunization issues. Drs. Zimmerman and Gardner noted that adult VPD burden is higher than that for children, and advised coalescing these recommendations in one place to be more useful. Dr. Guerra suggested integrating the

recommendations for foreign travel into both the adult and children's immunization recommendations. Dr. Peter advised coordination with NVAC's Subcommittee on Adult Immunizations. Dr. Orenstein commented on the massive undertaking that such work entailed, and hoped for substantial help from committee members. Dr. Modlin anticipated further discussion on these topics in October.

ACIP General Recommendations Workgroup

Dr. Chinh Le recalled the workgroup's proposal in February of a more technical General Recommendations document. Dr. Jay Watson presented the purpose of the General Recommendations, provided a rough Table of Contents to highlight the more complex issues of interest which may also have insufficient data for complete address, and proposed a timetable to completion.

The purpose of the General Recommendations is to: 1) provide practical technical guidance on the safe and effective administration of vaccines to infants, children and adults, for practitioners in the field and for health departments. They are also to provide help locating detailed information about specific vaccines, programmatic issues, etc.

Dr. Watson outlined a rough draft Table of Contents for the General Recommendations:

1. *Introduction* to provide technical guidance to health care workers administering vaccines, and summarizing the changes of this revision.
2. *Timing of Vaccine Administration.* This would include: an explanation of the general principles used to arrive at a vaccination schedule; non-simultaneous and simultaneous administration of different vaccines; interchangeability of vaccine products; and catch-up vaccinations/uncertain vaccination status.
3. *Vaccine Administration.* This would address: consent; prevention of adverse events; contraindications; precautions; syncope/anaphylaxis; the injection site; alleviation of pain and discomfort; and the avoidance of nonstandard practices.
4. *Special Situations.* This would include: hypersensitivity to vaccine components; issues of pregnancy/breast-feeding/preterm infants; altered immunocompetence; bleeding disorders; and interference by immune globulins.
5. *Other issues.* This would include: obtaining consent (may be in the previous section); vaccination records; issues of vaccination outside U. S.; reporting adverse events and finding out information on them; vaccine injury compensation; vaccine storage and handling; and obtaining additional information about vaccines and immunizations.

The workgroup decided not to include such regularly updated information as the childhood (and eventually adulthood) schedules; information in specific ACIP vaccine recommendations (rather, general principles and referral to the statement would be provided); programmatic issues regarding coverage (ACIP feedback on what to include or exclude was solicited); and specific and specialized issues such as bone marrow transplantation which are addressed in specific statements.

Areas if interest that are addressed include: 1) the question of intramuscular injection using prefilled 5/8" syringes (ACIP feedback was sought); 2) the 30-day interval between live virus vaccines not administered simultaneously. There are very limited data to inform this, but in general ACIP recommends immunization regardless of viral illness within the 30-day interval; and 3) acceptance of foreign vaccination records (allegedly-vaccinated infants from some areas have tested serologically low). The latter involves global issues, WHO and other organizations, all of which require consideration.

Finally, Dr. Watson reviewed the projected timetable. Using this Table of Contents, the draft will be written and reviewed by the working group (July-August, 1999) and distributed to the ACIP for feedback (August-September). A resulting revised draft and major issues can be addressed by the entire Committee (October-February), for final ACIP approval by spring 2000.

Discussion. Dr. Modlin asked for specific comments or suggestions. Dr. Katz advised including, in the pragmatic focus on injections, other methods such as oral and intranasal (when licensed). Dr. Nichol encouraged linkage to similar other efforts and including comments on recommendations of successful strategies. Dr. Halsey reported that the new edition of the Red Book will incorporate some of these issues. He strongly encouraged revision of the General Guidelines and found this described approach sensible. However, he also thought that the timetable may be overly ambitious in light of the total content and controversies involved, and suspected that it may have to be cut back in scope or expanded in time frame.

Workgroup on Decision Rules for Immunization

Dr. Guerra recalled this workgroup's original formation to discuss how best to use the emerging technology to comply with the ACIP recommendations for coverage. This activity is a work in progress which has evolved (now at "Version 1.3") which he hoped could be taken to the field soon. This is more than an attempt to use computerized registries, tracking systems, etc., but also to ensure that good science guides the decision rules regarding immunization Intervals and the different types of vaccines used (live, killed, etc.). He commended the work done on this document by NIP staff, particularly Dr. Roger Bernier and Ms. Suzie Feikema.

Dr. Roger Bernier referred the committee to a distributed "Dear Colleague" letter which outlined the group's activities and a proposed timetable. The public comment/review of the decision rules approved by the ACIP in February had resulted in only three minor changes suggested by the AAP Red Book Committee and subsequent to the February meeting of immunization managers: 1) the diagram was revised to show the recommended and accelerated points on one line; 2) the age and interval tables were combined into one table grouped by vaccine; and 3) more consistency was provided in the numbers used for the age-to-repeat or interval-to-repeat. A minimum age also was added to count the minimum doses of DTaP.

Outstanding and anticipated changes include the wording of the schematic's concepts (e.g., "age beyond which to only count doses), or a statement about the option of serotesting if there is resistance to repeating a dose or upon schedule violations. This document also will be used beyond clinical situations, as an operations manual for the computer programers writing the algorithms for registries and databases.

The dissemination plan (July-September 1999) includes posting the decision rules and Version 1.3 on the NIP's Website for public comment, and soliciting comments from several user groups (program managers, managed care organizations, private physician groups). A Michigan contractor will conduct physician focus groups on the decision rules, and a USC/San Diego investigator may pilot this version in 26 clinics. A Version 2.0 will be proposed at the October meeting, hopefully to be approved and published with the harmonized schedule in late 1999 or early 2000.Finally, Dr. Bernier requested suggestions of individual or group reviewers.

Dr. Modlin asked the members to closely review this draft in the next 4-6 weeks, and reported that the Influenza Workgroup had proposed a July 25 meeting at CDC. With that, the committee took a short break.

Revision of Polio Vaccine Recommendations

On reconvening, Dr. Modlin introduced the topic of a revision of the ACIP polio vaccine recommendations, focusing on the policy issues related to an all-IPV schedule.

Public Comment

Mr. John Salamone, President of Informed Parents Against VAPP (IPAV), congratulated Dr. Paul Offit and the workgroup on their efforts relating to a new polio vaccine policy, and thanked Dr. Modlin for his leadership. IPAV represents families affected by vaccine-associated paralytic polio (VAPP), which he termed the price of an OPV-dependent policy. IPAV has advocated for an all-IPV schedule since 1989. They support the U.S. immunization program, only urging use of the safest possible vaccines to maintain families' faith in immunization. He hoped that this day would begin a schedule of the exclusive routine use of an all-IPV schedule by January 1, 2000, eliminating OPV as a routine immunization schedule without loopholes. He hoped that the NIP Director would issue a letter to all providers by January 1 explaining the new schedule, and that the AAP and AAFP would do the same, to enable private physicians to prepare for the changeover.

Mr. Salamone stated that OPV has been the only source of polio in the U.S. for the last 20 years. ACIP's allowance of its use even for one schedule transition year risks tempting some physicians to continue the Russian Roulette of using it. This will cause more cases like Ciara Cevalos and Jay Vaughn, both of whom contracted VAPP from OPV administered after the last ACIP policy change because their physicians continued to use it. Three children with VAPP from childhood immunizations: Jenné from Missouri, Eric from Nevada, and Ryan from Florida, stood to be recognized at this meeting. Mr. Salamone assured the committee, as the father of a 9-year old who preferred no leg to a crippled one, that policy has personal impact. ACIP's policy must be compassionate, scientifically appropriate, and the right thing to do.

Statement by the National Medical Association. Dr. Rudy Jackson presented a statement on behalf of the NMA. In early discussions of this topic, the NMA stated the need to collect information about the impact of a schedule change on coverage rates, about parents/provider opinions, and about the need for a national education program. Dr. Jackson read the following statement, forwarded by the NMA's Pediatric Section to the NMA voting body:

> "Based upon ongoing evaluation of data received from the following sources to date, namely: the National Medical Association's Polio Compliance Membership Survey, questionnaires from the Polio Immunization Delivery Study done in collaboration with the Pediatric Research and Office Settings (PROS), and the NMA Pediatric Section, and other relevant reports from the CDC to date; all of which indicated no decrease in childhood immunization rates as a result of the amended IPV recommendations, and apparent acceptance of the transition to the IPV/OPV sequential schedule by both parents and providers. The Pediatric Section of the NMA has therefore recommended to the NMA's voting body the following recommendations:
>
> 1. That the National Medical Association joins in concert with the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians in recommending the use of the transitional IPV/OPV schedule for routine childhood polio immunization;
> 2. That the National Medical Association support the forthcoming transition to an all-IPV schedule as a polio vaccination policy for routine childhood immunization."

Presentation of the Polio Recommendation Workgroup

Timing of the Transition to an All-IPV Schedule
Dr. Paul Offit introduced issues raised by the Polio Working Group relative to the timing of a transition to an all-IPV schedule: the language to be submitted in the next month to *MMWR* as a Notice to Readers, and special situations in which OPV could be used after transition to an all-IPV schedule (e.g., large-scale outbreaks, catch-up immunizations, and travel to polio endemic regions).

Dr. Rebecca Prevots updated the committee on recent polio surveillance data. Four suspected VAPP cases occurred with onset in 1997-98. Four cases were confirmed in 1997 and one in 1998, one in a 4-month old OPV recipient. None have been confirmed in 1999. All-IPV constituted 35% of vaccine doses distributed through 1998 through federal contract, and 45% for the first quarter 1999.

Timing. Dr. Offit framed the question of the appropriate target date for transition to an all-IPV schedule. The options discussed by the workgroup were: 1) to recommend an all-IPV schedule by January 1, 2000, with the sequential schedule considered an acceptable alternative during the year 2000.An exclusive all-IPV schedule would then be recommended by January 1, 2001. Or, 2) to recommend an exclusive all-IPV schedule by January 1, 2000, with the sequential schedule considered an unacceptable alternative after that time.

The workgroup recommended Option 2, feeling that ACIP should recommend movement to an all-IPV schedule as efficiently and effectively as possible. The implications of choosing this option include: 1) the need to ensure an OPV stockpile in case of an outbreak (ACIP has already approved such use). It is hoped that contracts can be in place by no later than December 31, 1999; 2) including both the AAP and the AAFP in the harmonized schedule. They indicated that this could best be done with the year 2000 as a transition schedule; 3) the likelihood that a recommendation to include catchup vaccinations and travel to endemic regions will be ready by next year; and 4) the remaining education needed may be best done within a sequential schedule. But Dr. Offit reiterated the workgroup's wish to discuss ways to more quickly accomplish this all-IPV goal.

Discussion. Dr. Katz seconded Mr. Salamone's case. It has been 20 years since any naturally occurring polio in the U.S. and eight years since any in the Western hemisphere. He stated that the field had "been diddling over this for years," and found no justification to continue to support a sequential schedule. He urged the ACIP members to approve the all-IPV schedule now.

Dr. Halsey spoke both personally and for the AAP. The Red Book Committee has been on record since 1996 advocating an all-IPV schedule effective in 2001. They had reviewed all CDC's information and sent it to committee members for individual votes, producing divided opinion. The primary concern voiced was that a sudden change could require two visits in one year, potentially problematic in these days of fixed costs, and about administering five injections in one visit. Nonetheless, several members voted for 2000 for Dr. Katz's reasons. Officially, the AAP still supports a 2001 transition. Personally, Dr. Halsey supported as rapid as possible a move to all-IPV. He suggested a schedule endorsement such as "no later than 1/1/2001" to indicate a strong preference for all-IPV, with OPV as an acceptable option only when people would otherwise not receive all the vaccines indicated. He realized that Mr. Salamone may be disappointed, but commented that essentially his battle is over. All-IPV will most likely be the rule by 1/1/2001. The point is to accomplish that without compromising children's care.

Dr. Modlin asked if any programmatic issues could impede Option 2, particularly for the states to make the transition. Dr. Orenstein stressed the importance of getting the word out., He shared Dr. Halsey's concerns about getting everything necessary done (including having an outbreak OPV supply in place), but he supported strong language for an all-IPV schedule. However, Dr. Katz rejoined that unlike smallpox, a huge supply is not necessary for polio; an outbreak will only affect surrounding contacts and possibly surrounding areas. He asked about the likelihood of IPV combination vaccines. Dr. Howe reported SmithKline Beecham as in the late phases of developing a combination vaccine for diphtheria, tetanus, acellular pertussis, hepatitis B, and IPV.

Dr. Peter wondered if a limited supply of OPV would assure its limited usage, no matter the ACIP recommendation. Dr. Prevots could not comment, but reported the contract solicitation was mailed out June 3 and due back August 3. Dr. Orenstein reported the RFP issued to assure supply of OPV (from either foreign or current domestic manufacturers), ideally in the current licensed preparation, or as an IND product. Mr. Bill Nichols of NIP reported a contract in place through the end of 1999, and negotiations underway for supply beyond that. Dr. Bill Hausdorff of Pasteur Merieux Connaught reported IPV as widely available and expected no problem in meeting market demands.

Dr. Offit reported the workgroup's feeling that VAPP could still occur with the sequential schedule. After two doses of IPV subsequent to receiving the first dose of OPV, a child can still shed neurovirulent revertant virus. He was more worried about disease in contacts than in the primary recipient. Dr. Guerra commented on the >50% local-level uptake of IPV, and >70% among VFC providers. The latter network could rapidly increase uptake even further. Dr. Pickering called for increased educational efforts to speed this transition as much as possible.

Dr. Zimmerman, who personally favored an all-IPV schedule, suggested that the *MMWR* Notice to Readers publish a projection of a possible all-IPV harmonized schedule in 2000, in order to provide a strong message in itself. Dr. Helms asked if the increased IPV use to 45% was consumer- or supplier-driven, and whether the NIP expected another 10% increase this year. Dr. Orenstein responded NIP's experience that the physician and nurse most influences immunizations. He was unaware of a major parental effort to increase its use. But he expected that a recommendation from the ACIP and the Academies to place all-IPV in the harmonized schedule would speed its adoption.

Dr. Modlin summarized most ACIP comfort with Option 2, and asked under what circumstances OPV would be acceptable in 2000.Dr. Halsey foresaw only two possible exceptions: a parent refusing five needed injections but accepting four; and the case of children going to endemic areas. In the latter case, IPV alone could be sufficient, but he would prefer optimal intestinal protection if they travel and return.

Dr. Guerra thought it reasonable to postpone one injection and schedule a return for the IPV. Dr. Halsey agreed that this is an option, knowing some pediatric practices already doing so. Dr. Peter raised concerns related to the school entry requirements for immunizations by August. Some sites are strongly recommending varicella immunization, considering polio (and therefore OPV) as less of a risk.

Mr. Salamone warned that the term "acceptable" implies "OK." He agreed that in some cases OPV use could be defined as "acceptable under special circumstances" as long as those definitions closed the loopholes. But Dr. Griffin preferred to avoid that exercise, asking what special circumstances would apply for only one year.

In view of the discussions, Dr. Modlin called for a vote on the use of all-IPV by January 1, 2000 with no OPV use acceptable, and on a one year grace period with specifically defined circumstances. Dr. Offit read the recommendation:

> "In January 1997, ACIP recommended a sequential schedule with an all-IPV schedule as acceptable. This was a transitional schedule. Vaccination remained high in the past years despite extra injections. To reduce the risk of VAPP, in January 1999 ACIP recommended not using OPV in the first two doses. In January 2000, an all-IPV schedule will be recommended for exclusive use. All children would receive IPV at 2,4,6-12 months and at 4-6 years. Other language had been crafted to address catch-up and travel to endemic areas.

Dr. Modlin suggested text that "Use of OPV is no longer acceptable for routine use."

Dr. Fleming asked if state immunization programs need more than a 6-month lead time to such a switch, particularly with the newly-standard pneumococcal immunization. Dr. Johnson reported concerns about the implications of multiple visits in the second year of life when vaccinations could be otherwise accomplished; for example, DTaP could be postponed when pertussis still circulates. A statement is needed urging that no opportunities to vaccinate be missed. One year could make a difference to help state programs transition. Dr. Fleming agreed; alongside other factors such as funding reductions, the difference between 6 and 18 months is significant.

But Dr. Guerra offered a different perspective, citing Houston's success in recruiting private sector physicians to work with the VFC program. He felt that the ACIP could drive this, along with changes in the vaccine schedule. When asked the AAFP's guidance for second year visits, Dr. Zimmerman clarified that they only advise tasks, leaving the necessary visits up to the physician.

Dr. Halsey expected resistance to the "no longer acceptable" language of Option #2. He advised a second sentence recommending an all-IPV schedule in January 2000, with the sequential schedule as an acceptable alternative under special circumstances (e.g., for children whose parents refuse the number of injections needed to provide all of the vaccines recommended at that age). That would be acceptable to the AAP, allowing a year to transition during which a combination vaccine may be produced.

Dr. Offit pointed out the contradiction in defining the best and final option as all-IPV, except for certain circumstances in this year. But Dr. Halsey rejoined that this would convey the message without disrupting public health practice. Dr. Modlin agreed that this is a real issue, noting the several concerns voiced about potential missed immunizations. Dr. Jackson felt that a 6-month changeover period is unrealistic, commenting that the related education process has spanned 4-years process even for the NMA. He supported more time to get the message out, including the exceptions, to prepare for the final 2001 transition.

Dr. Fedson suggested the alternative of recommending OPV for doses 3 and 4 "only if the alternative is no dose of polio vaccine," to strongly convey the desire both for IPV and for fully immunized children. Dr. Gardner thought it important to state that all-IPV is the only acceptable "routine" immunization, coupled with Dr. Fedson's text to eliminate any idea of an acceptable alternative. Dr. Florian Schodel suggested stating that the "sequential schedule is no longer an acceptable routine alternative," then listing the exceptions.

Dr. Livengood addressed the concerns about injections in year two of life. He noted that while the sequential schedule calls for dose 3 at 12-18 months, an all-IPV schedule ranges from 6-18 months, allowing some flexibility to avoid 5 injections. Dr. Guerra suggested that dissemination materials cite examples on how physicians administering the doses can postpone or otherwise customize the immunization schedules. Dr. Modlin asked, if children could be fully immunized by 6 months, making the extra injections or return visits in second year less likely, if that would alter the state programs' opinions. Dr. Johnson thought that this would be useful in endorsing the transition, but did not expect it to be instantaneous.

Dr. France reported that physician's enthusiasm for the pneumococcal vaccines in Kaiser's trials was not dampened by the increased number of injections. After four shots, he observed, the fifth is just another. Dr. Peter commented that ACIP must be clear that the sequential schedule is no longer an alternative, but that OPV is under special circumstances.

Dr. Offit summarized that Option 1 was eliminated as a choice, and suggested a vote on Option 2: an all-IPV schedule by January 1, 2000 with the sequential schedule as an unacceptable alternative, or all-IPV in January 2000 with special circumstances stipulated. Mr. Salamone endorsed the latter.

Dr. Fleming hoped to avoid the wording of "sequential schedule," only stating special circumstances. Dr. Halsey stated that AAP would not accept the term "is not acceptable" because it could be used in litigation. Dr. Zimmerman also commented that this infers that using FDA-approved vaccines is unacceptable.

Six members of the committee (Fleming, Le, Helms, Guerra, Johnson, Modlin) agreed to language stating special circumstances in which OPV may be acceptable for a transitional year to January 1, 2000. Drs. Word, Griffin, Glode, and Offit disagreed. Dr. Modlin asked Dr. Offit to prepare appropriate wording for a vote on the next day.

Completion of Schedule for Children Who Received OPV
Dr. Offit read the draft proposal:

> "For children (aged <18 years) who have received ≤3 doses of polio vaccine, and who have received OPV, the additional doses of polio vaccine required to complete the schedule **should** be administered as IPV. Consistent with previous recommendations (MMWR 1997;46 [RR-2;14]), 4 doses of IPV or OPV in any combination by 4-6 years of age is considered a complete poliovirus vaccination series. A minimum interval of 4 weeks should elapse if IPV is administered after OPV or IPV. If three doses of OPV or three doses of IPV have been administered with the third dose given on or after the fourth birthday, an additional dose of poliovirus vaccine is not needed. (MMWR 1997;46 [RR-2;14])."

Dr. Helms moved to accept that language and Dr. Griffin seconded the motion. Dr. Johnson asked for clarification that this only applies to OPV vaccine. Dr. Offit confirmed that the recommendation will state that a series begun with IPV would finish with that.

VOTE:
In Favor: Word, Fleming, Griffin, Le, Johnson, Helms, Glode, Guerra, Modlin, Offit
Opposed: None
Abstained: None

Travel to Endemic Areas Prior to Receiving 3 Doses

Dr. Offit read the draft recommendation:

"For unvaccinated children (age <18 years), or those with unknown vaccination history:

- If >8 weeks are available before travel, 3 doses of IPV should be administered with a minimum interval of 4 weeks.
- If <8 but >4 weeks are available before travel, 2 doses of IPV should be administered at least 4 weeks apart.
- If <4 weeks are available before protection is needed, a single dose of IPV is recommended, with an additional dose administered as OPV or IPV."

Dr. Offit stated that this was perhaps the most difficult issue discussed by the workgroup. Two doses of OPV preceding IPV are 90-100% protective. But with <4 weeks available before travel to an endemic area, IPV is only 35% protective versus OPV's low-80% protection. So the workgroup recommended a single dose of IPV and getting a second dose of IPV there, or bringing the dose with them. All three paragraphs will state "at least three weeks later" to ensure a minimum interval of 4 weeks.

Dr. Fleming raised the ethics issue related to the fact that all-OPV is still acceptable for children in endemic countries. But Dr. Offit rejoined that this is a country-specific question. OPV is the best alternative in endemic areas, but this addresses an American child traveling in a transitional period. IPV is not only less protective, it would be hard to get in an endemic area. Dr. Fleming persisted that OPV is used in developing countries to protect society as a whole from viral shedding. Dr. Modlin agreed that this is not a straightforward issue and bears discussion, but not on this morning.

Dr. Orenstein advised the ACIP to retain the current recommendation for travel of one dose of OPV or IPV as acceptable to ensure the child's protection. In future when OPV is not available, that can be reconsidered. Dr. Offit reported this as discussed by the workgroup, which felt it would be disingenuous to base the recommendation on OPV supply. Dr. Modlin found it acceptable to recommend either IPV or OPV in this case if both vaccines are available. Dr. Stanley Plotkin reported that OPV is unavailable in France, where travelers get IPV. OPV was withdrawn from the market due to non-use. Dr. Jackson raised the difficulty of getting another dose of IPV in developing countries and the question of who would administered a dose carried along.

There was general agreement to Dr. Glode's rhetorical question of whether OPV is the better vaccine for an unimmunized baby traveling next week, upon which she advised simply saying so. Dr. Modlin suggested the text state that OPV is preferred, but IPV is acceptable. Dr. Gardner suggested following the yellow fever model to make OPV available through special sites such as travel clinics and health departments. However, Dr. Modlin cited supply problems; while yellow fever vaccine is continuously produced, but OPV must be replaced as the vaccine expires and its production will decline.

Dr. Orenstein agreed that if the main indication is travel in <4 weeks, this would at least make people comfortable that they can do something protective. Dr. Modlin suggesting stating a preference for OPV if only one dose is possible for an infant before leaving.

Dr. Offit asked if this would fall under the vaccine stockpile used for emergency use, but Dr. Prevots did not think that vaccine contract specifications for emergency use would address travel clinics. Dr. Snider also thought that control of supplies would not be an appropriate ACIP recommendation.

Dr. Modlin tried to bring the discussion to closure, proposing a vote on the language as presented, with text to be inserted that OPV is preferred if available and only one dose is possible. But Dr. Helms disagreed, pointing out that the difference between "acceptable" and "preferred" is significant and new. Dr. Modlin responded that this is a different circumstance to address travel to a country with likely exposure, and requiring the vaccine most likely to protect.

Dr. Peter stated that if that statement is made, the availability of OPV the following year must be ensured. The language used will be critical to the interpretation, particularly since most physicians are not educated on the difference between OPV and IPV, and think OPV should be recommended for travel under any circumstances. Dr. Modlin suggested adding text for travel that "either IPV or OPV can be given; with both available, OPV is preferred." Dr. Peter suggested adding that "this should be decided through a risk assessment balancing the greater immunogenicity versus the risk of VAPP."

Dr. Offit summarized that the options are 1) "a single dose of IPV or OPV is recommended" (no preference stated, the current ACIP statement) or 2) "a single dose of OPV is preferred, if available. If OPV is not available, a single dose should be administered."

Dr. Johnson urged the committee to retain the appropriate language in the current statement. Dr. Zimmerman commented that the best way to transition to IPV in 2000 is to not have OPV readily available to all providers through the VFC. Dr. Le observed that many travelers don't recall their vaccination history; and asked if they would be considered unimmunized as well. Dr. Plotkin wanted to discourage that, due to the lesser risk to adults than children. Dr. Prevots pointed out that these points were already addressed by the current ACIP recommendations for adult travelers, citing "unvaccinated or unknown vaccination history" as calling for IPV.

Dr. Modlin asked Dr. Offit to develop alternative language for a later vote and the discussion was tabled.

Report on a Model for Vaccine Development Prioritization

Dr. Robert Lawrence, of Johns Hopkins University, and Dr. Kathleen Statton, of the Institute of Medicine (IOM) and the this study's Project Staff Director, presented the IOM's report of the development of a model with which to prioritize vaccine development. This resulted from four years of committee work, during which time the rotavirus and Lyme disease vaccines were licensed.

Dr. Lawrence reported the committees charge, 1) to develop an analytic framework that would build on the 1985 IOM report and would be appropriate for prioritizing investment in vaccine development, and 2) to demonstrate the framework with a list of up to 13 candidate vaccines, with a time frame of up to 20 years before licensure. The committee's work was restricted only to conditions of domestic importance, and to exclude the HIV/AIDS candidate vaccines under rapid development. They focused on traditional therapies for infectious agents. They were specifically asked not to analyze every vaccine candidate or recommend on which vaccines should not be developed; nor to determine how much they should cost, recommend a target population, or conduct a cost-benefit analysis as to whether the costs to achieve the benefit are worth the effort.

Dr. Lawrence presented the algorithm used for the ratios explored. The analytic formula included the cost of vaccine development, the annual cost of immunizing a target population, the annual cost of care averted by the vaccine, and the annual health benefit from its use. The

estimated times to licensure examined were 3, 7, and 15 years. The amount to be invested ranged from $120 million to $400 million, based on industry data.

The Quality Adjusted Life Year (QALY) calculations were based on health status and used the Health Utility Index, which ranges from 0 (death) to 1 (perfect health). The program costs were driven by the target population, rounded to three doses and a cost per dose of $50-500.The savings in health care costs were estimated to be 75% for the preventive vaccines and 40% for the therapeutic vaccines. Types of data required included time and financial resources invested in vaccine development up to licensure; cost of the vaccine per dose; number of probable required doses; size and age of the target population; utilization and effectiveness of the vaccine; and clinical scenarios for each preventable disease (types of illness; severity, duration, age at onset, etc.).

The results were calculated in annualized present values of dollars per QALY if the vaccine were licensed and implemented. Using a standard 3% discount rate, the committee made conservative estimates. Sensitivity analyses also done, based on a 100% vaccine effectiveness and utilization, showed little change in vaccine priority placement.

The caveats of the model are that it doesn't consider how well the investment could be spent; distinguish who pays for the health care that could be avoided by vaccine use; the costs of adverse events (assuming vaccines with minimum adverse events); caregiver costs (which could have influenced the final rotavirus category) or the international burden of disease.

There were four levels of vaccine development. The most favorable group of vaccines predicted by the model: 1) saved dollars and QALYs; 2) saved QALY at good price (<$10,000); 3) saved QALY at a favorable price ($10,000-$100,000; the comparison to mammography was made. Its calculated savings of c. $80,000/QALY was and found to be a good bargain by HCFA); and 4) at a less favorable price (>$100,000).

The first category's ordered ranking of seven vaccines were: cytomegalovirus administered to 12-year-olds; influenza virus administered to the general population; insulin-dependent diabetes mellitus therapeutic vaccine; multiple sclerosis therapeutic vaccine; rheumatoid arthritis therapeutic vaccine; and streptococcus (Group B) to be incorporated into routine prenatal care and administered to women during their first pregnancy and to high risk adults.

The second category (<$10,000) priority list included vaccines for: chlamydia, *Helicobacter pylori*, hepatitis C virus, herpes simplex virus, human papilloma virus, melanoma therapeutic vaccine, tuberculosis, gonorrhea, and respiratory syncytial virus. Category 3 (<$100,000) vaccines included: parainfluenza, rotavirus, Group A streptococcus, and Group B strep administered to high-risk adults and to 12-year-old females or women during their first pregnancy. The last category, 4 (>$100,000) vaccines included: *Borrelia burgdorferii*, coccidiomycosis, enterotoxicogenic *E. coli*, Epstein-Barr virus, histoplasmosis, meningococcal disease, and shigellosis.

Finally, Dr. Lawrence described the report's uses. Its dynamic model, which is on the Web, can help program planning as well as research and development, aid decision tools to distinguish factors of cost effectiveness analysis in weighing interventions, and guide policy on the selection of vaccines candidates over a 20-year span.

Discussion

Dr. Peter noted that health care providers' time was not included in the model, important factors that if included would have lowered the cost effectiveness and cost benefit of the recently-licensed varicella and rotavirus vaccines. This risks a possible introduction of bias. Dr. Lawrence agreed; also excluded were the opportunity costs of days of work lost, as those data are too variable and unreliable.

Dr. Griffin asked if the influenza vaccine would be given to a high risk group. Dr. Lawrence thought that the most likely successful such candidate vaccine might be a polyvalent DNA vaccine, covering the breadth of what might emerge in viral evolution. Such a vaccine could be put on a sequential schedule to provide population coverage. Dr. Statton added that the model assumed administration to one-fifth of the general population per year.

Dr. Plotkin asked when the appendices would be available, and who should use this document besides, for example, NIAID for investing funds in vaccine preventable diseases. He also noted that historically, vaccine development costs have played little role in their eventual cost effectiveness. Dr. Statton hoped that the appendices would be ready soon. Dr. Lawrence agreed to the role of development costs, and commented that the manufacturers will decide the model's usefulness. It does create an argument supporting funds in some vaccine development. Although the disease burden might not seem great, the QALY could be surprising if consideration is given to who is affected and at what point in their life.

Dr. Breiman noted that many therapeutic vaccines are listed in Level One. The NVPO's Interagency Workgroup is also examining this model for program planning purposes, especially how to fill research gaps, and to catalyze and focus research toward vaccines indicated as likely by the model. They are also interested in how or if the model could be adjusted to look at vaccines globally, to persuade industry to develop what are now considered "orphan" vaccines.

Dr. Lawrence agreed. The project almost analyzed dengue fever because it is possible along the southern U.S. border in the next 20 years. But while the formula works well to plug in data, as with the 1993 World Bank report, the kind of data used for domestic disease burden are loose, essentially extrapolations from old (in some cases 15 years) primary data.

Dr. Peter asked how much age can be factored into the analysis, and how the Committee decided, for example, to look at cytomegalovirus at age 12 versus hepatitis C in infancy. The latter is not a pathogen of young children; both are adult viruses. Dr. Lawrence clarified that the Health Utility Index for disease state itself and then the calculated QALY for subsequent years allows the prevention benefit to be demonstrated independent of the time of vaccine delivery. This implies programmatic opportunities through windows of opportunity (e.g., to vaccinate the 12 year-old who may soon begin experimenting with sex or other risk behaviors). Dr. Statton added that age 12 was selected as a placeholder to vaccines for sexually transmitted disease and a portion of those maternally transmitted. There was much discussion of the best target population for the age. But this can be changed in the model to see how the results would change, although it is not easy. In general, they found that the longer the delay of immunization, the more postponed the benefits. A much better cost effectiveness emerges with immunization close to the time the infection is expected to occur.

Dr. Rabinovich recalled a previous NVAC report describing the "fragile fabric" of the U.S. players needed to develop a successful vaccine. This tool clearly enters into prioritization and decision making at multiple levels, and so could be of broad interest. Consensus is needed on the priorities, regardless of basic research. And, this analysis' examination of long-term (20 year) effects allows consideration of even as-yet undeveloped vaccines (e.g., for autoimmune

diseases). NIH asked IOM to make both the report and the model available. They feel that those with the expertise to address these areas will find it useful. With no further comment, the committee adjourned for lunch.

Draft Statement on Pneumococcal Conjugate Vaccine

Dr. Modlin opened the afternoon session, which began with a presentation of the draft statement on prevention of pneumococcal disease in infants and young children using the pneumococcal conjugate vaccine. He asked the members to focus on the policy issues inherent in the draft statement.

Dr. David Johnson introduced the presentation, which was designed to determine 1) whether there was general agreement with the draft table of recommendations (sent to members prior to the meeting), and 2) what additional data are needed to finalize the statement at the October ACIP meeting. He hoped that the statement could be finalized, citing the conjugate's exciting potential of disease reduction.

Data Presentations

Review of the Burden of Pneumococcal Disease

Dr. Chris Van Beneden of NCID's Division of Bacterial and Mycotic Diseases (DBMD), reported that the rates of invasive disease in children aged 0-2 years are high for all groups. High risk groups include Alaska natives, American Indians, and patients with sickle cell and HIV disease. Rates are still fairly high for children older than 2 years, with a rate of 63 per 100,000 among those aged 24-35 months. Rates continue to drop in children aged from 3-5 years, but remain high in sickle cell and HIV patients. Otitis media rates are highest at the end of the first year of life, but remain elevated through 7 years of age.

Efficacy Data Update: Kaiser Permanente Vaccine Study Center

Dr. Steven Black, of the Kaiser Permanente Vaccine Study Center, outlined the efficacy data of the conjugate vaccine trials. He provided the results on otitis media, the impact of the conjugate vaccine on clinical episodes of pneumonia, and updated the committee on invasive disease cases. The trial's objective was to gauge the vaccine's effectiveness against invasive pneumococcal disease.

The study population was of infants randomly selected at 2 months of age to receive pneumococcal (7-valent) or meningococcal conjugate vaccine in a four-dose regimen. The design was sequential, with an initial look at 17 cases of invasive disease of vaccine serotype in fully vaccinated children (presented at a previous ACIP meeting). Cases of otitis media were identified through Kaiser clinic and Emergency Room visits, and data scanned into a patient management database. An otitis media episode was defined as a child with no visits for otitis media in the prior 3 weeks, and an appointment made <3 days earlier (indicating acute illness). They also looked at outcomes of tube placement and serotype-specific efficacy in spontaneously draining ears. Cases of pneumonia were identified by coded (ICD9) data from hospital and out patient clinics and Emergency Rooms (patient management forms). Case confirmation came from clinical diagnosis and pneumonia clearly defined through x-rays.

The follow-up study population was followed in a blinded fashion through April 20, 1999. The initial efficacy for invasive disease was a 17:0 split, with a 100% point estimate of efficacy. The investigation began with clinical episodes of otitis media, of which 50-60% have a bacterial cause and 20-40% of those are due to pneumococcus. Of those, 60-85% are vaccine serotype compatible. This infers a potential impact of 6-20% against clinical episodes. The study's

47,300 otitis media visits involved 33,000 episodes, of which 3400 were defined as "frequent" (three visits within 6 months or 4 within a year). The study demonstrated an 8.9% reduction in fully vaccinated (protocol) children and 7.8% in those partially vaccinated (intent-to-treat).

Frequent otitis media (3,4,5,6 visits within 6 months) was analyzed; the group reaching five episodes showed a 23% reduction in the vaccinated group versus controls. The pneumococcal conjugate vaccine group received 20% fewer tubes than the controls (about the level of referral for tubes in their population). As the number of visits per episode increased, the study showed more of a vaccine effect.

Cultures from routine health care were used to investigate spontaneously ruptured eardrums (i.e., not a comprehensive ascertainment of all cases). The case split was 12:4 for fully vaccinated children, with an efficacy point estimate of 66% (not significant). But in the intent to treat group, the 17:6 split presents a slightly higher efficacy in the significant range. This was the first indication of effectiveness for otitis media.

Pneumonia data were compiled in an intent-to-treat analysis. In 1309 clinical episode cases, an 11% reduction was seen in clinical episodes of pneumonia. In children with x-rays which showed any abnormality (not consolidation), a 33% reduction was seen in the number of episodes. Regarding bacteremic pneumonia, there are now 10 cases in the study population, of which 3 have shown classic consolidation and 2 have fully normal x-rays. For fully vaccinated children, there is a 6:1 case split (not significant at 83%); the case split for the intent to-treat group is 7:1 (P-value=.05). The confidence intervals were very wide.

Regarding invasive disease, one vaccine failure appeared in a child with no indication of immunologic abnormality, who received four doses of vaccine. A 97.4% point efficacy was shown with an 83% lower bound of the 95% confidence interval. The intent to treat analysis includes 3 vaccinated children. One child received one dose at 2 months and developed pneumonia in the second year of life; still another child developed acute myelogenous leukemia (AML), was neutropenic, and was immunosuppressed upon developing pneumococcal disease.

In all, regardless of vaccine serotype, an 89.1% total disease reduction/effectiveness was seen in the study cohort. There may be some cross-protection. Regarding serotype-specific efficacy, there have still been no type 4 cases in the study population. In both the immunocompromised and partially vaccinated children, the case splits were was 7:1 and 13:2 respectively. None of the other study participants had any breakthrough disease and there is no evidence so far of an increase of non-vaccine serotype disease.

The study concluded that the vaccine was highly effective in preventing invasive disease, producing a significant reduction in otitis media and accompanying tube placement. The vaccine was also effective in preventing clinical and X-ray confirmed pneumonia. It is possible that the total disease burden due to pneumococcus may be significantly higher than previously estimated.

Discussion. Dr. Halsey asked about the age distribution of cases, particularly for pneumonia, wondering how high in age the conjugate vaccine should be used. Dr. Black responded that the data cited ended in August 1998 data, a year after follow-up. He hoped this summer to be able to analyze data on the disease burden in older children.

Dr. Peter asked the amount of data available on children getting 3 doses and not the 12-15 month booster, to address the necessity of the fourth dose, but this was outside the Phase III

study design. Dr. Jackson asked the number of children with sickle cell disease and whether any breakout occurred compared to controls. Dr. Black had no such information because children with sickle cell, identified by newborn hemoglobin screening, were excluded.

Dr. Peter asked if these results are expected to have an impact on antibiotic use. Dr. Black identified that as the first question asked by pediatricians. But this was a blinded study to prevent any labeling of the children by group, so the presumptive use of antibiotics may not have changed. Dr. Katz asked if the children were followed long enough to explore nasopharyngeal carriage. Dr. Black said no, but knew of other studies (e.g., among the Navajo nation) that may better answer that question. That also may help identify other serotypes. Dr. Rabinovich asked about the reactogenicity profile, and Dr. Modlin referred her to the statement's extensive information.

Cost Effectiveness of the Vaccine
Dr. Tracey Lieu, of the Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care and Harvard Medical School, presented a collaborative study of the projected cost effectiveness of the vaccination of healthy U.S. infants with this new conjugate. Collaborators included the HPHC, Kaiser Permanente Vaccine Study Center, Boston University Medical Center, CDC, and the Children's Vaccine Initiative.

The study's objective was to advise policy making committees such as the ACIP. To do so, it analyzed clinical outcomes (based on published and unpublished data and on expert opinion), and medical utilization rates and costs (from multiple sources). Outcomes were expressed in dollars per life-year saved and dollars per disease case prevented. They considered societal costs (the primary focus, including medical, non-medical, and lost future productivity due to death) and the medical payer perspective (medical costs alone). Dr. Lieu noted that cost effectiveness does not necessarily infer money savings. In fact, most health care interventions don't save money; they just prevent disease at what society agrees are acceptable costs.

The possible effects were projected of no vaccination versus vaccination of all healthy infants for meningitis, bacteremia, pneumonia, and simple and complex otitis. They considered that not all meningitis is pneumococcal, and not all pneumococcal meningitis is the vaccine serotype, and that only vaccine effectiveness for clinical otitis media is known since it is not routinely cultured.

The most generalizable and accurate models available were used; data came mostly from the Kaiser Permanente study just reported as well as another Kaiser study of work loss among parents with children with otitis media.

Dr. Lieu presented the analysis results for a hypothetical birth cohort birth cohort of 3.8 million healthy infants. They predicted the prevention of 560 cases of meningitis, 12,000 cases of bacteremia, 53,000 cases of pneumonia, and approximately 1 million episodes of otitis media. Society would save approximately $763 million in disease costs, mostly from otitis media (about $302 million in medical costs and $267 million in work-loss costs).

Dr. Lieu pointed out the differences in societal and health care payer savings, the latter often being less than half of society's. Most savings were from prevented parental work loss and the lost productivity of those who would have died. A cost savings for society from disease prevented per child vaccinated was estimated at $181, but far less for the health care payer.

Since the vaccine price was not known, the cost effectiveness ratios were calculated at a variety of prices, and those results compared to other vaccines and interventions. Most cases prevented were of otitis media, so that was the prevention analysis' cost focus. Vaccines for varicella and rotavirus are cost effective; pneumococcal vaccine would be at the lower end of a possible cost saving range at $40 per dose. But if this vaccine is priced higher, it would be the first modern vaccine to fall out of cost savings range. From the payer's perspective, the cost is about $60 per episode of otitis media. The higher the vaccine cost, the lower the cost effectiveness. Again, the comparison was made to mammography ($105,000 per life year saved).

To address the issue of catch-up vaccination of toddlers, Dr. Lieu presented the analysis results for toddlers in daycare for ages 1-3 years. For 24-35 month-olds and for 36-48 month-olds the vaccine is cost saving at a variety of prices. But for older children, it is not; in fact, the costs can rise in the model to $1000.If all toddlers are vaccinated, the cost effectiveness of vaccination depends greatly on age. It is cost saving from a societal perspective to 36 months of age, and depends on vaccine price from 36-47 months. At the higher end, it could cost several hundred dollars per otitis media episode averted; and it is not cost saving from 48-59 months.

Among the limitations of these analyses are that most assumptions are biased against immunization; that Kaiser could have low medical delivery costs; that future costs could rise with antibiotic resistance; and that no consideration was given to cross-reactive serotypes or herd immunity.

The study's conclusions were that from a societal perspective, routine pneumococcal conjugate vaccination program for healthy U.S. infants is potentially cost-saving or cost-effective for those aged 24-35 months and for the 36-47 month-olds in daycare, but is less likely to be cost-effective from 48-59 months or to offer savings to health insurers.

Discussion. Dr. Nichol asked if indirect costs for future lifetime earnings per life year saved were included in the estimates. Dr. Lieu said no, since cost savings from future productivity loss was included in the model. That would have been viewed as double counting. When Dr. Pickering asked how "daycare" was defined, Dr. Lieu cited Levin's May Pediatrics article definition: two or more unrelated children in care of an adult for ≥4 hours a week.

Dr. Fedson asked if life year saved was extended over the lifespan and Dr. Lieu confirmed that. He then asked how they accounted for residual protection from infant immunization that might last throughout life, perhaps boosted later on. She reported consultation with experts in projecting the meningitis savings, since there were no data beyond the Kaiser study. They recommended an assumption that vaccination lasts for 5 years. When Dr Fedson rejoined that this doesn't factor that a person might get meningitis at 35-40 years of age, a key consideration, Dr. Lieu agreed and reiterated that the model biases against immunization.

Discussion of Recommendation Aspects

Healthy Children Aged 0-23 Months: Dr. Van Beneden asked if there were any further discussion on vaccine use in the 0-23 month age group, for which the rates of disease strongly support vaccine use. Dr. Fleming asked how she would characterize the evidence without citing cost effectiveness as one supporting criteria. Dr. Van Beneden responded that the lack of a vaccine price prevented that. Dr. Snider added that neither the U.S. Preventive Services Task Force (USPSTF) nor the Task Force on Community Preventive Services use cost effectiveness data in assigning the strength of the evidence as A, B, or C. But it can be used in considering

whether or not to recommend. Dr. Johnson observed that the clarity of the evidence in this age group made that point moot.

Dr. France called for better delineation of the evidence supporting the doses. He also was unclear on what constitutes an "A" rating for the ACIP. Dr. Johnson responded that these parallel those of the USPSTF. Dr. Van Beneden acknowledged that the efficacy data supporting the schedule was absent from the footnote in the recommendation. It was based on Wyeth Lederle data on studies of ELISA levels believed to be protective. Those data would be added to the draft and provided to ACIP. Dr. France recommended they be put in the document itself as well as the footnote.

Dr. Zimmerman reported that the USPSTF considers two issues: the strength of the evidence and the strength of the recommendation, the latter of which considers evidence of cost effectiveness. He advised that the draft's table separate those, which now seemed mixed. Dr. Van Beneden preferred to have only one table, as done with other ACIP recommendations. Dr. Snider reported the intent when possible to convey both the strength of the evidence and the strength of the recommendation, whose ratings could differ. He advised pursuing that split delineation, because it gives more credibility to the recommendation. Dr. Modlin perceived a momentum to do so and thought this draft would be a good place to start. He asked for any further comments on the 0-23 month age group recommendation.

Dr. Debra Wexler suggested including a section on catch-up vaccinations, as in the Hib schedule (e.g., to indicate if a child receiving dose 1 at two month and then not again until 9 months needs 2 or 4 doses). Dr. Jackson asked how outcomes would be separated in a child receiving both the polysaccharide and conjugate vaccine. Dr. Johnson agreed that this was an important point, and deferred it to a later discussion. It may be addressed in a separate section.

Dr. Johnson summarized the agreement that for healthy children aged 0-23 months, the strength of the evidence and that of the recommendation should be separately stated; a catch-up schedule for gaps in vaccination should be inserted, and the data on efficacy and immunogenicity for children should be presented, especially for those aged 12-23 months.

Children in Other Age Groups . The draft recommended one catch up dose for healthy children aged 24-35 months. On Dr. Griffin's question, Dr. Van Beneden corrected the evidence as grade B for that group, and grade B for the 7-23 month age group. Dr. Plotkin suggested a separate section on simultaneous administration with other vaccines. Dr. Van Beneden agreed that this could be done for greater clarity.

Dr. Johnson summarized consensus to clarify the strength of the evidence and recommendation, but to continue recommending that all children have that vaccination. Dr. Fleming recommended that the focus be on using the opportunity of an office visit to vaccinate, rather than to recall the child for catch-up vaccination.

High Risk Groups/Conditions. Dr. Van Beneden reported the considerations for each special group in deciding to not recommend, recommend, or to be permissive with a health care provider decision on offering vaccine: 1) risk of infection and subsequent morbidity; 2) size of target population; 3) evidence of protection/efficacy; 4) vaccination feasibility; and 5) costs. The high risk groups identified in the following discussion are 1) children in day care, 2) children with recurrent otitis media, 3) sickle cell patients, and 4) HIV-infected children.

1. *Children in Day Care* have an elevated risk of pneumococcal disease (2- to 3-fold, as well as for otitis media and antibiotic-resistant organisms). An estimated 25-30% of children aged 3-4 of both working and nonworking parents are in daycare. Although there is no direct evidence, it is assumed that protection will be equal to that for healthy children and it is possible that unvaccinated children may benefit from herd immunity. However, this will require a separate visit to the health care provider, with unknown related costs.

The possible recommendations were: 1) no recommendation; 2) one dose; or 3) a permissive statement allowing the health care provider/parent to make the decision. Dr. Van Beneden asked if the members wished to recommend the vaccine for 3-4 year-olds in daycare.

Discussion. Dr. Le preferred to tie the immunization to disease. Since most children with recurrent otitis media begin to be affected in their first year or two of life, the link to daycare may not be appropriate.

Dr. Pickering raised the consideration that unlike daycare centers, home daycare is unlicensed and unregulated, and no one knows how many children are in those settings. He advised care in defining "daycare." Dr. Van Beneden cited the indication that disease risk rises with the number of children in a setting, and agreed to the challenge of the definition. Dr. Pickering added that small outbreaks have occurred in daycare homes and centers. While advice to use Rifampin for secondary cases can be added, that is different from treating all children just because they are in daycare. He preferred Dr. Le's idea of linking the recommendation to episodes of otitis media. Dr. Le stated that a child in daycare but without recurrent otitis media doesn't really need pneumococcal vaccine. But Dr. Johnson cited their 2- to 3-fold increased risk for invasive pneumococcal disease, not necessarily otitis media, which is the basis for this recommendation.

Dr. Zimmerman suggested, rather than relative risks and odds ratios, that the recommendation cite attributable risks and the necessary number to treat to prevent a case. Dr. Peter Paradiso offered data relevant to this conversation. Among 24-35 month-olds, 7 doses are required per case of otitis media prevented; 11 doses among the 3-4 year-old age group; and 26 doses in the 48-59 month age group. For invasive disease in the general population, there are 3400 preventable cases in 2 year-olds, 1400 in 3 year-olds, and 600 in 4 year-olds. There is a 2-fold decrease in cases preventable in each age group (I. e., in terms of rate, each year replicates the previous one if the risk doubles in a child care setting). Dr. Fleming asked if the package insert will discuss the acceptability of protection by a one-dose series, not wanting ACIP to diverge too much from the label use. Dr. Van Beneden said that this would be discussed by age group.

Dr. Modlin asked the members to address the daycare issues in their comments provided to staff.

2. *Children with Recurrent Acute Otitis Media, Aged 3-4 years.* Dr. Van Beneden noted that children in daycare are more likely to have acute otitis media, and children with recurrent acute otitis media are more likely to receive prophylactic antibiotics and to have tympanoscopy tubes placed. About 7-8% of children in this age group have had ≥3 episodes of acute otitis media per year, and 16-19% have ≥2 episodes.

One question is how to identify those children, since the Kaiser trial demonstrated increasing vaccine efficacy with increasing otitis media events. The feasibility is likely to be good in this

population because the child presents for treatment, although costs will depend on the vaccine price.

Dr. Van Beneden suggested several possible recommendations: 1) none; 2) one dose of the conjugate vaccine if recurrent illness fits the current standard definition (≥3 episodes within 6 months or ≥4 per year); or 3) one dose for a child with ≥2 episodes within 6 months or ≥3 in the last year; and/or 4) a permissive statement allowing the health care provider/parent to make the decision.

Discussion. Dr. Modlin posed the question of whether the ACIP wanted the challenge of defining "recurrent acute otitis media," and suggested discussion of the concept of recommending vaccine for children who appear to be prone to otitis.

Dr. France cited the difficulty of extrapolating from the Kaiser efficacy data, which was based on younger children. Natural history alone indicates that children will outgrow otitis. Information is needed about the ongoing risk for 3-year-olds who have recurrent otitis media in their first 2 years of life. Based on the lack of extensive evidence, he leaned toward a permissive recommendation. Dr. Johnson summarized his sense of the committee's preference for more data for this and the daycare recommendation, and for a more permissive recommendation.

Dr. Halsey reported the Red Book Committee's discussions on this issue. They are awaiting the pneumonia data and cost effectiveness data on preventing recurrent otitis, tube replacement, etc., among children with recurrent episodes who are above the recommended age for the vaccine. Dr. Guerra hoped for a better description of the child with recurrent otitis media than simply one who repeatedly visits Emergency Rooms and is diagnosed by different physicians.

3. Children with Sickle Cell Disease Aged 3-4 years. Children with sickle cell disease are currently recommended to receive the 23-valent vaccine from age 2. Their risk of pneumococcal disease is high (c. 1 case of invasive diseases per 100 child years). This is a small population, with no efficacy studies, but two immunogenicity studies among infants and children aged 2 have demonstrated vaccine immunogenicity. One study of those receiving the 7-valent vaccine followed by the 23-valent polysaccharide, versus the 23-valent alone, demonstrated both increased immunogenicity and a good safety profile from the combination. The feasibility is thought to be good, but cost is unknown.

Possible recommendations include: 1) one dose of the conjugate vaccine; 2) one dose of the conjugate vaccine followed by the 23-valent polysaccharide vaccine (to achieve greater serotype coverage); 3) two doses of the conjugate vaccine; or 3) two doses of the conjugate vaccine plus one dose of polysaccharide.

Discussion. Dr. Griffin asked how efficacious the current polysaccharide vaccine is in the 2-5 year-old age group. Dr. Van Beneden responded "not very;" although controversial, one CDC study pending publication confirmed that.

Dr. Peter called for discussion of the reliability of the correlates of protection. Many (the number is unknown) of these children should be on penicillin prophylaxis. These are likely the ones who would be vaccinated; those not on penicillin would not. Since penicillin prophylaxis has reduced the disease, this could support giving one dose followed by the 23-valent vaccine. The two doses of conjugate plus 23-valent may not be needed with penicillin prophylaxis. On Dr. Snider's question, Dr. Paradiso reported an indication of optimum protection from two doses in

one small study, but more data will not be forthcoming until next year. The ACIP would have make a recommendation based on the data available.

Dr. Halsey raised the issue that the vaccine could be recommended by ACIP to 3 years of age and available in the private sector early next year, but the VFC process will not have begun. He encouraged the manufacturer to set a price and begin negotiations with CDC. Dr. Paradiso agreed; they are now trying to anticipate and develop a stockpile plan for the catch-up doses for children up to 5 years of age. He raised an additional issue of what effect a permissive recommendation could have on vaccine use and coverage.

4. Children with HIV Infection Aged 3-4 Years
Dr. Van Beneden described the high risk in this group. There are no efficacy studies, but there are some immunogenicity studies in infants and toddlers of the 5-valent oligosaccharide (not polysaccharide) form. Immunogenicity studies showed the conjugate to be more immunogenic and to induce immunologic memory. Feasibility is good.

Possible recommendations are: 1) none for the conjugate vaccine and continue only with 23-valent polysaccharide; 2) one dose of the conjugate vaccine followed by the 23-valent polysaccharide vaccine, possibly using a >200 CD4 count as a marker; or 3) a permissive statement encouraging a health care provider/parent decision.

Discussion. Dr. Katz asked if the proposal was to use the conjugate only at 2,4,6 months and to continue with the polysaccharide at 2 ≥years. Dr. Van Beneden confirmed that, in the absence of efficacy data on older age groups. Dr. Johnson summarized that the workgroup would refine the recommendations for all children, include the additional data requested, and gather more information about the four special populations (daycare, otitis media, sickle cell, and HIV). Another draft of the recommendations will then be sent to the committee. Dr. Modlin requested all initial comments by the end of July .

Public Comment. Ms. Karla Newbie, General Manager for the Meningitis Foundation of America, recounted her son Jacob's death in October 1998 from pneumococcal meningitis. Some doctors refuse to conduct spinal taps, the only current diagnostic method, resulting in death. She encouraged the committee to recommend routine vaccination for all children, not just infants, to protect them from this vicious bacterium and to avoid for others the tragedy of having to watch their child die, incapable to help.

Safety of Revaccination With Pneumococcal Polysaccharide Vaccine
Dr. Lisa Jackson of the Group Health Cooperative discussed a prospective intervention trial conducted with the Vaccine Safety Data Link Project, the GHC, and the NIP. The purpose of the study was to see if revaccination precipitated more frequent or more serious adverse events than those following the initial vaccination among the population currently targeted for routine vaccination. Outcomes were compared between adults vaccinated for the first time versus those vaccinated at least five years after the first inoculation. The study's 1414 participants (901 initial vaccinees and 513 revaccinees) were GHC members aged 65-74, or adults age 50-64 with at least one chronic medical condition that is an indication for pneumococcal vaccination. Those with chronic conditions were divided according to their status of immune competence. The median time for revaccination was 6 years.

Adverse events were ascertained through the completion of a 14-day study diary, which recorded temperature twice daily for the first 6 days. Subjective symptoms were assessed as mild, moderate, and severe; and the diameter of local redness/swelling at the injection site was

measured. No hospitalizations or other severe adverse events were associated with revaccination.

Fever was rare and with no differences between the groups. Local symptoms included common arm soreness at the injection site (56% of first vaccinees, 72% or revaccinees, a significant difference), which reduced by days 3-6. Revaccinees were more likely to report limitations of arm movement, a few severe (unable to raise the arm above shoulder height due to pain), and more moderate (unable to raise above the head due to pain).

Three percent of the first vaccinees had swelling of 2"-4 versus 11% of the revaccinees (RR 3. 3, CI excluded 1. 0) within 0-2 days postvaccination. Among the immunocompetent group, the healthy revaccinees reported the highest rate of sizable local reactions (15%) as compared to the first vaccinees (3%) (RR 5). No trend toward a decrease in the size of local reaction appeared with increasing time since first vaccination. ELISA blood sample baselines of antibody concentration indicated that for both initial vaccinees and revaccinees, risk of a sizable local reaction increased with increasing concentrations of antibodies.

In summary, revaccination was associated with an overall risk about 3-fold greater for a sizable local reaction. Among the subset of immunocompetent healthy subjects, revaccination was associated with a 5-fold higher risk. In both groups, sizable local reactions had resolved by a median of 3 days postvaccination. Among revaccinees, the risk of significant adverse reaction was not associated with time since initial vaccination, and among both first vaccinees and revaccinees, the risk of a sizeable local reaction was positively correlated with pre-vaccination antibody concentrations.

Discussion. Dr. Ruben asked the needle length size in intramuscular injection, which can contribute to local reactions. Dr. Jackson reported a standard 5/8" needle used. Dr. Le wondered if boostering helped the healthy adult immunocompromised subjects increase in antibody titers. Table 5 of the study report indicates no more than a 2-fold increase, which weakens the case for revaccination of healthy adults. Some serological data in the JAMA paper show a small boost. Dr. Jackson clarified that this study focused on the risk of revaccination, found to be small, not the benefit. Only 3 of 23 serotypes were measured, and there is no standardized protective level of immunity for any of them.

Dr. Schaffner found this to be an important study. While it was comforting that these were self limiting reactions, the low antibody levels were of note. He also found sobering the notably larger reactions in degree and frequency than anticipated. The significance of 4" swelling and soreness so bad the subjects could not raise their arm over their head should not be diminished; this is the kind of reaction that "gives immunization a bad name. " This is of great concern to physicians, who are already aware of it. Dr. Le added his own concern that higher reactions occur in the healthy immunocompetent subjects than in those immunodeficient. Dr. Nichol agreed that the reactions were sobering, but pointed out that they were not serious. Such information could be used to advise patients of the possible downsides as well as benefits of the vaccination.

Presentation of CDC Case Control Study of Vaccine Use in HIV-Infected Persons
Dr. Ann Schuchat, of the National Cancer Institute, described a study conducted collaboratively with CDC, Emory University/Atlanta, and the University of California/Berkeley. The study rationale was based on the fact that pneumococcal bacteremia occurs 150-300 times more often in HIV patients than in other non-elderly adults. The efficacy of the 23-valent polysaccharide vaccine has been estimated at 56-81% against bacteremia in immunocompetent

adults, but data is limited about its clinical protection in HIV patients. ACIP recommended the vaccine among these patients in 1989 and 1997. The strength of the 1997 recommendation was a "C" (not proven effectiveness, but justified by high risk and potential benefits/safety).

The study objectives were to determine the effectiveness of the 23-valent polysaccharide vaccine, and to determine its efficacy against the serotypes included in the vaccine. It was conducted in 10 hospitals (4 in Atlanta; 6 in San Francisco) from February 1992 to April 1995. The subjects were 18-55 year-olds with HIV infection diagnosed prior to admission. There were 176 cases (mostly men, African-American, and smokers) and the median age was 37. 4 years. The two controls per case were matched by category of CD4 count on hospital admission, or in its absence by HIV clinical staging. Controls were aged 18-55 with an HIV diagnosis before hospital admission for another reason. They were excluded upon any potential of pneumococcal disease.

A matched univariate analysis revealed that cases were more likely to be black and current smokers. Paradoxically, the controls had lower CD4 counts than cases. No subjects were on the new antiviral combination therapies. Close contact with a child in the household was a risk factor, and cases were less likely to have received the polysaccharide vaccine. The vaccine efficacy in the univariate analysis was 41% (CI from 9-62%).

A multivariate analysis was done on 135 matched sets of cases and controls with vaccination history and confounder information. Adjusting for confounders, the vaccine efficacy was 49% within a CI of 12-70%. However, effect modification by race was indicated by a p value of 0.06. Overall, the efficacy against pneumococcal serotypes was 40%, but in whites it was 74%; African-Americans had no protection from the 23-valent vaccine in the study.

Efficacy didn't appear to vary by CD4 count prior to enrollment, but the study was limited in its ability to evaluate the impact of immunosuppression on vaccine efficacy.

In summary, the 23-valent polysaccharide vaccine had a 49% overall efficacy for invasive pneumococcal disease, with a higher efficacy of 74% in whites and no documented efficacy in African-Americans. Vaccine efficacy did not appear to differ by CD4 category. Risk factors including smoking, contact with children in the household, and African-American race. Additional studies are needed specifically regarding the racial difference. The study did show a shorter interval between HIV diagnosis to study enrollment in African-Americans (2. 8 years, versus 4 years for whites). African-Americans may be diagnosed at a later stage of illness or have a more rapid disease progression, which could affect vaccine efficacy.

Three previous studies have been done of the 23-valent polysaccharide vaccine in HIV populations. A Baltimore case-control study showed a VE of 78% if the CD4 count was >200, but no efficacy at lower counts. A Ugandan RCT among HIV-positive adults found no efficacy against bacterimic pneumococcal disease or against pneumonia. And the large Adult-Adolescent Spectrum of Disease (AASD) cohort study found significantly lower pneumococcal pneumonia rates among persons vaccinated when their CD4 counts were higher compared to those with low counts or unvaccinated. No VE difference was found for race.

Dr. Schuchat pointed out that no study has evaluated the 23-valent vaccine's performance in patients receiving highly active antiretroviral therapy. The high risk to this population and apparent lack of efficacy for African-Americans are alarming. This underscores the need to maximize access to HIV therapies and preventive services in minority populations. However, this study does pose some implications for ACIP or other groups' recommendations. The

continued recommendation of the vaccine for HIV patients was suggested, emphasizing administration early in the course of HIV, or in the presence of low CD4 counts, after a successful administration of anti-viral therapy.

Discussion. Dr. Griffin asked the vaccination prevalence in hospitalized controls and whether this was similar to community controls, pointing out the difficult in demonstrating efficacy if few are vaccinated or with underlying differences between cases and controls. Dr. Schuchat reported it more common in whites than in blacks, but the AASD study documented a substantial vaccination increase in that cohort. Coverage data for 1998 are not yet available, but this study's controls had vaccine coverage of 37% (29% blacks and 45% in whites). But other studies, such as that in Baltimore, used clinic controls and matched over the duration of follow-up.

Dr. Jackson asked if viral loads were done (no); and the degree of illness between the black and white patients. Dr. Schuchat reported adjustments made for other than HIV disease which could be risk factors, but this did not change the findings. The matching done ensured that, if anything, the controls were more immunosuppressed than the cases. Dr. Jackson then asked the study's conclusions when comparing the response of the African-Americans versus Ugandans. Dr. Schuchat responded that the studies approaches were too different to allow that comparison. This study focuses on invasive pneumococcal disease in patients, one-fourth of whom received AZT or DDI, or both. The Ugandans had nothing except perhaps fairly aggressive TB interventions. But she reiterated that the AASD study found no efficacy difference among races, controlling for confounders.

Dr. Guerra asked if comorbidity with IV drug use was found and whether Hispanics were included in the group of whites. Dr. Schuchat reported no difference in VE by risk factors (e.g., injection drug users and men having sex with men), but was unsure about Hispanic participants. Dr. Helms asked if there was any seasonal correlation, such as with influenza. Dr. Schuchat reported a striking seasonality for pneumococcal disease, but that had not yet been analyzed for this particular study. Dr. Gardner was a little troubled that the overall risk group supports vaccine use in people with AIDS, but not the most high risk group, African-Americans, who bear the higher disease burden for every encapsulated bacterial disease. He was also disturbed that this is the first study to indicate a racially different protective rate.

However, Dr. France was loath to accept the efficacy disparity by race without first exploring a larger study with greater power. Dr. Schuchat agreed that more data are needed, and cited the AASD study as the best way to get good observational data (with, so far, 85,000 person years of data, including on viral load and CD4 counts upon immunization). CDC is committed to get better data. Dr. Jackson asked if the study could determine any greater history of injection drug use among one group than another. Dr. Schuchat reported this as more common in the African Americans in this study than among whites, but the small numbers prevent any definitive conclusions.

Report on Congressional Hearing on Hepatitis B

Continuing the presentations of the past two meetings on vaccine safety, Dr. Ben Schwartz reported on the May 18 Congressional subcommittee fact-finding hearing about the potential adverse health effects of hepatitis B vaccine. In attendance were Reps. Mica (R-FL), Tierney (D-MA), Waxman (D-CA), and Towns (D-NY).

Rep. Moakley (D-MA) testified in support of hepatitis B vaccination, as did four panels of witnesses. The latter include individuals with hepatitis B disease and those alleging harm for

the vaccine; Dr. Hal Margolis (CDC) and Dr. Susan Ellenberg (FDA); a panel of non-government scientists including Dr. Sam Katz; and advocacy groups. In response to public interest, the record was left open for 30 days after the hearing for further input, which was provided by a wide range of organizations including the AMA, AAP, AAFP, the Vaccine Initiative of the IDSA, and State and local health departments.

Rep. Mica's approach was to determine whether the vaccine is doing more harm than good. He referenced VAERS data and state case reports, such as New Hampshire reports of 16 times more adverse events than cases reported in a particular age group. An MMWR report also cited 100 reported cases versus VAERS' thousands of reported adverse events. Dr. Margolis presented serological surveillance data indicating thousands of cases a year including among children, but Rep. Mica challenged the validity of those numbers, which he termed estimates. He asked what scientific data suggested an association between adverse events and hepatitis vaccination and what studies were addressing those adverse events. Finally, he asked on what data the 1991 ACIP childhood vaccination recommendation was based. Opinions have been expressed that the data were insufficient and that ACIP conflicts of interest led to that recommendation. A request under the Freedom of Information Act has been filed for all information leading to that decision.

Other issues relevant to all immunization programs were also raised: 1) mandatory vaccination versus parental choice (one witness said she should be able to choose whether her child gets a disease or a side effect); 2) informed consent: (the Vaccine Information Sheet–VIS–is often incomplete or not provided); 3) whether risk groups could be identified on the VIS, such as family history of autoimmune disorders relative to hepatitis B; 4) families are discouraged from reporting adverse events by their physicians, leading to fear that many serious adverse events are undetected by the VAERS system; 5) concern was expressed that the NVICP does not work. It was never reviewed by Congress and another hearing on NVICP is likely; 6) The question of who should generate the further data on adverse events needed was raised, and government's role in allocating research money. The NIH peer review process was attacked as favoring efficacy studies for new vaccines rather than vaccine safety; 7) The sufficiency of data to support the hepatitis and recent ACIP rotavirus recommendations for vaccination among premature infants was questioned, and 8) the impact of conflict of interest on the entire ACIP process was raised. The overall theme was CDC's need to better communicate the science associated with both the risks and benefits of vaccination.

A number of CDC studies using the Vaccine Safety Datalink Project's Large Linked Databases were recently completed (one of fever and suspected sepsis in neonates after hepatitis B vaccination which found no increased risk; and a case-control study of alopecia showing no increased risk in children, but continuing data collection for adolescents and adults). Ongoing case-control studies include those on multiple sclerosis and optic neuritis, on the timing of vaccination regarding diabetes mellitus, and on rheumatoid arthritis. A study is planned of those with systemic lupus erythematosus and other autoimmune diseases, and of hepatitis B and other vaccinations related to febrile seizures, ataxia, encephalopathy, wheezing, anaphylaxis, and fatal outcomes. Data should be available in the next year or so.

Discussion. Dr. Katz outlined the hearing's attendees, ranging from genuinely concerned families who have been harmed, those philosophically objecting to mandated school entry requirements, and charlatans. He stressed the importance of having good science to ensure that the charlatans are not heard as well as everyone else with legitimate concerns.

In response to Dr. Le, Dr. Schwartz expressed some concern about potential legislation which may affect the process of ACIP membership and its recommendations. Dr. Evans did not expected further formal hearings on the NVICP since the General Accounting Office is already planning to issue a report on the program, expected in the fall. Dr. Halsey appreciated the media's even handling of the issue, indicating some progress in educating them about what constitutes sufficient science to separate temporal versus true causal events. He recommended, though, that ACIP review the transcripts of the attacks made upon it regarding conflicts of interest, how recommendations are made, etc. He described the Congressmen's confusion, due in part to information provided to them earlier which was not balanced by the CDC or FDA perspective.

Dr. Guerra agreed to the need for immunization providers to better inform the public and for ACIP to re-examine the VISs with these concerns in mind. Dr. Peter commented that more work is needed to assess vaccine safety, such as the as yet unfunded DHHS Vaccine Safety Action Plan. Such unfortunate events as this hearing actually offer an opportunity to inform the public that these activities need to be funded, and listing such studies can itself reassure the public that such monitoring is in place. Dr. Schwartz suggested that other Subcommittee members could be contacted for further input. He offered to provide a list of those with their states and party affiliation. With no further comment, the committee took a short break.

Review of the Hepatitis B Statement
Dr. Modlin applauded the revised hepatitis B statement as comprehensive and current, and hoped that it could be approved at this meeting.

Dr. Hal Margolis presented the statement, which had been distributed prior to the meeting. The ACIP members offered comments, as follow:

Dr. Egan suggested adding people with chronic liver disease, such as those with hepatitis C infection, who have a higher risk of acquiring hepatitis B. Dr. Snider suggested clarifying this group as at risk on page 30 and adding them as a twelfth category under "Vaccination of Adults at Increased Risk for Infection" (page 67).

Dr. Katz suggested specifying on page 67, "those adoptees found to be antigen negative. "

Dr. Schaffner noted that page 35 references "all immunocompromised persons," a broad category. Dr. Margolis explained this as an extension of data on hemodialysis patients in the absence of efficacy data on other immunocompromised groups, based on the assumption that other people being vaccinated may be even more immunocompromised than those on dialysis. Dr. Schaffner recommended text discussing what "immunocompromised" includes. Similarly, the implication on page 73 of a needed serology to check titer at 1 and 11 months after dose #2 is routine for hemodialysis patients. Dr. Griffin advised more explanation of who is at increased risk. Dr. Margolis agreed that the text can comment on the absence of data (other than those for dialysis and HIV patients) and leave this as an individual clinical decision.

Dr. Zimmerman advised inserting an evidence table and commenting on the strength of the recommendation.

Dr. Schaffner questioned the statement on page 36-37 ". . . asymptomatic infections are unlikely to be cause of further HBV transmission, and are not associated with chronic liver disease or HCC. " He thought that asymptomatic childhood infection is likely to become chronic liver disease. Dr. Snider advised linking the routine antibody testing to the risk behavior to

avoid causing concern about expanding antibody testing too far. Dr. Margolis clarified that Table 5 refers only to people with anti-core seroconversions among those HbsAg negative. The text will be clarified to provide context.

Dr. Egan suggested on page 36's bullet 2, clarifying that this is "chronic infection. "

Dr. Le recommended clarifying on page 50 that "current blood donor screening practices exclude those anti-HBC positive. " And the page 64 reference to routine vaccination at age 11 and 12 should instead urge the use of all vaccination opportunities to avoid, for example, a managed care refusal to pay at 9 years of age. Dr. Pickering suggested using the wording of the routine immunization schedule, that . . . "all children and adolescents through 18 years of age not immunized against hepatitis B may begin the series during any visit" Dr. Orenstein suggested replacing #1 (page 64) with that sentence.

Dr. France noted the page 63 recommendation that ". . . populations at high rate of infection should be immunized by 12 months of age." But there are rarely records in place to identify such children to ensure immunization. He suggested simply recommending a policy that the third hepatitis B vaccination routinely be done by 12 months, rather than providing an option extending to 18 months.

Dr. Halsey suggested clarifying in recommendation #1 that the intent is to receive two doses by 18 months; currently, it implies that administering dose 3 after 18 months requires starting over again. And 2) he suggested mention that data show that annual immunization for hepatitis B given at yearly intervals to children at 5-17 years produce the same antibody response as vaccine administered at 0,1,6 months. This simplifies catch-up immunization without forcing extra visits. Dr. Margolis noted that this was addressed under the section on adolescents by simply referring to the table.

Dr. Peter advised adding a subtitle on page 42 to offset the new sentence about the interchangeability of products. Dr. Margolis agreed; a text box might also be added. Dr. Peter recommended further advice to give the vaccine to people with chronic liver disease, since the severity of such disease acquired is likely be greater. In the absence of data, perhaps this could be couched in text citing an empiric recommendation based on logic. Dr. Margolis responded that the absence of data is why the text relies on risk groups. Dr. Schaffner noted that anyone could be at risk of hepatitis A. In the absence of data that hepatitis B can make you sicker, or in the absence of being in one of the risk groups, most physicians would be less receptive to immunizing their patients against hepatitis B. Dr. Margolis noted that an NIH Consensus Conference on hepatitis C did advise to immunize even in the absence of data. This could be addressed with "should be considered" language. Dr. Guerra reported Houston's practice as a rule, among patients with chronic liver disease but an unknown hepatitis type, to protect them from both A and B.

Dr. Gardner asked why the recommendation against immunization included some groups with known lower responses and not others, specifically, those based on age. Dr. Margolis cited reliance on the issue of disease/infection prevention within populations. In this case, the likelihood arose of having to retest substantial numbers of health care workers over age 50, which is highly cost ineffective. Health care workers are already tested for risk of repeated exposure, not by age considerations.

Dr. Siegel raised a contradiction on page 69 (line 21) between text stating that adequate antigen levels require no further treatment, but also suggesting another booster. Dr. Margolis reported

this as intentional to offer the choice to health care professionals. This will be reviewed via e-mail with the HICPAC members, since their next meeting is in November. Dr. Fleming was amenable to deleting this text upon HICPAC agreement. This was a last-minute addition attempting more to represent the views of the field than those of the committee.

Dr. Word asked the rationale of the page 24 text that pregnant women with vaccination history should be tested. Dr. Margolis reported the practical risk that a woman in prenatal care who is surface-antigen positive may be revaccinated. Data support a routine testing of each pregnancy. While an individual clinical decision is welcomed, as a general recommendation this was felt to be warranted to educate the field about that risk. Dr. Word concurred, adding one further editorial note that post-exposure prophylaxis for newborns should be administered within 12, not 24, hours.

Dr. Snider stated that the document submitted to the MMWR would be sent to the committee for their review as well. Dr. Margolis asked if the vaccine safety section was acceptable as distributed, to general agreement.

VOTE: Dr. Johnson moved to approve the hepatitis B statement as presented, with the understanding that the final version will be distributed to the ACIP members before publication. Dr. Fleming seconded the motion. Conflicts involving SmithKline Beecham affected five members, leaving six eligible to vote. At least 7 were needed for a quorum. Dr. Snider deputized the ex-officio members who felt comfortable voting, to do so.

In Favor: Fleming, Johnson, Helms, Glode, Modlin, Rabinovich, Egan, Graydon, Trump, Evans, Breiman, Word
Opposed; None
Abstained: Griffin, Le, Clover, Guerra, Offit

PASSED

Consolidated VFC Resolution for Hepatitis B
Dr. John Livengood introduced the last ACIP resolution to be consolidated. If passed, this resolution on hepatitis-B would be #6/99-1. It repeals and replaces VFC resolutions 2/94-14, 6/94-A1, 6/94-9, 6/94-17, 2/95-2, 2/95-3, 6/95-1, 2/97-3, 6/97-2, and 10/97-1.

The eligible groups include all previously unvaccinated children and adolescents from birth through 18 years. Although not normally included, recommendations on post-exposure prophylaxis is incorporated for three eligible groups: infants of HbsAg-positive mothers, persons whose sexual partners have acute hepatitis B, and persons with percutaneous or mucosal exposure to blood containing or potentially containing HbsAg. As required by law, a schedule is included for each group and was outlined for the committee, as were the dosage intervals, contraindications and precautions. Contraindications to administering hepatitis B vaccine are 1) anaphylactic reaction to a previous dose of hepatitis B vaccine, 2) known allergy to yeast or yeast products, 3) administration of COMVAX® vaccine or other hepatitis B/Hib vaccines to infants younger than 6 weeks of age, and 4) moderate or severe illnesses with or without fever. Contraindications to HBIG are 1) anaphylactic reaction to a previous dose of any immune globulin preparation, and 2) serum immunoglobulin A deficiency.

Discussion. Dr. Margolis suggested, to be consistent with the recommendation, including in the post-exposure prophylaxis section a fourth category of a not-fully vaccinated infant whose

primary caregiver has acute hepatitis B; and 2) repeating the note about COMVAX® in the text on infants born to mothers of positive and unknown status.

VOTE: Dr. Helms moved to approve the VFC resolution as drafted, and the motion was seconded.
In Favor: Fleming, Word, Johnson, Helms, Glode, Modlin, Egan, Graydon, Trump, Rabinovich, Breiman
Opposed: None
Abstained: Griffin, Le, Offit, Guerra, Clover

PASSED

Dr. Livengood asked to be advised as early as possible what VFC resolutions should be reviewed at the next meeting (e.g., on conjugate pneumococcal vaccine), as these votes must be announced in the Federal Register well before the meeting. Dr. Johnson recommended that the pneumococcal resolution be prepared, whether the committee is able to vote upon it or not. Dr. Guerra also supported developing a resolution on polio and the availability of providing OPV through the VFC program, in order to help accelerate and drive the changeover process.

With no further comment, the meeting adjourned at 5:40 p. m.

JUNE 17, 1999

Update on Influenza
Presentation on the Use of Live Attenuated Vaccine in Adults
Dr. Kristin Nichol, of the Minnesota Veterans Administration Center, presented data on a clinical trial exploring the effectiveness of the use of live attenuated influenza vaccine (LAIV) in healthy working adults. The trial was cosponsored by NIAID and Aviron Corporation and was conducted in the 1997-98 season, in which the A-Sydney drifted influenza A virus predominated. These data will be published soon in JAMA.

The intranasally-administered LAIV vaccine is made by reassorting cold-adapted virus strains with wild virus strains. It is designed to contain strains equivalent to what is contained in the inactivated vaccine for the particular season. LAIV has already shown to be effective in children, with a demonstrated efficacy of 93% against culture confirmed influenza in the 1996-97 and 1997-98 seasons. LAIV was also associated with reductions in febrile illnesses and febrile otitis media in children.

This was a double-blind, randomized, placebo-controlled trial conducted in 13 sites throughout the U.S. It enrolled healthy adults ages 18-64 who work at least 30 hours a week, who were not in a group already targeted for routine annual influenza immunization (e.g., health care workers), and who had no other contraindications (e.g., acute sensitivity to eggs/egg products). The outcomes assessed were vaccine safety, tolerability, and reactions in days 0-7 (through symptom card completion) and serious adverse events at 0-28 days and the entire 5 months of the trial outcome period (11/97-3/98). Clinical effectiveness outcomes included episodes of febrile illness, work loss, and health care resource use. The participants received bi-weekly telephone reminders to assure compliance with the symptom recording. About 90% completed cards; 88% returned 4 or more, and 96% returned at least one card.

The outcome periods were based on local influenza surveillance data, supplemented by CDC data. The three outcome periods included site-specific peak outbreak periods; pooled 14-week

total outbreak periods; and the entire 5-month reporting period. The duration and peaks reflected in national influenza surveillance data were parallel to cases among study sites. Most were influenza A; of the subtype, 80% were the drifted variant A/Sydney.

The participants had a mean age of 38.3 years (3041 receiving vaccine and 1520 receiving placebo; 54.7% were female 54.7%; 84.7% were Caucasian; and nearly 10% were African American. Reaction data collected for days 0-7 reflected the proportion of participants who reported symptoms: fever, runny nose, sore throat, cough, headache, muscle aches, chills, or tired/weak. The data showed two symptoms as more likely in vaccine recipients: runny nose (44.3% versus 26. 6% of placebo recipients) and sore throat (26.6% versus 16.3% of placebo recipients). Other symptom proportions were equivalent, including duration (median = 2 days).

Dr. Nichol presented the study's outcomes data for febrile illness, defined as 2 days of symptoms, self-reported fever (>100° F) on at least one of those days, and one day of at least 2 of the above symptoms. Data indicated 13. 2% of vaccine recipients with febrile illness, similar to 14.6% of among placebo recipients. However, the vaccine group had a 22.9% reduction in days of illness, and a 13.1% reduction in days lost from work. Days of antibiotic use were reduced by 42.9%.

For severe febrile illness, defined as 3 days of symptoms, data showed an 18.8% reduction in the numbers of episodes, 27.3% reduction in days of illness, 17.9% reduction in days of missed work, and 47% reduction in days of antibiotic use. Those for febrile upper respiratory illness (URI, which required the presence of respiratory symptoms) were similar .

The study concluded that for this trial were LAIV was safe and generally well tolerated, reducing the number of illness episodes, work absenteeism, and health care use across a number of illness syndromes.

Discussion. Dr. Offit asked the length of time of URI shedding or about evidence of contact spread of the vaccine virus. However, laboratory specimens or confirmations and contact interviews were not included in this trial. It was designed to assess clinical outcomes in the community. Dr. Griffin asked the results for other than peak influenza periods. Dr. Nichol reported similar findings from the pooled 14-week period, with commensurately larger differences in event rates compared to the longer period of time.

Dr. Kristine Severn of Dayton, Ohio, asked what was in the placebo used. Dr. Nichol reported it as the vaccine vehicle, identical in taste, appearance, and smell to the vaccine but without the virus itself. Dr. Rudy Jackson asked about the data delineation by college status. Dr. Nichol reported this as reporting any college education, not specifically limiting the cohort to college students. This is more specifically described in the paper.

AAFP Recommendation for Universal Influenza Vaccination Starting at Age 50 Years
Dr. Richard Zimmerman described the membership of clinical practitioners within the American Academy of Family Practitioners (AAFP). Its 50,000 members are somewhat over-represented by small rural practices. The AAFP policies adopted by their Board of Directors are often based on the advice of committees. Three in place are 1) the Commission on Clinical Policies and Research (CCPR), which provides evidence-based advice on preventive issues, such as cancer screening, anticipatory guidance, counseling, and immunizations. The CCPR states the strength of the evidence and also accounts for patient preferences. The strength of the policies are standard (equivalent to that ACIP's "strongly recommended, Level 1, "A"), Guideline (based on weaker evidence and/or other possible factors such as patient resistance), and Option.

The disease burden of influenza causes an estimated 20,000 excess deaths annually, 35%-46% of hospitalizations for influenza-like illness (ILI), and 10% of office visits. Most of the influenza related excess deaths occur among the elderly, but the death rate among such healthy older persons is less than that for persons 45-65 with two high-risk conditions (as demonstrated by the Barker data: e.g., rheumatic or ischemic heart disease, asthma, emphysema, nephritis, diabetes mellitus, and malignancies).

Vaccine efficacy is approximately 70% in healthy persons, up to 90% for some military personnel and very healthy persons. It has been shown to reduce hospitalizations from influenza, pneumonia, and congestive heart failure (CHF). It reduces all-cause mortality by 27%-54%, and is routinely used among healthy persons by a growing number of employers to lower absenteeism and expenses.

The Nichol et al study published in the New England Journal of Medicine in 1995 demonstrated the benefits of vaccination in healthy working adults in a randomized double-blind, placebo controlled trial. Reduced rates were shown of URI episodes (25% VE), sick days (43% VE), and visits to physicians' offices for URI (44% VE). The cost savings were estimated at $46.85 including work loss avoided, vaccination costs, medical costs for side effects, medical costs avoided, work loss for vaccination, work loss for side effects, and work loss avoided by the vaccine.

The AAFP also noted the limitations of a high-risk strategy, the lack of success of which was evident in the 1980s strategy to advance hepatitis B vaccination. Most physician offices lack computers, staff, or systems to conduct high-risk diagnosis code interventions; most computers are used for billing. The 1995 NHIS data show that 24% of those aged 50-64 have an underlying medical condition that places them at high risk for influenza complications (unpublished data), but only 38% of those aged 50-64 were vaccinated in 1995. A universal strategy would be easier to implement in a practice.

So, for Fall 1999, the AAFP Board of Directors recommended (Guideline strength) offering influenza annual influenza vaccine to all persons aged ≥50 years, acknowledging that physicians may need time and resources to incorporate this into practice. In the event of vaccine shortage (not anticipated), persons with high risk conditions and the elderly should have the highest priority.

Discussion. Dr. Marchessault reported a similar recommendation discussed in Canada. A decision will be made in October. Dr. Ray Strikas of NIP commented that the 20-year old Barker data are being revisited, a consideration for the ACIP's Influenza Workgroup. He asked if the AAFP also looked at data for those aged ≤65 years. Dr. Zimmerman clarified that their recommendation was based on the entire age range. Dr. Snider asked about the Influenza Workgroup's discussion of reducing the recommended age. Dr. Zimmerman reported their feeling that more population data is needed about the burden of disease, vaccination feasibility, etc., for the healthy 50-64 age range, which they hope to glean from a managed care study by Dr. Nichol with the NIP.

Dr. Jon Abramson, of Wake Forest University and the AAP's Committee on Infectious Diseases, noted that recent data indicate the second highest risk group for hospitalization to be among children aged <3 years, and asked if a recommendation for that group was also considered. Dr. Zimmerman reported the AAFP to be waiting on the licensure of the intranasal LAIV, but was unaware of recent such hospitalization data. That will be explored.

Dr. Griffin reported consistency between her own recent data, Barker's, and other 20 year-old data on children' rates of hospitalization, if not mortality (which are hard to get). Dr. Keiji Fukuda clarified that the ACIP Influenza Workgroup is working on two tracks: very young children and this older age group under discussion. They are balancing the risk of disease against the feasibility of implementing recommendations. More information on the relative risks is needed, especially for the healthy 50-64 year-old group versus those at high risk.

Dr. Fedson reported data from his studies in Manitoba that support the effectiveness of hospital based immunization programs. They target those discharged in the age groups beyond 65 years to prevent serious complications of hospitalization and death. For example, only about 3% of those hospitalized in the vaccine season were aged 45-64, but they account for half or more of influenza-related deaths. So, although the cost benefits are clear for everyone aged >50, if resources must be focused, he would recommend such hospital-based programs for those aged <65.

Dr. Peter suggested adding to the recommendation a note about reduced antibiotic use, a benefit to prevent emerging antibiotic resistance. He also noted past failure to maximize implementation (e.g., in only 25% of hospital workers). He asked how many people aged >50 visit their physicians, and how vaccination use could be augmented in health care workers and hospital employees.

Dr. Zimmerman agreed that implementation is to challenge. He expected a gradual phase-in period of several years in physician practices and multi-specialty groups. Recommendations are just the starting point to change physician behavior. He expected that NIH may have some data on the number of visits by 50-year-olds physicians. But age 50 was pragmatically chosen as a sentinel changeover year because such preventive services (e.g., mammography, colon and prostate cancer screening, etc.) begin at about that age. Dr. Modlin asked if the AAFP's providers' feedback had been sought. He said no, but they had pooled some external advice.

Dr. Strikas noted that NHIS data on physician visits among high-risk people of this age group indicate that >90% reported contact, although that could have included telephone contacts. The rate for those without high risk conditions was >70%, and that of those for a checkup was >60%.

Dr. Fedson noted the success of influenza vaccination, in that the U.S. uses influenza vaccine almost twice as much as any other country, in part due to Medicare reimbursement.

Dr. Peter suggested consideration of recommending nontraditional sites for influenza vaccination (e.g., by pharmacists) to aid implementation. Dr. Fukuda asked if the AAFP recommended vaccination for those with close contact to high-risk groups, and Dr. Zimmerman answered no.

Dr. Gardner cited the demonstrated cost benefit of immunizing the elderly and young workers, and advocated a universal recommendation for this vaccine on a societal/cost basis. He compared this to the MMR second dose, administered even though 95% are immunized by dose one, in order to catch everyone. Dr. Griffin commented that there also is a recommendation to vaccinate anyone who wants to avoid influenza, which most do. Standing orders are one way to address high-risk groups who will see their physicians frequently; and once an annual influenza shot begins, they are likely to continue it.

Dr. Clover noted that most of the data on children is on those aged 1 and 2 years. The question is how the vaccine affects pregnant women and in the first 6 months of life. He was also concerned, in light of low implementation of pneumococcal vaccination at age 65, about splitting off the now-concurrent influenza vaccination. Dr. Zimmerman knew of no such concern by the AAFP. Although some wanted to lower the pneumococcal polysaccharide vaccination to age 50 as well, the data were not strong enough to do so. A survey about compliance to lowering the pneumococcal age below 65 would be of interest.

Dr. France wondered how the difficulty of identifying those at increased risk and aged 50-64 contributed to this recommendation. If health plans mature to that capability, it seemed more logical to focus on those at risk than to vaccinate everyone aged >50.But Dr. Zimmerman cited in response the Nichol data on benefits to healthy adults, and industry data on reductions in absenteeism and costs to treat.

Dr. Frederick Rubin, of Pasteur Merieux Connaught, commended this initiative. He reassured the committee from a manufacturer's standpoint that increased influenza vaccination demand could be met, but noted that a more expeditious strain selection process (than waiting to March) is needed. He also suggested a recommendation to schedule influenza vaccination clinics over time (e.g., to November/December) to disseminate the vaccine.

Dr. Helms asked if the AAFP would follow up to determine the actual practice around the country. Dr. Zimmerman reported that the AAFP has no evaluation plan for the policy, such as awareness/adherence model process. But his group is doing a study in Pennsylvania funded by the AHCPHR, of a university clinic setting, and settings that are rural urban, suburban, inner city, and in a VA hospital. A cluster sample of those aged 50 in a clinic will be done along with physician and staff interviews, followed by interviews of 50 patients to determine the actual practice.

At this point, Dr. Modlin left to take an outside call and Dr. Glode assumed the Chair in his absence. Dr. Rudy Jackson asked if any data were available on supermarket influenza immunizations done in the last season. Dr. Peter reported a workshop done to explore that kind of feasibility. There are no data yet from the past year, but anecdotally such community programs have been quite successful. Dr. Strikas expected data about location of vaccination from the 1999 Behavioral Risk Factor Surveillance System (BRFSS), which should be available in mid-2000.

Teaching Immunization in Medical Education (the TIME Project)

Dr. Zimmerman reported on the Teaching Immunization in Medical Education (TIME) Project. Its development began about 10 years ago, and is used in medical schools, residencies and CME courses. It was begun by Bill Barker, Ray Strikas, and Pat Brugliera, in a cooperative effort between CDC, the Association of Teachers of Preventive Medicine (ATPM), and the University of Pittsburgh. The project's objective was to develop and evaluate case-based curricular materials on immunizations that promote preventive medicine skills. The materials were evaluated in a before-and-after trial involving medical schools and primary care residency programs from 20 institutions across the U.S.

When ATPM-CDC surveys of current immunization education indicated deficiencies, the University of Pittsburgh was contracted to produce curricula materials for influenza, hepatitis B, measles, and pertussis. These were produced in three active-learning formats: Problem-based learning (PBL), multi-station clinical teaching scenarios (MCTS), and self-study materials for providers. These were to respond to rapid changes in vaccination recommendations and

proper vaccination procedures, the advent of new vaccines, and higher than expected provider concerns about vaccine safety.

A national survey of primary care physicians showed how beliefs impact provider behavior. For example, overall, 82% would be likely to give DPT to a 7-month old with a URI and temperature of 37.5° C. And while 85% would give DTP during a cold, only 26% if they thought it would increase risk of side effects. An unpublished survey of family medical educators showed the three top education issues to be information on schedule changes, ways to increase immunization rates, pragmatic office system issues, and vaccine safety and anti-vaccine issues.

The project considered several theoretical models to explain practitioner behaviors: the Health Belief model (focusing, e.g., on disease risk, severity, vaccine efficacy, and adverse effects and barriers); and the Awareness to Adherence model (stage progression from awareness to adherence). Issues lie in between, in agreement and adoption. Mailings alone will not change these behaviors.

In developing the TIME project's training materials, they used a multidisciplinary team (health services, primary care, management, prevention, infectious disease, educational evaluation), conducted a literature search, and used learning objectives targeted to educational or behavioral outcomes. The teaching principles in the case-based modules focus on team work, the use of references, and addressed scenarios (e.g., disease severity and communicability, and methods to increase compliance). They used abstracted real cases, active teaching, and considerable pilot and field testing.

The MCTS materials divide learners into small groups of 3-5, who work on a scenario for 5-10 minutes. The questions are provided with the answers to be found. The facilitator then discusses the teaching points, and the process is repeated through 3-6 scenarios. The PBL approach is mostly used in training medical students, while MCTS is used for residents. The strategic elements of the influenza MCTS module were outlined: a sample case scenario presented the patient's symptoms of influenza, disease suffering, noted a missed vaccination opportunity, and followed through to how to treat influenza. In the childhood modules, a case scenario of measles transmission in an office setting was used as an example.

A partial list of field testing sites for this model was shared, as was a JAMA article on this approach. It has been well accepted; residents in particular liked being able to discuss as opposed to sitting through lectures.

CME materials address the health belief model issues, which mostly affects physician knowledge. This has had a modest impact on performance which is hoped to improve with a greater targeting of known behaviors and skipping some details such as electron microscopy and genetics. The limitations of the TIME project are its as-yet untested long-term retention (in residents; it will be years to see an effect from residency to an established practitioner). Finally, several examples of the project's material data were distributed, and further available information will be disseminated through the MMWR. Comments were welcomed both on the material and on its dissemination.

Discussion. When asked if this project could be used for varicella vaccine, Dr. Zimmerman said no; they were contracted to address measles, Hib, pertussis, influenza, hepatitis B, and a "general child" and a "general adult." Dr. Peter asked if other medical schools were using this

model, agreeing to its usefulness. Dr. Zimmerman reported modest uptake; about 10% in a survey by a risk communication group.

Dr. Fedson asked if the materials emphasize the importance of organizational change and administrative procedures to implement vaccine delivery in patient populations. Dr. Zimmerman reported that every module has a scenario oriented to vaccine delivery. Influenza has 6 scenarios, of which #3 is vaccine delivery (assessing what are immunization rates and what can be done about them). Dr. Strikas reported that ATPM sent letters out to the Deans of medical schools and the chairs of primary residency programs to advertise these materials. An MMWR Notice to Readers will be published on these and materials for nurses. Dr. Glode asked if there is a particular time this is recommended for residents (e.g., in clerkships). Dr. Zimmerman; the model is flexible.

Continuation of Discussion of Polio Immunization Policy
Dr. Paul Offit presented the new wording subsequent to the previous day's discussions:

"An all-IPV schedule is recommended for routine childhood polio immunization as of January 1, 2000.All children will need to receive four doses of IPV at 2, 4, 6-18 months and 4-6 years of age. Until January 1, 2001, OPV is acceptable only for special circumstances such as: children of parents who do not accept the recommended number of injections and imminent (i.e., <4 weeks) travel to poliovirus-endemic areas may receive OPV for the first dose."

He then suggested amending this to read "Until January 1, 2000, OPV is acceptable only for special circumstances such as: 1) children of parents who do not accept the recommended number of vaccine injections may receive OPV only for dose 3 or 4 or both; and 2) unimmunized children whose travel to polio endemic areas is imminent (i.e., <4 weeks) may receive OPV for the first dose.

Discussion. Dr. Glode agreed, only modifying the second to read dose 1 and 2. Dr. Johnson suggested dropping the words "such as," which may suggest that other circumstances might be possible; and clarifying the current inference that OPV for imminent travel after vaccinating a child is not acceptable after January 1, 2000.Dr. Modlin linked this to expected limited availability of OPV, although all would agree that for such travel by an unimmunized child, the lower efficacy of one dose of IPV for type 1 polio makes one dose of OPV preferable. He suggested a policy to specify OPV for that one contingency even after January 1, 2000, if OPV is available. Dr. Fleming suggested a clear statement that OPV is not expected to be available after 2001.

Dr. Pickering suggested text calling for all the "injections necessary to provide all the vaccines needed according to the recommended childhood immunization schedule." Dr. Helms thought the last sentence to imply that after January 1, 2000 OPV may be acceptable for other things. He suggested removing the last sentence. Dr. Livengood proposed simply stating that "OPV is acceptable until January 1, 2000." He also urged retaining the reference to the "third or fourth dose in a polio vaccine series"

Dr. Fleming proposed that the text state that "After January 1, 2000, we anticipate OPV will not be available" Dr. Katz noted, though, that OPV will remain available throughout the world where the disease remains endemic. Parents will get it as they can of they are convinced it is necessary. Dr. Orenstein suggested clarity that limited availability in the U.S. is expected, and that this is not the reason why IPV is preferred. Dr. Plotkin suggested, since VAPP prevention is the point, including the statement that OPV is "not recommended for dose 1 or 2," since some

physicians are still using it; and he suggested a reference to the sequential schedule. Dr. Halsey advised removing the availability issue from the recommendation, since it is not the point, and making it a prelude to the recommendation.

Mr. Salamone stated that IPV was recommended to totally remove the risk of polio, but the current wording would allow a parent to vacillate. A parent sufficiently attentive to these issues will return for another visit if only the fear of injections is an impediment. He suggested including language to imply that this be decided after some substantive discussion with the physician, and reversing the order of #1 and #2 to reduce the emphasis that parents can refuse injections.

Dr. Offit agreed that the real risk is that the first dose of OPV. Recommending IPV is the best medical advice, and it is incumbent on the ACIP to educate physicians that this is what they must do. He agreed that it should not be inferred that the number of injections should outweigh the risk of VAPP. Dr. Halsey concurred; the parent must be clear that there is another option than the choice between 5 injections or OPV. The recommendation can suggest the option of other visits, which is in fact the current reality. But Dr. Orenstein voiced real concern, from a public health perspective, about those children not making the regular visits who may be behind in immunizations and most in need of 5 injections in the second year of life.

Dr. Modlin asked if this could be placed in the statement update rather than the recommendation. Dr. Halsey responded that he would delete this from the recommendation and put it into the text. The real recommendation is for the IPV schedule; how to handle the schedule could be in the text. Dr. Katz commented that two doses of IPV is sufficient for protection in the U.S., and any missed third dose will be accomplished for school entry. He urged the FDA and the manufacturers to license combination vaccines to eliminate this argument.

Dr. Fleming proposed, as in other ACIP statements (e.g., DTaP), language allowing the vaccine to be provided if the provider believes that missing this opportunity means the child will not receive that immunization. Dr. Deborah Wechsler suggested reiterating the normal ACIP recommendation to give the child all vaccine doses at any visit, but making this an exception. Dr. Halsey agreed. However, Dr. Abramson was uneasy that parents who refuse the first two doses of IPV are offered no alternative, which could delay any immunization until school entry. Dr. Modlin stated that this could be addressed in the Notice to Readers, noting the existing ACIP recommendation for only IPV use in the first two doses.

To no objection, Dr. Modlin expressed his sense that the ACIP members were inclined to issue the recommendation for all-IPV by January 1, 2000, with special circumstances stipulated for the use of OPV. The committee moved on to discuss the text on travel.

Stipulations of Polio Vaccine Administration Prior to Travel
Dr. Offit presented the proposed text:

"For unvaccinated children (age <18 years), or those with unknown vaccination history:
1. Unimmunized children whose travel to polio endemic areas is imminent (i.e., < 4 weeks);
2. Children of parents who do not accept the recommended number of vaccine injections may receive OPV only for dose 3 or 4 or both. OPV should be administered only after extensive discussion between parents and providers of the risks of VAPP. The results of this record should be included in the medical record.

"Limited availability of OPV is expected after January 1, 2000."

Discussion. Dr. Modlin suggested adding "in the U.S." to the last sentence. Dr. Halsey wished to encourage the third dose of IPV between ages 6-15 at any visit, perhaps as a prelude to the MMWR Notice to Readers. Dr. Snider agreed, and stated that other such peripheral comments at this meeting will be incorporated to the article.

Dr. Peter suggested abbreviating "extensive discussion" to "discussion," and noted that documenting extensive discussions is a new standard potentially applicable to any immunization. Dr. Glode agreed that such a standard may be inappropriate, and Dr. Zimmerman expected the AAFP to dislike the stipulation of recording these discussions in the medical record.

Dr. Jackson raised the remaining mention of the expected unavailability of OPV when that is not the reason for the recommendation. Dr. Orenstein responded that this statement could help physicians accustomed over decades to using OPV to know they need to rethink this. It would be an important information point to communicate in the introductory text. Dr. Katz advised, rather than citing 2000 for limited availability, that "increasingly limited availability" be cited.

Therefore, the final text for the vote on this recommendation read as follows:

"An all-IPV schedule is recommended for routine childhood polio immunization as of January 1, 2000. All children will need to receive four doses of IPV at 2, 4, 6-18 months and 4-6 years of age.

"OPV is acceptable only for the following special circumstances:

1. Mass immunization campaigns to control outbreaks due to wild-type polio virus;
2. Unimmunized children whose travel to polio endemic areas is imminent (i.e., <4 weeks) may receive OPV for the first dose;
3. Children of parents who do not accept the recommended number of vaccine injections may receive OPV only for dose 3 or 4 or both. OPV should be administered only after discussion of the risk of VAPP.

"Limited availability of OPV is expected in the future in the U.S."

VOTE: Dr. Glode's motion to accept the text of the amended recommendation was seconded. Conflicts with Pasteur Merieux Connaught and Wyeth Lederle applied only to Dr. Le.

In Favor: Word, Fleming, Griffin, Johnson, Helms, Offit, Glode, Modlin
Opposed: None
Abstained: Le

PASSED

Dr. Modlin congratulated Dr. Offit, Dr. Prevots, and all those who spent so much time on this issue.

Presentation on Bioterrorism Preparedness Activity

Dr. Scott Lillibridge, of NCID, discussed the issues of the CDC's Bioterrorism Preparedness program and the related vaccine issues addressed by the NIP and pertaining to the work of the ACIP. This is the largest preparedness response program ever developed at CDC.

A covert bioterrorist release involves a different and more complex approach than the traditional public health response to a hazardous release, including emergency medical and surveillance systems and laboratory, diagnostic, and therapeutic responses. It will require tight coordination at the state and local level. For example, there is no current active program to respond to an attack with previously eradicated disease agents, such as smallpox, which is now only in U.S. and Russian labs.

The 1996 Olympics prompted the first organized national approach to merge the technology, diagnostics, and therapeutics involved in issues of terrorist disaster response. Its focus was on early detection (surveillance), rapid laboratory diagnosis, epidemiologic investigation, and implementation of control measures. Initially, much of the technology was not portable. The federal agencies and Armed Forces brought laboratories to CDC: chemicals from the Army, rapid assay labs from the Navy and a communications network from the FBI, and other contributions from the Departments of Energy, Defense, etc., along with about 200 staff for diagnosis, treatment, and support activities. The state of Georgia and CDC's Public Health Practice Program Office (PHPPO) developed surveillance to trigger a response, either a public health emergency from food or water contamination or from biological or chemical terrorism. The Department of Veterans' Administration activated their stockpile program of pharmaceutical agents (not vaccine) for infectious diseases or chemical antidotes.

Dr. Lillibridge provided a flow chart of the resulting system, which provided the groundwork for a national system. The lessons learned were that large-scale public health population emergencies require public health thinking, planning, and infrastructure for response. Additional sites for detection surveillance and improved technology are needed, and more (and the right) rapid diagnostic skills on the local level, to enhance epidemiologic investigations and to implement control measures (vaccines). The bioterrorist agents that have been identified as critical are anthrax, botulism, brucellosis, plague, Q fever, smallpox, staphylococcus, and tularemia.

In FY99, CDC received $121,750,000 to develop bioterrorism preparedness, much of which was distributed to states in the form of cooperative agreements. This was disbursed as: $51 million for the stockpile (critical therapeutics, antibiotics); $28 million for the Health Alert Network (communications); $23 million for laboratory activities (validate assays, particularly for agents not previously a public health consideration); $16.75 million for response (to support state/local surveillance and epidemiological capacity which declined with managed care cost containment); and $3 million for planning (planning grants to states to organize a linking local system).

Priorities for CDC extramural activities include preparedness, surveillance and epidemiology, laboratory capacity for biologic and chemical agents, health communication systems, training, and establishment of key liaisons. The latter is to expand on already good interagency relationships in preparedness (e.g., with DOD, FEMA, law enforcement). Priorities intramurally are to expand CDC capacities for epidemiologic response (with 80-90 new FTEs); create a rapid diagnosis laboratory system connecting state grantees to CDC, DOD, and the laboratory community; maintain a national drug and device stockpile, attend to training, and administer the "Select Agent Rule" which regulates the interstate shipment of laboratory agents potentially used for bioterrorist attack.

This effort involves emerging vaccine issues, expected to continue over time with increasing public and political attention: the routine vaccination of civilian populations (not a recommendation to ACIP, but there is some interest) and of special populations (first responders, lab and military personnel, U.S. government personnel overseas). The latter may

be covered by existing DOD regulations or the State department could make its own recommendations.

Civilian vaccination concerns after a bioterrorist event are analogous to those of pandemic flu: logistics, massive mobilization, training, stockpile issues; monitoring for adverse events; evaluation for efficacy and coverage; special populations (immunocompromised, children, pregnant women, e.g., regarding liability for the use of investigational new drugs).

Dr. Lillibridge outlined the status of some vaccines of concern: smallpox, and anthrax are licensed, with limited availability; plague vaccine is licensed but of limited or questionable efficacy; and the tularemia vaccine is an IND, with limited availability. Updated recommendations are needed for their use (including allaying public concern; for example, there is no need to vaccinate all EMTs), and there is a need for a new generation of vaccines with lesser side effects, wider indications, and less costly manufacture.

NIP/Potential ACIP Involvement in Bioterrorism Preparedness
Dr. Ben Schwartz, of the NIP, outlined NIP's involvement in CDC's Bioterrorism Preparedness Response activities and the ACIP's potential role.

The NIP's role to date has been to 1) collaborate with CDC's Office of Bioterrorism Preparedness and Response on overall planning; 2) provide technical assistance pertaining to stockpile contracts and vaccine supply (e.g., as now done with the VFC); 3) contribute to developing vaccination strategies for various groups including delivery and monitoring of impact and adverse events (e.g., updating and applying the smallpox plan); 4) consult with partners (e.g., FDA, DOD) to assure appropriate adverse event reporting and evaluation for vaccines currently in use (e.g., as done with anthrax for military personnel); and 5) ensure that State Immunization Programs are fully informed and, as appropriate, engaged in bioterrorism health initiatives.

Dr. Schwartz then outlined potential ACIP engagement in vaccine and bioterrorism issues: 1) review data and provide advice on vaccination recommendations for specific populations (first responders, military, etc). Vaccinating U.S. personnel overseas is already being considered by the Surgeon General, and ACIP input would be of value); 2) review and comment on scenarios for civilian vaccination in the event of a bioterrorism act; 3) provide guidance on research and data needs; and 4) consider forming a subcommittee or designating contacts for bioterrorism vaccination issues, for consultation when questions arise and to help consider what issues would benefit from Committee input.

Discussion. Dr. Le asked about the needs of civilian U.S. travelers or missionaries, and commented on the ease of an anthrax attack through a cruise ship's ventilation system. Dr. Schwartz acknowledged the challenge of endless potential scenarios. Most likely, the system would act upon warnings from DOD or the FBI and intervene before an attack. Dr. Lillibridge added that many public concerns can be allayed with education on the smallness of the risks, to help focus on better yield activities. But he agreed to the ventilation system threat; for example, the systems of many urban office buildings and hotels are so interconnected.

Dr. Pickering asked how the multiple advisory groups would be coordinated. Dr. Modlin expected that an ACIP Workgroup probably would only advise CDC, primarily the NIP. But Dr. Schwartz added that ACIP guidance on controversial issues would be helpful (e.g., the debate that anthrax vaccination could be related to Gulf War Syndrome). Dr. Snider stated CDC's realization that the nature of the diseases/vaccines under discussion would require

supplementing the committee's expertise. But in terms of general vaccine issues and their use in populations, the ACIP would provide the most expert guidance.

Dr. Halsey stated that these issues go beyond vaccines. He asked how CDC plans to educate primary care providers about their role (e.g., in surveillance, identification of an event, management of potentially exposed people, etc.). They also hope to have a simple central contact in the response system. AAP is preparing to send a document about these to CDC. Dr. Lillibridge outlined some of the initial short- and long-term strategies under discussion. The issues will be introduced at the Public Health Grand Rounds and discussions are planned this week with the AMA about including bioterrorism in medical school residency curricula. Later this summer, CDC and DOD will present a biologic preparedness defense course by satellite to about 65,000 people, open to both the military and civilian sector. A number of publications are planned, including a JAMA series this summer on biological agents. At CDC, PHPPO is organizing a distance-based training curriculum to improve awareness of the Health Alert Network at the local level.

Dr. Halsey encouraged a broadening of the pediatric involvement in this work, noting discrepancies in dosages, especially with antibiotics, and different adverse events in children that are not generally covered. Dr. Peter reported NVAC's interest in participating in this effort and suggested a joint NVAC/ACIP workgroup. Drs. Snider and Modlin endorsed this idea. ACIP volunteers to the Bioterrorism Workgroup, which will probably be a standing workgroup, were Drs. Abramson, Clover, Helms, Trump, and Carlton Meschevitz from Pasteur Merieux Connaught. Dr. Peter commented that NVAC could provide the state/local public health representation.

Discussion of the Use of Standing Orders for Adult Immunizations

Dr. Strikas drew the members' attention to the draft recommendations in their meeting book on the use of standing orders. Adult vaccination levels are suboptimal, particularly for influenza and pneumococcal disease. Standing orders have been recommended by various groups to improve that record. ACIP has done so for reminder/recall, feedback of immunization information to providers, and use of the WIC program to improve vaccination. While ACIP has implied the usefulness of standing orders as a mechanism, a specific recommendation would be helpful in improving vaccination levels. The NIP, CDC's Office of Health Care Partnerships, and HCFA jointly developed this draft recommendation for standing orders.

Pneumococcal/Influenza Burden of Disease and Vaccination Status

Dr. Vishnu-Priya Sneller outlined the disease burden of influenza and pneumococcal disease and the estimated vaccination level in the U.S.

The ACIP annual influenza vaccination and a single dose of pneumococcal polysaccharide vaccination for older and at-risk adults. Among those aged >65 years, 20,000 to >300,000 cases of influenza-related illness may occur. Hospitalizations range from 2-10 per 1,000 persons aged ≥65. For all age groups, an estimated 500,000 cases of pneumococcal pneumonia, 50,000 of pneumococcal septicemia, and 3000 of pneumococcal meningitis occur. Current data indicate the highest incidence of pneumococcal disease to be among children aged ≤2 years, but mortality is highest among adults aged ≥65 years.

The Healthy People 2010 Objectives raise the target level for immunizations of adults from 60% to 90% for three groups: 1) noninstitutionalized adults aged ≥65, 2) noninstituionalized high risk adults, and 3) institutionalized adults.

Vaccine use data come principally from the National Health Interview Survey (NHIS) and the National Nursing Home Survey (NNHS), both conducted by the National Center for Health Statistics, NCHS; and the BRFSS, done by the National Center for Chronic Disease and Health Promotion (NCCDHP).

The 1995 NHIS estimate for influenza vaccine use in non-institutionalized persons aged ≥65 years was 58%, a 26% increase since 1989. The 1997 BRFSS self-report data indicate a rate of 65.5%, exceeding the Healthy People 2000 goals. Pneumococcal vaccine usage was 32% by 1995-NHIS, an 18% increase since 1989; the current BRFSS rate is 45.4%. In those aged 18-64 years, influenza vaccine usage was <35% in 1995, and <20% for pneumococcal vaccine.

The 1997 BRFSS state-specific estimates for 45 of 52 areas had influenza vaccination use at ≥60%, and 9 at ≥70%. Since 1995, only 5 states have not reached the Healthy People 2000 goals. But reported pneumococcal vaccine use had not reached the 60% coverage goal as of 1997. All states but Arizona were 5%-28% points from the Healthy People 2000 goals.

The National Nursing Home Survey showed few nursing homes with organized vaccination programs, and even fewer with reliable systems for recording vaccination. This prevented deriving estimates for vaccination use data; the 1995 estimated range for influenza vaccine usage was 63%-74%. For pneumococcal vaccine, 43% of residents surveyed in 1995 had no documentation indicating whether vaccinations were offered and accepted. Vaccine receipt was estimated as a range of 24-42%. On the other hand, nursing homes with organized vaccination programs had better records and a higher proportion of vaccinated residents: 64% had documented pneumococcal vaccination status (versus 46% with no program) and nearly 80% for influenza (versus 54% with no program).

To improve vaccination services, the vaccine delivery behaviors of providers and their assistants must be changed. Knowledge of vaccine indications alone has not done so. Strategies that modify existing vaccine delivery systems have been more effective than strategies that target individual providers. Standing orders is one such strategy that has proven effective.

Effectiveness of Standing Orders

Dr. Linda McKibben, of CDC's Office of Health Care Partnership, presented evidence supporting standing orders as a strategy to improve vaccination coverage in adults. Much of these data were drawn from the Guide to Community Preventive Services (the Guide), whose Vaccine Preventable Diseases chapter was to be issued in the MMWR on the following day (6/18/99). Dr. McKibben provided definitions of the interventions involving Standing Orders, and outlined the Guide's rules of evidence and the key studies of effectiveness of interventions involving standing orders.

Standing order interventions are a quality improvement program to increase vaccine coverage rates. The are classified as provider-based vaccine delivery strategies to reduce missed opportunities in the health care system. The Guide defined them as the administration of vaccination by non-physician health care personnel to a patient or client without direct physician intervention at the time of vaccine delivery. The key elements of Standing Orders are: 1) a policy statement is given; 2) a system to identify eligible candidates is in place; 3) consent is obtained and documented; 4) vaccine is ordered and 5) delivered and documented by trained health care personnel.

Implementation options include traditional and nontraditional settings, standing orders alone or with other strategies, and vaccine ordering mechanisms (a standing order developed by the medical director or institutional policy committee, or advance physician orders of vaccination for a class of patients).

The Guide's Vaccine Preventable Diseases chapter reviews 18 interventions to improve coverage rates in children, adolescents, and adults. The Guide reviewed evidence to judge how effective vaccination strategies are in delivering immunizations. They conducted a systematic review, a broad search with specific inclusion criteria, with an explicit process of recommendation developed based on evidence. The entire process and the findings were then reviewed by an expert panel for each public health question.

Dr. McKibben listed the Guide's seven unprioritized strategies which were strongly recommended: provider-based interventions (standing orders for adults, provider reminder/recall, and feedback to providers), access to vaccination services (reducing out-of-pocket costs, multi-component interventions to expand access to health care services); and increased community demand (client reminder/recall, multi-component education). The Guide reviewed 16 studies of the effectiveness of standing orders in delivering vaccination to adults. Five were excluded; of the 11 remaining, 8 were judged suitable in design. Standing orders used alone in four studies showed an absolute percent change, ranging from 33%-80% (median=51%) in hospitals, long-term care facility, and a teaching hospital outpatient clinic. Standing orders combined with other strategies showed less impressive gains, but the baselines were also higher than those using standing orders alone (23%-66%, with an improvement from 5%-25% [median=16%] in HMO settings, private practices, a VA outpatient clinic, and an academic clinic.

After the cutoff date for Guide inclusion, another study was published on a multicomponent VA hospital program. This had grown from influenza to include pneumococcal disease and from out patient to also include in-patient populations. A bar chart showed significant gains achieved from a reminder-recall system and a dedicated immunization clinic during the fall. Coverage rates for pneumococcal vaccine were >60%, and >80% for influenza were achieved over 10 years.

No adverse or unwanted effects beyond local reactions were found in any of the studies of standing orders. At least one study found good acceptance of standing orders among physicians. Interventions including standing orders alone or embedded in other programs can address missed opportunities in the national health care system to protect older and at-risk adults against pneumococcal and influenza disease. Standing orders work in traditional and nontraditional settings to reach vulnerable populations, and can be safely recommended to health care providers and institutions to accompany other standards of care and best practices.

HCFA Perspective

Dr. Steven Jencks, Director of HCFA's Quality Improvement Group, offered their perspective. He stated the importance of this topic to HCFA, which has committed to improving the pneumococcal and influenza vaccination status of its clients. Measures of success are now incorporated into the Government Performance and Results Act (GPRA) and into the National Partnership for Reinvention of Government. Influenza vaccination status is part of HEDIS measures for all Medicare health plans and pneumococcal may be added as well. The HCFA Peer Review Organizations (PROs) contracts include performance-based requirements for improving immunization. HCFA is, therefore, broadly committed, and could use ACIP's help.

A HCFA Study by RAND concluded that standing orders are the most effective method for improving immunization coverage. HCFA is interested in all settings with vulnerable patients, particularly in hospital, nursing home, and skilled nursing facility settings, and home health agencies. All these have low immunization rates. He stated HCFA's policy, in exerting quality improvement efforts in operational systems, to implement experts' (e.g., ACIP's) points of view. That facilitates practitioner agreement.

He defined two related issues: 1) are standing orders clearly the standard of care, especially at the institutional level?If so, it may be necessary to approach Congress about regulations regarding standing orders; and 2) are there secondary benefits, such as that immunization is necessary to create a safe environment in nursing homes or elsewhere. If it is true that immunizing staff and patients of a nursing home protects those who are immunized (i.e., lower risk of disease or complications), then a different level of argument applies, because institutions are charged to provide a safe environment as well as safe individual care.

So, Dr. Jencks posed several questions: 1) Are standing orders the most effective or only really effective way for nursing homes to achieve immunization for their residents?; 2) Is it appropriate, given the evidence, for a nursing home to not have standing orders?; 3) what about settings such as hospitals and home health, with low immunization status?; and 4) does immunization of staff/other patients reduce the risk of disease risk and adverse outcomes even for immunized patients?

Discussion. Dr. Clover supported standing orders as an important communication loop between providers and insurance carriers. Dr. Le thought standing orders could be included, for example, in the recommendations for hepatitis B in jails and juvenile detention, but that was outside this discussion of influenza and pneumococcal vaccine. Dr. Helms asked if HCFA was willing to expedite billing, charging, etc. to ease the reimbursement process for those implementing standing orders. Dr. Jencks expressed HCFA's understanding that easier billing encourages implementation. They instituted roster billing to facilitate that, and also wish to put a field on the UB92 hospital discharge form. However, the American Hospital Association is not supporting that. He welcomed all suggestions to help this process.

Dr. France cited the 4" local reactions to pneumococcal revaccination reported on the previous day, which may occur more frequently with standing orders. Dr. Word cited her concern that a disproportionate number of urban dwellers do not have primary care physicians. However, Dr. Strikas noted that ≥90% of the elderly have such access, and thought that most of the settings for this recommendation would alter primary care (nursing homes, hospitals, home health agencies). ACIP also has the option of defining this recommendation by specific setting or specifying any kind of health care system.

Regarding the question of immunizing staff, Dr. Fedson cited the recently-published Potter study (Journal of Infectious Disease), indicating that immunization of residents is less protective than immunizing health care providers. Dr. Fedson advised caution about accepting those data conclusions as applied to illness in a residential setting, thinking the data analysis to be epidemiologically incorrect; data from institutionally-based immunization programs were analyzed based on individuals. The study's flaw was in its methodology, and so its conclusions are debatable. But data support that vaccination protects older patients and healthy working adults, making it clearly justified to immunize both based on their individual protection and making the safe environment argument unnecessary.

Dr. Griffin agreed that Potter's evidence was insufficient. But it also is known that influenza vaccine is not as efficacious in the frail and elderly as in the young, and even without direct studies, the evidence is strong enough that immunizing staff protects patients. That was the basis of ACIP's health care worker recommendation. Dr. Strikas expanded on that, however, commenting that this recommendation's focus is on patient population and health systems, not the health care workers already addressed.

Discussion of ACIP Recommendation on Standing Orders
Dr. Strikas presented two optional paragraphs for selection in the ACIP statement.

Option 1: "The ACIP recommends that standing orders be used in nursing homes to ensure the administration of recommended vaccinations for adults. Standing orders should also be considered for vaccination of adults in inpatient and outpatient facilities, managed care organizations, assisted living facilities, long-term care facilities, skilled nursing facilities, home health care agencies, and correctional facilities."

Option 2: "The ACIP recommends that standing orders be used to ensure the administration of recommended vaccinations for adults in nursing facilities, in inpatient and outpatient facilities, assisted living facilities, long-term care facilities, skilled nursing facilities, and by managed care organizations, home health care agencies, and correctional facilities. Both influenza and pneumococcal adult vaccinations should be public health priorities for implementation of standing orders."

Dr. Griffin suggested recommending for all settings in which health care is provided, and strongly recommended in the primary care setting. Dr. Strikas thought that all of Option #2's settings provide primary care; the phrase "such as..." could be inserted. Dr. Griffin further suggested excluding in-patient facilities. Dr. Schaffner found this idea intriguing, but complex. All the cited institutions are very different from each other, and many assisted living facilities are not primary care facilities. Implementation will be similarly different. He recommended a workgroup to examine the related issues more closely. Dr. Zimmerman, however, supported Dr. Griffin's points and suggested using Option #2 with some caveats about special situations. Dr. Clover suggested that a workgroup join the Adult Immunizations Workgroup to discuss these issues. Drs. France and Fedson volunteered for that workgroup. With no further comment, the committee adjourned for lunch.

Rotavirus Post-licensure Surveillance Update
Dr. Livengood presented some late-breaking data from CDC's enhanced rotavirus surveillance of VAERS data which reflected a number of reports of intussusception. This also was noted but not significantly elevated in the vaccine's pre-licensure trials, but they had insufficient power to distinguish the occurrence of the event. The VAERS data have been interpreted as a signal event; that is, something occurring at a high rate but too early for interpretation. CDC proposed to conduct a rapid investigation of any association this summer. Dr. Livengood also noted that there is not yet a federal contract for RotaShield®; it is only available in the private sector.

Dr. Peggy Reynolds reviewed the data presented by the ACIP Working Group on Rotavirus Vaccine to the ACIP two years earlier. The evaluation of serious adverse events among vaccine recipients in all the trials revealed five cases out of 10,922 vaccinees. One had received the monovalent vaccine, two had received a tablet formulation, two received RotaShield.® All these cases occurred after dose 2 or 3 of the vaccine. There was one case among placebo recipients.

CDC investigated the literature for an association between natural rotavirus infection and intussusception, and found no controlled study. Three available studies present conflicting results (only one suggests a relation). Natural disease does not appear to be an important cause of intussusception. New York hospital discharge data for 1991-95 were charted, showing no correlating peaks between intussusception and rotavirus and indicating that natural rotavirus is not an important cause of intussusception. They then analyzed the age occurrence of intussusception in the background population and in vaccinees. Almost the cases occurred in children aged <12 months, most peaking between 3-10 months of age, between doses 2 and 3.

The vaccinees' intussusception was then compared to those among the Northern California Kaiser Permanente data, the New York discharge data, a German DTaP trial, all rotavirus vaccinees, and the Rotashield® vaccinees. All the rates were equivalent. They interpreted these data as not reflecting a causal relationship between vaccine and intussusception.

Review of VAERS Data
Dr. Melinda Wharton of the NIP reviewed the VAERS system data on intussusception. As of June 16, 1999, 12 cases of intussusception among rotavirus vaccine recipients had been reported to VAERS from November 1998 to May 1999. All diagnoses were confirmed by laparotomy or x-ray. Ten of the 12 cases had onset within 7 days of receipt of the vaccine, and 9 of the 10 simultaneously received other vaccine. All the children survived.

The incidence was 3 cases each at 2,3,4 months of age, and single cases at 6,7,11 months of age. This does not fit the background pattern of peaks at 4-9 months of age as reflected in the Vaccine Data Safety System, 1991-97. Another striking feature of the reports is the interval between receipt of the vaccine and symptom onset. The reported cases are fairly evenly distributed since licensure, the first reported in November and the last in May. Reporting delays to VAERS up to 13 weeks have occurred; other delayed reports are expected.

As of June 1, 1.8 million vaccine doses have been distributed, of which an estimated 15-20% has not yet been administered. The vaccine has been administered at a constant rate since licensure. CDC's calculation assumes the administration of 1.5 million doses, with at least one dose to 900,000 children. Using 0.4 per 1,000 infant-years as the baseline rate of intussusception (from the Vaccine Safety Data Link data), CDC estimated a likely 1167 cases among infants under 12 months of age; 146 cases among infants receiving at least one dose; and 11 cases among infants receiving the vaccine in the week prior to onset of symptoms of intussusception. Ten such cases have been reported to the passive VAERS system and under reporting is likely.

Discussion. Dr. Offit asked about any increased rate of side effects within a few days of vaccine administration in the children with intussusception, which could indicate increased replication; or if the children were tested for shed rotavirus. Dr. Modlin also asked about any clinical data on the diseases. Dr. Wharton responded that these data were not yet available, but assumed shedding to be expected given the recent vaccination.

Current Status of Active Post-Licensure Surveillance
Dr. Peter Paradiso presented for Dr. Steven Black the status of the Phase IV post-marketing surveillance study ongoing at Northern California Kaiser Permanente. The study, which began in December 1998, will include 20,000 children who have received three doses of vaccine. The outcomes assessed include medical utilization of Emergency Rooms, clinics, hospitalizations, and mortality. Rates of events by diagnosis and site of care will be compared to three control groups: themselves 30-60 days post-vaccination versus 0-30 days; age- and sex-matched to

prior year controls, and similarly matched to those receiving non-rotavirus vaccines in the same year.

From December 1998-May 10, 1999, preliminary data on the last category are as follows: 9860 children were enrolled; 4653 children received 1 dose, 3594 received 2 doses, and 1613 received all 3 doses of vaccine. Eight cases of intussusception occurred overall, all in children <1 year of age. Six occurred in children with no vaccine exposure aged between 4-9 months of age; one 15 days after dose 2 at 4 months of age; and one in a child found to have a congenital polyp as the cause of the intussusception. This is an incidence rate of 6 cases per 18,140 for the unvaccinated group, or 33 cases per 100,000; the one case in 9860 of the vaccinated children is a rate of 10.1 cases per 100,000 vaccinees.

The conclusion reached from this preliminary analysis was that to date there is no evidence of an increased risk in rotavirus recipients. Additional analysis incorporating exact person-time denominators is planned.

Discussion. Dr. Offit asked how many two-month olds were followed after dose one, but Dr. Paradiso did not have an age distribution.

CDC Follow-up Plans
Dr. Trudy Murphy, of the NIP, reported a planned retrospective, matched case-control study by CDC to determine if rotavirus vaccine is associated with the occurrence of intussusception in children <12 months of age. A questionnaire will explore risk factors from the period November 1, 1998 through June 30, 1999. The analysis will investigate vaccination status of cases and controls by interval of time after vaccination by week, and any association with which dose of vaccine preceded the intussusception.

The assumptions are 1.2 million first doses delivered, a coverage of <30% in the control group, and an incidence rate of 40 per 100,000. The study design's limitation is sample size; a prospective study may be necessary to achieve adequate statistical power to detect an odds ratio of ≤3.0. Completion is expected in three months.

Discussion. Dr. Johnson asked if the 10 VAERS cases would be included, and Dr. Murphy said only if they are detected as patients during the case finding. Dr. Fleming thought the design ambitious, and hoped for active state-level involvement. He suggested also pursuing methods supplementary to a case-control study to explore this issue. In response to Dr. Le's question, Dr. Murphy stated that no other side effects would be simultaneously explored (e.g., excessive fever).

Dr. Livengood summarized that CDC concluded that these cases represent a signal requiring analysis. The trials' power was too low to detect low-level occurrence in a few cases, and doses are expected to rise with increased penetration of the private sector market. Importantly, unlike the prelicensure cases after doses 2 and 3, 11 of these 12 were after dose 1. CDC will activate all EIS officers in collecting data for this study; will continue to follow up with VAERS; and will release an MMWR summarizing these data in the next 3-4 weeks. One benefit of this situation is that it demonstrates that VAERS can work well.

He reviewed the current statement on rotavirus, which parallels the package insert text.

"In all studies of rhesus rotavirus vaccines combined, intussusception was noted in five of 10,054 (0.05%) recipients of any reassortent rhesus vaccine (two of these five children received RRV-TV) compared with one of 4,633 placebo recipients. The difference between the

rates of intussusception in these groups was not statistically significant (p=0.92 for children receiving vaccine; p=0.45 for children receiving placebo), and the rates observed among vaccinated children were similar to those seen in comparison populations. Although the association of these events with RRV-TV appears to be temporal rather than causal, post-licensure surveillance is needed for these and other rare adverse events that might occur"

Dr. Livengood expressed his own comfort with this language at this time, but requested discussion of this language as to whether other actions should be taken by CDC. Dr. France recommended a link with the Cancer Research Network, part of the HMOs' research network (the Principal Investigator is Dr. Robert Wagner at GHC), in which 10-14 centers are pooling data for cancer prevention. That program might be able to match cases and controls.

Dr. Offit agreed that a clustering in 2 month-olds 7 days post licensure is worrisome. But he had a question related to biological plausibility, asking how the vaccine differs from natural infection. There is a good deal of natural infection in the 2-6 month old group, without any peak in the winter months, and the pathology of rotavirus patients does not reflect any intestinal lymphoid hyperplasia. He found it hard to believe that the attenuated rotavirus tetravalent vaccine, which replicates less well in the human intestinal tracts than natural infection, would be more likely to cause intestinal lymphoid hyperplasia. However, he was keeping an open mind on the matter.

Dr. Livengood reported some agreement within CDC that rotavirus is not a major cause of intussusception. However, the FDA pointed out the possibility that a non-human virus could cause lymphoid reactions different from a human virus at low levels. This is being discussed. Currently, CDC is only seeking an association; then if there is one, to assess whether it is causally associated. Even an odds ratio in a matched case-control study will not give an attributable risk.

Dr. Fleming called this a "suspect" potential outbreak, suggesting the conduct of rapid case finding to see if this is the tip of the iceberg, particularly with the likely media attention after the MMWR article. If CDC desires individual physician reports as opposed to VAERS data, he suggested discussion with state and local health departments on how to handle those reports. Dr. Snider reported discussions planned with the CSTE on the following week, which could include how to involve state and territorial epidemiologists in ascertaining cases. Dr. Livengood demurred somewhat, though, that having another dozen cases will not necessarily tell CDC what they need to know. Dr. Orenstein thought it already clear that the study needs to be done on a population basis to get as unbiased as possible ascertainment of intussusception cases.

Dr. Modlin expressed the committee's appreciation that the signal was detected in a timely manner, and of the appropriateness of the steps taken. He voiced the full support of the ACIP to the plans outlined, and looked forward to the data.

Presentation on Coccidioidomycosis Vaccine

History/Burden of Disease

Dr. Rana Hajjeh of NCID's DBMD, provided background information on Coccidioidomycosis. Coccidioidomycosis is caused by inhalation of spores of Coccidioides immitis, a dimorphic fungus which is endemic in the southwestern U.S., Central and South America. About 40% of infected person develop symptomatic disease ranging from extended flu-like symptoms to severe pulmonary disease to disseminated extrapulmonary disease (meningitis).

Infection provides lifelong immunity, making it a good vaccine candidate. Various groups in endemic areas seem to be at increased risk of disseminated disease (e.g., African-Americans, Asians, as well as third-trimester pregnant women and the immunocompromised). However, there have been no systematic epidemiologic studies to clearly defined these risk factors. With the California State Health Department, CDC developed a standard surveillance case definition which was accepted by CSTE. It includes both lab and clinical criteria.

Coccidioidomycosis is a reportable disease in the southwestern U.S. In a California epidemic in the early 1990s, rates reached up to 14 per 100,000, mostly in the Central Valley/Bakersfield/Kern County area. The epidemic was attributed to environmental conditions, most likely severe dry weather followed by extremely heavy rains in 1990-1991, and another outbreak after the Northridge earthquake in 1994.

CDC conducted active surveillance in Kern County (population, 600,000) with the state health department, revealing 486 cases in a single year, of which 19% required hospitalization. Rates in non-whites were elevated: three times for Filipinos (255/100,000) and double for African-Americans (104/100,000). A concurrent case-control study also explored the risk factors for severe pulmonary disease (diabetes, smoking) and for disseminated disease (African-American race). Hispanic ethnicity, originally thought a major risk factor, was not found associated with high risk; it was most likely due to higher exposure (e.g., agriculture occupational exposure). However, the Filipino/African-American link in focal counties could indicate justification for vaccine.

In 1996, CDC reviewed Arizona's surveillance data from 1980-1998, which indicated a gradual increase in the number of cases reported. Higher risk groups included the elderly (a 3-fold higher incidence). These may be new residents moving in, because a multivariate analysis found the highest risk among those who are residents for <4 years. Underlying conditions common in the elderly (congestive heart failure, diabetes, cancers) are also risk factors. HIV-infected persons and those with AIDS had about 100 times the incidence of the general population (almost 47/1,000).

No formal cost studies are yet available, but an estimated $45 million was spent on hospitalization and outpatient care in Kern County from 1991-1993, and Arizona spent an estimated $19 million on coccidioidomycosis-related hospital admissionsin 1993 alone. Their average estimated cost per hospitalization was $24,000 for an average 10-day stay.

In summary, Dr. Hajjeh defined as groups potentially benefiting from a coccidioidomycosis vaccine counties with high rates of diseases and high-risk populations, and military personnel (many training bases are in the southwestern deserts). Coccidioidomycosis also is listed as a biological warfare agent, potentially used in bioterrorism.

Epidemiology of Coccidioidomycosis
Dr. George Rutherford, of the University of California/San Francisco and and formerly the California state epidemiologist, reviewed the epidemiology of coccidioidomycosis. He expressed his belief that the burden of this disease has been severely under-reported and that coccidioidomycosis is a major public health problem.

Some of the earliest data on coccidioidomycosis comes from an early prevention trial by the Army/Air Force in the early 1940s. German POWs in an adjacent camp were used as controls in an experiment on paving Kern county to reduce dust exposure. The Germans demonstrated a 10% skin test conversion in the 6 months before they were moved out.

An estimated 30 million U.S. residents, military personnel and tourists are at risk of coccidioidomycosis, as well as a substantial population in northwestern Mexico. An estimated 100,000 new infections occur annually, and 4,000 cases of disseminated disease. This is also a significant factor in the veterinary market, posing a problem among pets (dogs, cats), livestock, and horses).

Prevention strategies to date have included dust control, paving, occupational controls (HEPA filters), fungiciding soil, early recognition and therapy of primary infection, and a possible vaccination strategy. A vaccine developed by the Navy in the 1930s protected against death in mice and monkeys at a dose of 35 mg/kg, but the maximum tolerable dose in adult males was set at 0.08. An RCT in 1980-85 of a whole formalin-inactivated spherule vaccine was found to be ineffective.

Valley Fever is a clinical form of coccidioidomycosis. The Valley Fever Vaccine Project seeks to identify antigens sufficiently immunogenic in vivo and in vitro for use to develop a candidate subunit vaccine to prevent clinical manifestations of infection with coccidioidomycosis in humans, and to develop/test a candidate vaccine through Phase III trials (C. immitis is a Biosafety Level 3 agent). The project involves 5 investigators and several funding partners to develop a vaccine program. Work is currently in the antigen discovery phase (all cell-wall associated spherule phase) and is well funded at $10-15 million.

The activities in FY99-2000 are to identify and characterize the immunogenic antigens and do selective sequencing; test antigens and antigen combinations in mice with intranasal challenges; continue work on basic human immunology; develop a primate model; design an incidence and natural history study; move to trials of antigen and antigen combinations in larger mammals (eventually humans); conduct cost and feasibility studies; prepare a 5-year project proposal that includes human Phase I, II trials; and hire a full-time project manager with industry and regulatory experience.

Discussion. Dr. Rabinovich asked about any participation interest expressed by a manufacturer or the military. Dr. Rutherford reported their representation on the project's advisory committee (Merck, North American Vaccine, and Wyeth), but the group is still trying to interest a manufacturer. They are developing a business plan with cost-effectiveness data based on current cost-effectiveness studies and modeling.

Dr. Jackson asked the role of the Santa Ana winds, which blow off the desert. Dr. Rutherford confirmed were blowing at the time of the Northridge outbreak, an area of formerly very low endemicity. In fact, a U-2 photo has been released showing an immense cloud of dust over the county, which produced 250 cases of symptomatic infections.

Closing Comments
With no further comments, Dr. Modlin thanked all the attendees, and the meeting adjourned at 2:38 p. m.

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

John F. Modlin, M.D., Chair

3 Feb 2000

Date