DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

CENTERS FOR DISEASE CONTROL AND PREVENTION

Minutes of Meeting

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

February 9 & 10, 1995

Atlanta, Georgia

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
Centers for Disease Control and Prevention
February 9-10, 1995 - Auditorium A

FEBRUARY 9

8:30 AM	**Introduction**	**Dr. J. Davis** **Dr. D. Snider**
9:00 AM	**Recommendations for Prevention of Hepatitis A: Hepatitis A Vaccine and Immune Globulin**	**Dr. C. Shapiro**
10:00 AM	**BREAK**	
10:30 AM	**Revised Recommendations for Hepatitis B Vaccination**	**Dr. H. Margolis**
11:30 AM	**Vaccines for Children**	**Dr. S. Hadler**
	Influenza Vaccine in VFC	**Dr. H. Margolis**
	Hepatitis B for Adolescents in VFC	**Dr. S. Redd**
	Hepatitis A	**Dr. W. Williams**
	MMR2 - Expanded Use in VFC	
12:30 PM	**LUNCH**	
1:15 PM	**Revised Plague Recommendation**	**Dr. K. Gage**
2:00 PM	**Update on Varicella Vaccine**	**Dr. C. Hardegree** **Dr. S. Holmes**
2:15 PM	**Pneumococcal Polysaccharide Vaccine**	**Dr. R. Breiman** **Dr. J. Butler**
3:30 PM	**BREAK**	
4:00 PM	**Update on Simplification**	**Dr. J. Gindler**
4:30 PM	**Poliomyelitis Prevention**	**Dr. B. DeBuono** **Dr. K. Stratton** **Dr. R. Sutter** **Dr. M. Wharton**
6:00 PM	**ADJOURN**	

FEBRUARY 10

8:15 AM	**Influenza**	**Dr. N. Arden**
	1995-96 Influenza Vaccine Strain Selection	**Dr. B. Chen**
	1995-96 Influenza Vaccine and Antiviral Recommendations	**Dr. N. Cox** **Dr. P. Glezen**
	Influenza-Associated Morbidity During Pregnancy	**Dr. M. Miller**
	Assessment of GBS Risk Associated with 1993-94 and 1994-95 Influenza Vaccination	**Dr. R. Strikas**
	Optimal Needle Length for IM Injection Into The Deltoid	
	National Estimates of Influenza Vaccination Rates	
10:15 AM	**BREAK**	
10:45 AM	**Adolescent Vaccination**	**Dr. W. Williams**
11:45 AM	**Acellular Pertussis Vaccine Trials Update**	**Dr. P. Strebel**
12:00 PM	**LUNCH**	
12:45 PM	**Report of a Meeting Regarding Conflicting Immunization Guidelines**	**Dr. N. Halsey**
	Harmonization of ACIP/AAP Recommendations with FDA Labeling	**Dr. S. Hadler** **Dr. M. Wharton**
	Status on Principles and Guidelines for Combination Products	
1:45 PM	**Update on Meningococcal Recommendation**	**Dr. J. Wenger**
2:15 PM	**Recommendations for Immunization Linkage with WIC**	**Dr. E. Maes**
2:45 PM	**Vaccine Safety**	**Dr. B. Chen** **Dr. P. Rhoades** **Dr. S. Rosenthal**
3:15 PM	**Injury Compensation Update**	**Mr. T. Balbier** **Dr. G. Evans**
3:30 PM	**National Vaccine Program Update**	**Dr. R. Widdus**

4:00 PM Public Comment

4:15 PM ADJOURN

ATTENDEES:

Committee Members
Dr. Jeffrey Davis (Chair)
Dr. Barbara Ann DeBuono
Dr. Kathryn Edwards
Dr. Marie Griffin
Dr. Fernando Guerra
Dr. Neal Halsey
Dr. Rudolph Jackson
Dr. Steve Schoenbaum
Dr. F. Thompson
Dr. Joel Ward

Ex Officio Members
Dr. Geoffrey Evans, (VICP)
Dr. Carolyn Hardegree (FDA)
Dr. G. Rabinovich (NIAID)
Dr. Jerry Zelinger, (HCFA)

Liaison Representatives
Dr. William Buttler (DOD)
Dr. Richard Clover (ATPM)
Dr. Thomas Copmann (PhRMA)
Dr. David Fleming (HICPAC)
Dr. Stanley GA (ACOG)
Dr. Pierce Gardner (ACP)
Dr. William Blezen (IDSA)
Dr. Caroline B. Hall (AAP)
Dr. Edward Mortimer (AMA)
Dr. Kristin Nichol (VA)
Dr. Georges Peter (AAP)
Dr. William Schaffner (AHA)
Dr. David Scheiffle (NACI)
Dr. R. Widdus (NVP)
Dr. Richard Zimmerman (AAFP)

Acting Executive Secretary
Dr. Dixie Snider

Office of the Director
Dr. Alan Hinman

Attendees Continued:

Office of the General Counsel
Mr. Kevin Malone

Office of Public Affairs
Barbara Reynolds

CDC Clinic
Greg Kasting

National Center for Infectious Diseases
Dr. Miriam Alter
Dr. Joseph Breese
Dr. Robert Breiman
Dr. Ken Gage
Dr. Frank Mahoney
Dr. Harold Margolis
Dr. Helen Regnery
Dr. Craig Shapiro
Dr. Ted Tsai

National Center for Prevention Services
Jennifer Cleveland
Rosamond Dewart

National Immunization Program
Dr. William Atkinson
Dr. Francisco Averhoff
Dr. Siiri Bennett
Dr. Bob Chen
Dr. Steve Cochi
Dr. Jose Cordero
Dr. Vance Dietz
Dr. Elias Durry
Dr. Marc Eiseman
Dr. Gary Euler
Judy Gantt
Edith Gary
Dr. Jacqueline Gindler
Dr. Steve Hadler

National Immunization Program

Dr. Iain Hardy
Rafael Harpaz
Dr. Sandra Holmes
Dr. Sonja Hutchins
Hector Izurieta
Dr. Alan Kendal
Martha Mayfield
Dr. Mark Miller
Dr. W. Orenstein
Dr. Steve Reef
Dr. Susan Reef
Dr. Steve Rosenthal
Linda Schultz
Lone Simonsen (Orkand)
Dr. Robert Snyder
Dr. Peter Strebel
Dr. Ray Strikas
Dr. Roland Sutter
Dr. Frederick VanLoon
Dr. Walter Williams
Dr. Melinda Wharton

Navy Environmental Health Center
Ben Mitchell

National Vaccine Injury Compensation Program
Leslie Ball

National Vaccine Program Office
Dr. Joel Breiman

Food and Drug Administration
B.F. Anthony
Dr. Karen Goldenthal
Phil Krause
Karen Midthun
Dr. Peter Patriaraca

Health Care Financing Administration
Jerry Zellinger

Others Present

Sherman Alfors, Glaxo
S.M. Arnold, SmithKline Beecham
Paul Bolton, Johns Hopkins University
Dr. Dee Breeden, S.C. Department of Health and Environmental Control
Jill Chamberlin, Vaccine Bulletin
Todd Cooper, Ogilvy
Paul Coplan, Merck
Ben P. Daugherty, SmithKline Beecham Pharmaceuticals
Dr. Ruth Ann Dunn, Michigan Department of Public Health
Amy Furrar-Roff, Slack Inc.
Paula Goldberg, SmithKline Beecham
Dan Granoff, Biocine Corp.
Jesse E. Greene, R.N., S.C. Department of Health and Environmental Control
Dr. Jill Hackell, Lederle-Praxis Biologicals
Valerie Hayes, Merck & Co.
Kaenan Hertz, Macro International

Attendees Continued:

Others Present

Barbara Howe, SmithKline Beecham
Clare Kahn, SmithKline Beecham
Foong-Khwantiew, Merck Vaccine Division
Bernie King, Connaught Labs
Robert Kohberger, Lederle-Praxis Biologicals
Dr. David Drause, SmithKline, Beecham
Toni Krzesowski, Parke-Davis
Barbara Kuter, Merck & Co., Inc.
Lucinda Long, Lederle-Praxis
Brian A. Lortie, SmithKline, Beecham
Charles Marwick, Journal of the American Medical Association
Carol McPhillips-Tangum, Prudential Center for Health Care Research
Paul Mendelman, Merck Research Laboratories
Dr. Carlton Meschievitz, Connaught Laboratories
Wayne Morgers, AMVAX
Dr. David Nalin, Merck Research Laboratories
Chris Nuncio, Parke-Davis
Peter Paradiso, Lederle-Praxis
Stan Plotkin, Pasteur-Merieux-Connaught
Rhea Pridgen, Eastman Kodak Co.
Eileen Provost, Connaught Labs
Frederic E. Shaw, M.D., J.D., Health Policy Group
Judith Shindman, Connaught Laboratories, Ltd.
Dan Soland, SmithKline Beecham
Dale Spriggs, VRI Inc.
Joseph Sullivan, Merck Vaccine Division
Ron Thiboutot, Wyeth-Ayerst
Miriam Tucker, Pediatric News
Thomas Vernon, Merck Vaccine Division
Wanda Warner, SmithKline Beecham
David West, Merck Laboratories
Dr. Jo White, Merck Research Laboratories
Edward Zitoi, Wyeth-Ayerst Research

Attendees Continued:

National Immunization Program
Dr. Iain Hardy
Rafael Harpaz
Dr. Sandra Holmes
Dr. Sonja Hutchins
Hector Izurieta
Dr. Alan Kendal
Martha Mayfield
Dr. mark Miller
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Ben P. Daugherty, SmithKline Beecham Pharmaceuticals
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Paula Goldberg, SmithKline Beecham
Dan Granoff, Biocine Corp.
Jesse E. Greene, R. N., S. C. Department of Health and Environmental Control
Dr. Jill Hackell, Lederle-Praxis Biologicals
Valerie Hayes, Merk & Co.
Kaenan Hertz, Macro International

ACTION ITEMS

Comments on the hepatitis A recommendation are due to Gloria Kovach by February 23.

Comments on the Hepatitis B recommendations are due no later than March 3. The program will provide a revised document to the committee by march 31, and comments on this revised document will be due to Gloria Kovach by April 21.

Comments on the varicella recommendation mailed to the Committee on January 26, are due to Gloria Kovach by February 17.

March 15 is the deadline for comments on the Plague recommendation.

Provide comments on the proposed working on "Influenza Vaccination of Persons with a History of GBS" and "Proposed Revision: Side Effects and Adverse Reactions ACIP Influenza Vaccine Recommendations, " by February 24.

Also due on February 24 are comments on needle length for influenza vaccination.

The assessment of adult immunization article for the MMWR should be commented on by February 17.

By February 24, comments should be submitted on the IOM statement for the MMWR.

Comments are due on March 3 for the adolescent statement.

March 3 is the due date for comments on the draft statement, "Prevention and Control of Serogroup C Meningococcal Disease: Evaluation and Management of Outbreaks." A revised draft will be mailed to the Committee by March 10, and any additional comments are to be submitted back to Gloria Kovach by March 24.

Comments are due by March 17 on the discrepancies between package inserts and ACIP recommendations.

A working group was formed to address pneumococcal immunization for adults. The members and consultants are: Dr. S. Schoenbaum (Chair), Dr. R. Clover, Dr. P. Gardner, Dr. M. Griffin, Dr. F. Buerra, Dr. P. Mendelman (Merck), Dr. K. Nichol, Dr. W. Schaffner, and Dr. J. Ward. Final comments on this recommendation are due March 3.

Be sure to mark the calendars that were in your notebooks with the days you are not available to attend an ACIP meeting and return the calendars to Gloria Kovach no later than March 1.

Advisory Committee on Immunization Practices
Meeting Minutes

February 9-10, 1995

The Advisory Committee on Immunization Practices (ACIP) convened at 8:30 a.m. on February 9, 1995 at the Centers for Disease Control and Prevention (CDC) in Atlanta. Dr. Jeffrey Davis, ACIP chairperson presided.

Dr. Dixie Snider, the Acting Associate Director for Science at CDC and ACIP Executive Secretary, welcomed new liaisons including Dr. Jerry Zelinger, Health Care Finance Administration (HCFA), and Dr. Stanley Gall, American College of Obstetricians and Gynecologists. He also welcomed Dr. Roy Widdus representing the National Vaccine Injury Compensation Program.

Dr. Davis congratulated Dr. Barbara Ann DeBuono on her appointment as the new Commissioner of Health for New York State and Dr. Richard Clover on his appointment as the Chairman and Professor of the Department of Family and Community Medicine at the University of Louisville.

The committee members were asked to fill out a scheduling calendar for future meetings of the ACIP meetings in 1996.

A working group consisting of Dr. Joel Ward, Dr. Neal Halsey, and Dr. Jeff Davis was appointed since the last meeting to work with Dr. Roger Glass and his staff on rotavirus vaccine recommendations. There will be a meeting in October prior to the ACIP meeting to discuss this.

ACIP members who may have a potential conflict of interest were asked to make it know. All members, regardless of a potential conflict, may participate in discussions of all issues provided they fully disclose any potential conflict. However, those persons cannot vote on any issue related to the potential conflict.

Dr. Joel Ward reported no financial interest in any pharmaceutical companies. His salary is derived entirely from the University of California, County of Los Angeles, and the REI Institute. He has not received any honoraria in excess of one thousand dollars. As Director of the UCLA Center of Vaccine

Research, he acknowledges the Institute does receive grants from SmithKline Beecham and Merck & Company Inc. and understands this represents a potential conflict.

Dr. Kathryn Edwards reported no financial interest in any vaccine manufacturing or manufacturing companies. She is currently conducting research at Vanderbilt University which is funded by Biocine-Sclavo. She is a consultant for SmithKline Beecham. She has given speeches with honoraria of less than a thousand dollars from Lederle and Connaught.

Dr. Fernadnado Guerra, Director of Health for the City and County in San Antonio, reported no financial interests with any companies manufacturing vaccines. He is presently serving as a co-principal investigator for a field trial with acellular pertussis vaccine for young infants which is manufactured by the HailVax Company. This study will be completed within the next several contractor which conducts occasional site visits for the CDC to assess immunization coverage levels in community and migrant health centers.

Dr. Neal Halsey reported no direct financial interest in any vaccine manufacturer. He has received a small portion of salary support from SmithKline Beecham to study the hepatitis B vaccine. He is currently serving on a data and safety monitoring committee for SmithKline Beecham regarding a Lyme disease vaccine trial. He has also entered into a verbal agreement with Connaught Laboratories to tentatively serve on the data and safety monitoring committee with regard to pneumococcal vaccine. He asked if serving on data and safety monitoring committees represents a conflict of interest. Dr. Snider said it did not represent a conflict of interest.

Dr. Rudolph Jackson, Professor of Pediatrics at Morehouse School of Medicine, reports his entire salary is derived from the Morehouse School of Medicine. He has no financial interest to report, nor any consultancies to report.

Dr. Stephen Schoenbaum, Harvard Community Health Plan, reports no potential conflict of interest. He reports his wife owns stock in Abbott Laboratories, Amgen, Bristol Meyers Squibb, Glaxo, and Merck Sharpe & Dohme.

Dr. Marie Griffin reports no financial interest in any of the vaccine manufacturing companies. She also reports no consulting with honoraria greater than one thousand dollars. *Dr. Griffin later recalled consulting for Wyeth. She disclosed this to legal counsel and withdrew her vote on influenza.

Dr. Jeffrey Davis, Chief Medical Officer and State Epidemiologist for Communicable Diseases with the Wisconsin Division of Health, reports no potential conflicts of interest.

Following the disclosure of potential conflicts of interest introductions were made.

Recommendations for Prevention of Hepatitis A: Hepatitis A Vaccine and IG - Dr. Craig Shapiro

Dr. Craig Shapiro discussed the draft recommendations for the prevention of hepatitis A. Dr. Davis stated the licensure of the vaccine may occur soon. To impact this disease in the United States, routine childhood immunization would be desirable. However, further immunogenicity data among infants and the development of combination vaccines are necessary for routine childhood immunization. Until then, the recommendations will represent essentially a targeted approach focused on persons living in areas with high endemic rates of hepatitis and on other recognized risk groups. The recommendations are organized into three sections: a section on pre-exposure prophylaxis against hepatitis A, a section on the use of hepatitis A vaccine or IG in ongoing outbreaks, and a section on postexposure prophylaxis against hepatitis A.

Recommendations for Hepatitis A Vaccine and IG in Travelers

The recommendations for the use of hepatitis A vaccine or IG in travelers were first addressed. The recommendations are for persons traveling or working in countries with high endemicity of infection. for travelers, the recommendation is to receive either vaccine or IG. The vaccine is preferred. IG should be used for infants if they are traveling. Vaccinated travelers can be assumed to be protected four weeks after receiving the initial vaccine dose. Since protection from the vaccine does not occur immediately after the vaccination, travelers who are departing in less than four weeks should be administered vaccine and IG. If practitioner or traveler wish to use IG alone, dosage

recommendations are presented. Recommendations pertain to travel to intermediate and high prevalence countries. Use of vaccine of IG is not recommended for travel to low risk countries or regions such as Canada, Australia, New Zealand, Japan, Western Europe, and Scandinavia.

The interval of four weeks was based on immunogenicity data among vaccine recipients four weeks after an initial vaccine dose was administered which shows 99%-100% of persons have detectable antibodies against hepatitis A virus (anti-HAV). Thus, a conservative approach would be to use IG in addition to hepatitis A vaccine for persons beginning travel to endemic areas less than 4 weeks after the initial vaccine dose.

A suggestion was made to consider demographics as a possible factor. Persons who travel once to high or intermediate risk countries may be more inclined to travel to such countries again. Therefore, it would be prudent to protect this population with vaccine and IG prior to the initial trip and on future travels ensure their protection is adequate.

FDA has requested that when ACIP recommendations like this are based on expert opinion and not on data, this point should be clarified in the recommendation. This clarification will be made in the statement.

A concern was expressed on behalf of the American Academy of Pediatrics regarding short term travel. It is unclear exactly who should be getting either vaccine or IG. Thus, the AAP encourages the incorporation of consideration of the interval of travel and type of risk exposure.

Recommendations for the use of vaccine in communities that experience outbreaks and that overall have a high rate of hepatitis A:

Previous drafts have included provisions for the use of hepatitis A vaccine in American Indian reservations, Alaska Native villages, and certain religious communities. Characterizations and classifications have been established to provide more guidance in defining communities classified as having highly endemic hepatitis A (Type 1) and communities of intermediate endemicity (Type 2).

In type 1 communities, rates of hepatitis A during outbreaks are higher than rates in type 2 communities. In addition, cases generally occur among young children and not adults. In type 2 communities, cases occur among both children and adults. The recommendations as written are to prevent outbreaks in these communities by routine vaccination of children living in such communities, beginning at the earliest age when the vaccine has bee shown to be immunogenic. To effectively prevent these epidemics, it is also recommended that vaccination of older children should be accomplished within five years of initiation of the childhood vaccination program.

A suggestion was made and approved to define the communities by their description rather than by a number.

A decision was made to include recommendations for vaccination of groups having established higher risks of infection compared to control populations including homosexual men, injecting drug users, non-injection street drug users, certain persons at occupational risk, and persons with chronic liver disease.

A concern regarding the sexual spread of hepatitis A virus was expressed. The committee felt the outbreaks that occur among homosexual and bisexual men and the elevated seroprevalence of anti-HAV observed in studies of homosexual men compared to heterosexual men are due not to sexual transmission but fecal oral transmission. A suggestion was made to write a simple and straightforward recommendation about giving hepatitis A vaccine to a patient who is using or suspected of using drugs.

Although it is understood that the licensure of hepatitis A vaccine is for persons two years and older, the addition of language encouraging the generation of additional data on children under two years old was recommended and approved.

In listing communities, it was requested that the Hispanic, Latino, and particularly the Mexican-American communities be addressed specifically, and that seasonal migrant farm workers be considered.

Recommendation for using the hepatitis A vaccine in outbreak settings:

It is believed most hepatitis A in the United States occurs in large community wide outbreaks. In Alaska and New York State,

widespread vaccination of children in this type of community has rapidly decreased the number of cases. Based upon this experience, the routine use of hepatitis A vaccine among children in type 1 communities with ongoing outbreaks is recommended. Catch-up vaccination of older children should be based on local epidemiologic features.

The committee felt type 2 communities could benefit from the vaccine. It was suggested a more permissive statement be considered to facilitate use of vaccine by health departments that wanted to use it to control an ongoing community outbreak.

CDC was asked to comment on a pilot project being conducted in Butte County, California involving vaccination in several schools and focused on children from ages two through eleven years. The first round of vaccination will not be complete for several months.

The need for recommendations for using hepatitis A vaccine in the food service industry was discussed and the issue of foodhandlers was addressed. The food service industry is complex with many different levels of workers. Often the entry level foodhandlers come from parts of the world where the basic personal hygiene is typically poor. Foodhandlers with poor personal hygiene can potentially place many people at risk by their handling food products. A suggestion was made that the vaccine be used in postexposure situations rather than using IG. Others suggested the use of both IG and vaccine in these instances. The committee suggested developing a specific section which addresses foodhandler-related concerns to provide concise and comprehensive guidelines specific to this industry.

A suggestion was made for the inclusion of a statement that gloves might be an effective protective barrier, but to avoid a categorical statement which infers that wearing of gloves alleviates risk.

Restrictive language in the package insert may prohibit the simultaneous use of hepatitis vaccine with other killed antigens or other live antigens. In cases lacking data to sufficiently address simultaneous use the general recommendations will be referenced.

A large study in German travelers has found no interference

following simultaneous administration of hepatitis A vaccine and a variety of other vaccines. It was recommended that the promotion of reporting adverse instances be addressed in the statement.

Recommendations for outbreaks in other settings:

Hepatitis A outbreaks in other settings such as day care centers, hospitals, schools, and institutions can occur. The frequency is not high enough to warrant routine hepatitis A vaccination of persons in these settings. IG has been shown to be effective in controlling the outbreaks and, therefore, IG should be used. The role of using hepatitis A vaccine to control and prevent these outbreaks has not been investigated.

A suggestion was made to include a statement in the postexposure prophylaxis section to give IG in addition to hepatitis A vaccine to attendees and staff in day care centers where an outbreak has been recognized.

A suggestion was made to include a statement about the continued need for IG during day care center outbreaks since hepatitis A vaccine is licenses only for children age two years and older.

Postexposure Prophylaxis:

Recommendations regarding use of IG for postexposure have been essentially restated in the current statement. IG is recommended for all persons who have household or sexual contact with a person with confirmed hepatitis A. The language regarding IG use for foodhandlers and also the considerations for using IG among patrons of food establishments where a foodhandler with hepatitis A is identified is included verbatim from the 1990 recommendations. The recommendations for use of IG in hospitals, schools, and work settings are the same as the 1990 recommendations but the language is condensed.

The committee recommended that in the section on pre-exposure prophylaxis, consideration could be given to using hepatitis A vaccine in persons who receive IG for any reason.

Regarding day care centers, the committee recommended clarification that IG modified illness but did not prevent infection while vaccination prevents infection and the addition

of a paragraph about using hepatitis A vaccine combined with IG when IG is used to control these outbreaks. It was acknowledged there has been a shortage of IG due to extensive use of IG by the Department of Defense in the deployment of troops. concerns about the overuse of Ig in day care centers were voiced. Clarification of who would need to receive IG during an outbreak was added to the draft language. A desire to have a section devoted to day care centers was expressed to facilitate a concise and complete recommendation.

Representatives of vaccine companies stated they have been working closely with the FDA and with the CDC in developing the use indications for licensure which, for the most part, closely reflect the draft recommendations so far. Data are being collected regarding vaccination of persons with chronic liver disease. Data regarding use of hepatitis A vaccine to help control communitywide outbreaks, specifically from the experience in the Alaska villages, has not been submitted as part of the NDA, but will be submitted shortly after licensure. There will be a few discrepancies between ACIP recommendations and the package insert indications regarding travelers, homosexual men, and injection drug users.

Currently, 2 doses of vaccine are recommended for those over age 18 years; a 3 does schedule is recommended for children. The committee requested the evidence which pertains to the need for a third dose.

There are studies showing a two does vaccination schedule in children using 720 units per dose instead of 360 unites results in one hundred percent immunogenicity.

The need for immunogenicity data in the draft proposal was discussed. It will be included.

A new section has been added about surveillance for hepatitis A. The committee was asked if it wished to recommend surveillance practices. Promotion of the reporting of adverse events should be encouraged since there is little experience with this vaccine.

Update on Varicella Vaccine

Development of the varicella statement began in the 1980's and has evolved for some time. Dr. Sandra Holmes was complimented on

her excellent work on this statement.

Dr. Carolyn Hardegree of the FDA stated the license application for this product was filed with the FDA in May, 1993. And update on the status of the review of the application was provided to the Vaccines and Related Products Advisory Committee at FDA on January 27. Information on duration of response was presented. This data was based on materials submitted to FDA in late December, 1994. Included was information on children who had been actively followed. Data on the simultaneous use of varicella vaccine with other vaccines remains incomplete but additional data on simultaneous use with MMR have been received, while data on use with acellular DPT vaccine, OPV, and Hib is still very limited.

Dr. Jo White, Merck Research Laboratories, updated the committee on the lots proposed to be distributed after licensure. They contain around 3000 PFU's, per dose. Data was presented on children actively followed up that have received vaccine from the lots to be marketed. In the first year after vaccination a very low break-through rate, 0.6%, was observed. In those who had break-through infection the cases were mild. In the second year of follow up, the break-through rate was still very low. Adults have also been actively followed. These individuals received two doses eight weeks apart. Break-through rates in these individuals were very low as well.

A Committee member requested information regarding whether it is likely, given the storage requirements for this vaccine, that the vaccine effectiveness will approach the efficacy noted in the clinical trials. Merck has educated physicians and family practitioners about the necessity of freezing this product for storage and using it within 30 minutes of reconstitution.

Active surveillance for varicella involved three sites in full operation: West Philadelphia, Travis county, Texas, and a section of Los Angeles County. Case reporting began in December and January and information should be forthcoming next year.

Comments and language modification recommendations to a draft proposal need to be returned so a final draft can be completed in preparation for licensure. Members were urged to return these to Dr. Sandra Holmes no later than February 17, 1995.

Disclosure was provided by members arriving after the meeting had commenced. Dr. Barbara Ann DeBuono, M.D., Commissioner, State of New York Department of Health, reports no potential conflicts of interest.

Dr. Fred E. Thompson, Jr., M.D., state Health Officer Mississippi State Department of Health, reports no potential conflicts of interest.

Vaccines for Children - Dr. S. Hadler, Dr. H. Margolis, Dr. S. Redd, and Dr. W. Williams

ACIP is charged with the responsibility for determining the vaccines, schedules, dosages, and contraindications for vaccines used in the Vaccines for Children Program. Vaccines have been recommended to prevent measles, mumps, rubella, diphtheria, tetanus, pertussis, polio, hepatitis B, and Hib infections. Issues today involve four vaccines: Influenza vaccine for high risk groups, expanding MMR dose 2, hepatitis B vaccine for adolescents and for high risk children, and discussion of recommendations for hepatitis A vaccine, although this vaccine has not been yet licensed.

Dr. Walter Orenstein updated the Committee on the status of the Vaccines for Children Program (VFC). It is operational in 49 states and the District of Columbia. A number of states have utilized existing VFC provisions to purchase vaccines at federal contract prices and protect many children. Currently, contracts exist for all of the vaccines the ACIP has recommended for VFC purchase; for most vaccines for which there is more than one manufacturer there are contracts with multiple manufacturers.

During the June 1994 ACIP meeting, the working group on Vaccines for Children made a proposal to the full committee recommending influenza vaccine for persons in high risk groups should be added to the VFC Program in fiscal 1996. This measure passed 5 to 1 with the stipulation that precise groups to be included in the VFC program would be determined by a separate vote in 1995.

The ACIP recommendations for children who are recommended to receive influenza vaccination include those with chronic disorders of cardiovascular and pulmonary systems including

asthma; those who have required regular medical follow up or hospitalization during the preceding year because of chronic metabolic diseases such as diabetes mellitus, renal disfunction, hemoglobinopathies, or immunosuppression; children who are receiving long term aspirin therapy and therefore may be at risk of Reye Syndrome after influenza infection; and children in households with high risk persons.

The Committee was asked to consider the following language for addition to the recommendations for the Vaccines for Children Program. The proposed language to be voted on was:

Option 1

The ACIP recommends influenza vaccination of children less than or equal to eighteen years of age in high risk groups as described in the ACIP recommendations of May 27, 1994 be added to the VFC Program effective in September 1995. Children who are household contacts of high risk persons but are not themselves at high risk of influenza will not be eligible for influenza vaccination.

Option 2

The ACIP recommends influenza vaccination of children less than or equal to eighteen years of age in high risk groups as described in the ACIP recommendations of May, 1994 including those who are household contracts of persons at high risk of influenza infection be added to the VFC Program effective in September, 1995.

The options were discussed with regard to the potential cost, lack of clear effectiveness, lack of data on vaccine effectiveness in some of these groups, implementation issues, and the intent of the legislation to vaccinate children.

The options were then brought to a vote. Those having interest in Wyeth-Ayerst Laboratories, Connaught Laboratories, Parke Davis, and Evans Medeve from the UK distributed by Adams Labs in the United States were asked to abstain from the voting.

Dr. DeBuono made a motion that Option 1 be adopted by ACIP. Dr. Ward seconded that motion. The motion carried with 7 in favor (Davis, Ward, Halsey, Schoenbaum, Griffin, Thompson, and

DeBuono), one opposed, two abstained.

Dr. Steve Redd discussed vaccination with a second dose of MMR vaccine for more than one cohort of children. In June 1994, the ACIP voted to expand VFC coverage for second dose MMR to one full age or grade cohort, and to cover children who were already required under existing state laws or regents policies to be immunized with second dose MMR. There was discussion about whether a second cohort of children should be included to speed up full implementation of the ACIP recommendations that school age children receive two doses of MMR vaccine.

The language to be voted on was stated as:

> The ACIP recommends the VFC Program for FY 1996 provide second dose MMR for:
>
> (a) All eligible children in cohorts included in the FY 1995 statement who have not been previously received the second dose including any required by state laws, or state university, or college regent policies to receive a second dose of MMR or measles vaccine prior to attendance in schools or college and
>
> (b) one additional cohort for a total of two cohorts, birth or grade cohorts or equivalent of children who are less than or equal to eighteen years of age. For example in FY 1996 children entering kindergarten and children entering seventh grade could be covered. In the following year kindergarten and first grade students, and seventh and eighth grade students could be covered. In addition all children who are required by state laws, or state university, or college regent policy to receive a second dose of MMR or measles vaccine prior to attendance in schools or colleges will be covered.

The need to clarify this language resulted in a delay in the voting until after a final written draft of the proposal could be reviewed by the committee.

Dr. Margolis presented the recommendations for hepatitis B

vaccine. There are two new items in the current recommendation. One focuses on catch up vaccination of children at high risk of infection. It states:

> All children less than eleven years of age residing in households of Pacific Islanders or first generation immigrant refugees from countries where HBV infection is of high or intermediate endemicity should be routinely vaccinated with the age appropriate vaccine dose and schedule.

Further discussion to clarify specific issues followed:

For the purposes of VFC a contract already exists for hepatitis B vaccine, the question is when does this become implementable? The ACIP proposes for the purposes of VFC that implementation not occur until the recommendation is published in the MMWR.

The recommended dosages and schedules were provided in tables 1 and 2 on a handout from the new statement. For the purposes of the resolution it is interpreted to mean children born after October 1, 1983.

This language considered for this vote supersedes language of the previous VFC recommendation on high risk children approved in June, 1994. There are approximately one million children in this age group. It is anticipated they will not be vaccinated in one year. Based on rough estimates of the number of persons who might be vaccinated each year and the current contract price, the estimated costs associated with this recommendation are about 32 million dollars a year.
Dr. Margolis explained that a map will also be included in the new hepatitis B recommendations, to clarify the statement regarding other refugees or immigrants from countries of high or intermediate endemicity.

Discussion of when a new recommendation becomes implementable for VFC purposes was considered with regard to two issues:

1. Whether there is a federal contract establishing a price to purchase vaccine. For influenza, there is no current contract that could be applicable before this fall. Work will begin to obtain getting estimates of vaccine needs from states and

developing a contractual agreement. With hepatitis B this is not an issue.

2. Whether the currently existing contract has a maximum number of doses stipulated which would accommodate the VFC needs. The group of individuals who would be effected by the implementation of the VFC recommendation would require the universal infant dose. The currently maximum doses supplied by the current contract are sufficient to accommodate this group. With the vote for adolescent vaccination, it would be possible to exceed the maximum number of doses of either the SmithKline infant formulation or the Merck adult formulation that are in the current contract.

Advantages of potentially beginning implementation with the new fiscal year were discussed regarding the public sector. There are a number of other children who need to be served who are not eligible for the VFC program. There will be a need to identify the funding and resources to cover children not eligible under the VFC program. There will be a need to identify the funding and resources to cover children not eligible under the VFC program but who would qualify for state vaccine. Otherwise we risk a two tiered system even within the public health structure.

The statement voted on was:

> The ACIP recommends hepatitis B vaccination of all children less than eleven years of age residing in households of Pacific Islander ethnicity or who are first generation immigrants or refugees from countries where HBV infection is of high or intermediate endemicity be included in the Vaccines for Children Program as described in the above paragraphs.

Dr. DeBuono moved that the recommendation be adopted. It was seconded by Dr. Guerra. The notion was carried with six in favor (Davis, DeBuono, Thompson, Griffin, Jackson, and Guerra), none opposed, four abstained (Ward, Edwards, Halsey, and Schoenbaum).

The following recommendation was discussed:

> All individuals not previously vaccinated with hepatitis B vaccine should be vaccinated at eleven to twelve years of age with the age appropriate dose of vaccine. The vaccination schedule should take into account the feasibility of delivering three doses of vaccine to this age group.

The recommendation was offered with the following footnotes for clarification:

> The implementation would be activated by publication in MMWR of the revised Hepatitis B vaccine recommendations.
>
> Recommended dosages are provided in tables one and two (appended) which are the tables in the new Hepatitis B vaccine recommendations.
>
> The intent of the recommendations is to achieve the vaccination of a single cohort of adolescents each year. Because vaccination of this age group may occur in settings other than clinics or providers offices, program providers can determine whether younger or older aged children or adolescents need to be included to achieve the intent of the recommendation. For example, if vaccination is carried out in the single grade of an elementary, middle school, or junior high school, all children in that grade would be eligible for inclusion regardless of their age.

Discussions about resources, cost, making ACIP recommendations versus funding the recommendations, and the rationale for vaccination of adolescents ensued among the committee.

Subsequently, Dr. Ward made a motion to put the following question to a vote. Dr. Guerra seconded. The statement read:

> The ACIP recommends hepatitis B vaccination of adolescents be included in the Vaccines for Children Program as follows:
>
> 1. For the purposes of VFC, implementation will not

occur until the revised Hepatitis B vaccine recommendation is published in the MMWR and until a contract to purchase the hepatitis B vaccine for adolescents has been completed.

2. The recommended dosage and schedules for hepatitis B vaccination of adolescents are shown in tables one and two (appended).

3. The intent of the recommendation is to achieve the vaccination of a single cohort of adolescents each year. Because vaccination of this age group may occur in setting other than clinics or providers offices, program providers can determine whether younger or older ages need to be included to achieve the intent of the recommendations. For example, if vaccination is carried out in a single grade of an elementary, middle school, or junior high school, all children in that grade would be eligible for inclusion irrespective of their age.

In favor (Davis, Griffin, Jackson, Guerra) opposed (DeBuono, Thompson) abstained (Ward, Edwards, Halsey, and Schoenbaum). The vote was 4 in favor, 2 opposed, 4 abstained. The motion carried.

The ACIP also considered whether the use of the Hepatitis A vaccine should be recommended for use in the Vaccines for Children Program.
Without the ACIP statement on recommendations for the use of Hepatitis A vaccine a committee member felt this discussion was premature and proposed to resume this discussion in the future.

The committee discussed several issues for consideration since hepatitis A vaccine could be licensed soon. In theory the contract related activity could begin and states could be solicited regarding how much vaccine states would use. Also considered was the fact the Indian Health Service would be dependent on the ability to purchase hepatitis vaccine through the VFC program. Another important consideration is that immune globulin is currently not readily available and the use of hepatitis A vaccine may be a mechanism for timely hepatitis A control. After further discussion, it was decided the committee would address whether hepatitis A vaccines should be included in the VFC Program after more data has been collected.

Consideration of this issue was postponed until the next meeting.

The committee returned to the issue of second dose MMR. The language of the recommendation was modified and now reads:

> The ACIP recommends that the VFC Program beginning in October, 1995 provide a second dose of MMR vaccine to (a) two cohorts (birth or grade cohorts of equivalent) of children less than or equal to eighteen years old and (b) all eligible children and cohorts previously covered by VFC, but who have not previously received the second dose, including any required by state laws or state university or college regent policies to receive a second dose of MMR or measles vaccine prior to attendance in schools or colleges.

Dr. Halsey moved that this recommendation be adopted. This was seconded by another committee member. Those is favor (Davis, Edwards, Guerra, Halsey, Griffin, and Jackson), opposed (Thompson), abstained (Ward, Schoenbaum), and absent (DeBuono). The motioned carried 6 to 1.

Revised Plague Recommendation - Dr. K. Gage

The formalin-inactivated plague vaccine recently has been relicensed and is now manufactured by Greer Laboratories. It is basically the same vaccine that previously was made by Cutter Laboratories.

A revised recommendation on the plague vaccines has been drafted to reflect the changes in the new vaccine. There are no recommendations made for persons under eighteen years of age. The previous recommendation, published in 1982, contained a dosage chart for children. This recommendation was removed because there are no safety or efficacy data available for persons under eighteen. Interest in plague vaccine has increased considerably after the reported outbreak in India and CDC has received numerous inquires about plague vaccines since that time.

The immunogenicity of the vaccine is relatively poor. The immunogenicity and efficacy data provided by Greer Laboratories indicates that fewer than 60 percent of the persons in their trial developed levels of antibodies that were considered

protective for mice. However, these individuals received only the initial injection of 1.0 ml of vaccine, followed one month later by another dose of 0.2 ml. The actual vaccine recommendations indicate that the primary immunization series should consist of an initial dose of 1.0 ml of vaccine and two subsequent doses of 0.2 ml at 1-3 months and 5-6 months, respectively. It is not known what percentage of individuals develop protective levels of plague antibodies after a third dose of the Greer Laboratories vaccine.

The adverse reaction data available for the Greer Laboratories vaccine also were derived from individuals receiving only the initial 1.0 ml dose of vaccine and a second injection of 0.2 ml at 3 days. It should be noted that previous reports indicate that the frequency and severity of reactions increase with the number of injections given. Unfortunately, antibody levels decrease relatively rapidly after immunization so that, within a matter of a few months after their last injection, persons are likely to require an additional booster dose to maintain what are considered to be protective levels of antibody. Based on our experience at CDC, persons who have been repeatedly vaccinated over a period of many years are often reluctant to be re-vaccinated because of increasingly severe reactions.

This vaccine has relatively limited applications. The recommendations are primarily for laboratory personnel and those who routinely work with potentially infectious animals. The latter would include individuals such as mammalogists who are likely to have contact with plague-infected rodents or handle animals infested with infected fleas. It should be noted that the vaccine's efficacy against aerosol or droplet transmission has not been determined and there are some limited data to suggest that it might not be effective for preventing pulmonary infection. Vaccination of selected military personnel also must be considered. CDC believes that most of the vaccine will be used by the military.

In addition to the vaccine recommendations for groups at risk, we have included alternatives to vaccination. Basically, these are standard recommendations given to reduce risks of exposure to infected fleas, infected rodents, or infectious materials from patients with Yersinisa pestis infection.

Pneumococcal Polysaccharide Vaccine - Dr. R. Breiman and Dr. J.

Butler

Two issues have come up since 1992-1993. One is the American College of Physicians has recently revised their recommendations regarding the use of the pneumococcal polysaccharide vaccine. The tow major points to consider are; one, at age 50 there should be a time to review all preventative health measures with special emphasis on identifying risk factors indicating a need for pneumococcal vaccination. The second point is all persons should receive pneumococcal vaccine at age 65 regardless of a history of prior vaccination provided six or more years have past since receiving the first dose. The second issue is the drug resistant strains of the pneumococcus have become increasingly prevalent in recent years.

Dr. Paul Mendelman of Merck discussed a study Merck initiated in 1986 which is listed in the package circular as being unpublished data. The design of the trial was a randomized double blind placebo controlled trial with 98 people who had previously received Pneumovax 14, the fourteen valent vaccine. The objective of the study was to compare safety and tolerablity of Pneumovax 23 versus placebo. The rate of local reactions were higher in the re-vaccinee group than placebo group, but were not significantly different from the rate with new vaccinee. The rate of systemic complaints were similar for all three groups, and the conclusion was re-vaccination with Pnemovax 23 for this age group immunized six years earlier was as safe, and generally well tolerated, as initial vaccination in this study. There was one serious adverse experience which was a fatal myocardial infarction in one of the revaccinees and it was determined by the investigators not to be vaccine related.

Addressing the original question of whether or not revaccination is even needed, the clinical significance of these findings is open to debate. The epidemiologic data suggests vaccine efficacy may not be life long, but just how long and what time is the appropriate time to readminister the vaccine is not known. It may differ in different subgroups of patients.

The safety of revaccination was discussed with consideration of the pros and cons. The incidence of adverse reactions appears low in revaccination, however, extensive studies have not been conducted. Data was presented to show that with revaccination there is generally an elevation in antibody response, although

for several of the antigens it was not to quite as high a level as following the primary vaccination. This could be related to the immunogenicity of polysaccharide vaccines or the advancing age of the patient.

Linda Schultz, National Immunizations Program, addressed the question of adverse reactions following re-vaccination. Adverse events following initial vaccination are mild local reactions, erythema, swelling, and pain at the injection site. In less than one percent moderate systemic and severe local reactions are noted. Severe systemic reactions are very rarely noted. The rate and severity of adverse reactions after revaccination is higher than the rate of reactions seen upon initial vaccination. Ms. Schultz presented information and data from several studies which varied in design, length of duration, and population demographics. Beyond a four year interval between doses there are fewer reports of an increase in adverse events at revaccination. Differences of antibody levels were found between persons who did not react upon revaccination and those that did react. The literature suggests antibody levels are related to the incidence and severity of adverse events following a second dose.

The Vaccine Adverse Events Reporting System is a passive reporting system receiving 800-1000 reports per month, mostly from health care providers, vaccine manufacturers, and vaccine recipients. Eighty-five percent of all reports of VAERS are not serious, and two percent of all reports involve pneumococcal vaccine. Since the system is passive, there is under reporting of adverse events. Some of the forms are incompletely or inadequately filled out. Data were presented comparing the rate of adverse events in those who received one dose with those of persons re-vaccinated. The data demonstrated reactions are associated with antibody levels and with time since last vaccination. The reactions were generally localized and it does not appear that serious life threatening reactions occur more frequently with revaccination. The benefits of revaccination compared to the risk of adverse events should be considered with the precaution of vaccinating in no less than four year intervals.

The committee considered streghtening the statement for booster for individuals 65 years old and older. The issue of waning efficacy is potentially suggested from the data in the model, at

least in individuals over age 65 years. There is a fairly significant increase in risk for pneumococcal disease in this group. There are implementation problems of verifying whether somebody had or had not been given a vaccine and there are more individuals entering nursing homes after age 65 years. Giving a routine booster every 5 years after age 65 might be worth while. Although the data on safety is not definitive, a review of the literature, the VEARS data, and the data presented by Merck does not indicate there is a major problem.

Reasons not to revaccinate were considered with regard to those who have not received the first dose. The recent publication of data from controlled trials of pneumococcal vaccine suggest that the effectiveness of the vaccine is greatest in the lowest risk people. Data are lacking regarding evidence of incremental effectiveness of these additional doses. The most cost effective and advantageous approach could be ensuring that the first dose is received rather than the second.

The age 50 is a milestone to review the medical records to determine whether there are indications for vaccination. Age 65 represents another age milestone that is likely to be easy to remember. At age 65, if there has been no prior adverse reaction to pneumococcal vaccine, everyone would get a dose as long as there has not been a dose within 6 years to avoid adverse reactions. However, there may not be additional benefit in administering another dose of vaccine. The ACIP recommendations are designed to make is easy for the physician to increase coverage in those groups know to be at increased risk for pneumococcal disease, people with underlying illnesses and those who are age 65 and older. Medicaid currently requires a physician order for every dose of vaccine administered. The observation of no increase in adverse events upon revaccination would allow easing of that requirement allowing nurse practitioners and others in community clinics and elsewhere to give the vaccine without worrying a great deal about the previous dose.

Drug Resistant Strains

Strains of Streptococcus pneumoniae that were resistant to penicillin were first identified in Australia in the 1960's. During the 1970's resistant strains were identified in a number of countries around the world. In the United States resistance

appeared to be fairly uncommon throughout the 1980's. Drug resistant strains of pneumococci in the United States have increased rather dramatically during the past couple of years and, although there is geographic variation, they are widespread.

Dr. Jo Hoffman, from the Respiratory Disease Branch, presented data from an Atlanta based surveillance of invasive pneumococcal disease to review current epidemiologic features of drug resistant Streptococcus pneumoniae, or (DRSP). In addition, preliminary data from a cohort study of invasive pneumococcal infections among the same population was presented in order to discuss the prevalence of underlying conditions currently recognized as indications for the pneumococcal polysaccharide vaccine. The Atlanta Metropolitan Active Surveillance for Invasive Pneumococcal Infections was started in January 1994 by CDC in collaboration with Emory University. Twenty-eight acute care hospitals in the eight county metro Atlanta are participate with the surveillance population of 2.3 million. All sterile site pneumococcal isolates are collected with limited clinical and demographic data from the hospital microbiology labs. Antimicrobial susceptibility testing and sero typing are done at CDC. A review of findings during the first ten months of data collection indicate 96% of all documented invasive pneumococcal isolates were received from participating laboratories. Antimicrobial susceptibility data from 431 isolates include: 25% of isolates were resistant to penicillin, 7% had high level resistance; 9% of isolates were resistant to extended spectrum celphosporin, 4% had high level resistance; 15% were resistant to erythromycin; 25% were resistant to trimethroprim/sulfisozazole; and all isolates to date are susceptible to vancomycin and rifampin.

Previous studies have focused primarily on pediatric populations. Both children and adults in metropolitan Atlanta had high levels of antimicrobial drug resistance. Underlying conditions representing risk factors for pneumococcal disease excluding age were reported in 65 percent of the patients. In patients age 50-64 years only 17% lacked a reported indication for pneumococcal vaccine. Therefore, for patients in this study age 50-64, 83% had a recognized risk factor for pneumococcal vaccine. HIV infection, alcohol abuse, chronic lung disease, and age greater than 64 were the most common risk factors for pneumococcal disease among patients in this study. To date there is not a significant association between infection with penicillin

resistant isolates and the presence of underlying risk factors. The increasing incidence of DRSP highlights the need to maximize the use of the 23 valent polysaccharide vaccine in the current focuses populations and the importance of the rapid development of effective conjugant vaccines for children less than 2 years old.

A working group was appointed to review and update the ACIP recommendations on pneumococcal vaccine: Dr. Schoenbaum, Dr. Griffin, Dr. Gardner, Dr. Schaffner, Dr. Clover, Dr. Ward, and a consultant from Merck.

Poliomyelitis Prevention -
Dr. B. DeBuono, Dr. K. Stratton, Dr. R. Sutter, and Dr. M. Wharton

Dr. Roland Sutter updated the committee on the work being done in poliomyelitis prevention. The need for a decision on the review process for polio vaccination policy was expressed.

Dr. DeBuono summarized the issues related to polio. The polio working group had three conference calls during November, 1994 and January, 1995. It was concluded as a result of those conference calls that a review of this subject is required to change any recommendations regarding the use of OPV and IPV.

An opportunity is needed to discuss this topic in more detail and to be educated about the implications of such a change. To facilitate a review a forum could be arranged (a full one or two days discussion) whereby a group of experts would be convened and would present the different options and discuss in depth issues important to poliomyelitis control. The purpose of the forum would be fact finding and information gathering. Options include the ACIP asking CDC to convene this forum or the Institute of Medicine (IOM) could be asked to convene this workshop through the use of its forum mechanism. To have a policy developed by ACIP during the June, 1995 meeting, this forum or workshop must be held before the June meeting.

Dr. Kathleen Stratton, IOM, discussed the option of IOM facilitating this workshop. The Vaccine Safety Forum is funded by the National Vaccine Program Office. Forum members hold discussions on topics which they decide are important and appropriate. It was suggested this may be a way to facilitate a

polio discussion and a letter was submitted to the IOM to consider ACIP's request to hold a workshop on polio vaccination policy options. This will be addressed at the IOM meeting on February 17, 1995. The stipulations important to ACIP with regard to the meetings are: (a) helping to participate in planning the workshop, (b) naming some of the ACIP members to be part of the workshop, (c) the opportunity to ask questions, and (d) making sure the AAP and AAFP are represented. Concerns that the whole ACIP will not be attending this forum were expressed. The IOM has not been asked to make recommendations. They will review the data but, if the ACIP is going to issue the recommendations, it is important the ACIP be present at this forum. A member of the ACIP and the AAP should be on the planning committee to ensure all of the issues would be covered. Two members of the ACIP and two members of the AAP should be on a panel and be able to query the people who are presenting. It was also suggested that one polio expert from CDC participate in the panel. It was also suggested it would be desirable to convene this forum accomplished prior to the May meeting of the AAP. If this workshop cannot be facilitated in this manner, the other option is to have CDC organize and convene it.

A vote of the committee was taken on the issue of:

> To have the ACIP, under the signature of the chairman, make a request to the IOM to set up a workshop to discuss the issue of changes in recommendations,with the stipulations and conditions outlined above.

A motion was made. The motion was seconded. Sever were in favor, none opposed, none abstained. The motion carried. Comments were solicited from the committee members and to be returned by February 10, 1995.

The second item for discussion regarded deferring all discussions regarding the change of the polio recommendations and finalizing any polio statement pending information from the workshop. Some thought that the necessary changes need to be made by the ACIP with the provision for further changes later. Other options would be to put together a brief statement to be inserted into an issue of the MMWR saying, in essence, that updated recommendations will be available soon or, lastly, to not deal with the issue at all and revise any polio document after

conclusions following the workshop policy discussions are made. The consensus among the committee was to postpone any statements regarding polio recommendations until after the forum or workshop.

The meeting was adjourned for the day with the reminder for committee members to bring their comments on the draft of the letter to IOM on February 10, 1995. The meeting will reconvene tomorrow at 8:15 a.m.

The meeting was opened at 8:15 a.m. by Dr. Jeffrey Davis. He asked for a review of the minutes from the last meeting in anticipation of a vote for their acceptance later in the meeting.

Influenza 1995-1996 Vaccine Strain Selection - Dr. Nancy Arden

Components of domestic surveillance for influenza include weekly reports from state and territorial epidemiologists, sentinel physicians who report directly to CDC, about 65 WHO collaborating laboratories, and 121 city mortality data, and information from outbreak reports and state epidemiologist, and other calls. The first reports of regional activity came from New York for the week ending December 10, 1994. By the end of December more states in the northeast were reporting regional activity. IN early January widespread activity was first reported in the northeast. Most of the isolates have been influenza type A, although types A and B have been isolated. Regional activity is now beginning to occur outside the northeast with reports of widespread activity that have not been confirmed from Alabama, North Carolina, and Colorado. P and I mortality hovered around the baseline all season.

Strain Characterization - Dr. Nancy Cox

Worldwide influenza activity has been moderate during the past 15 months. The southern hemisphere had relatively low levels of influenza A and B activity during the influenza season. In North America there has been mainly sporadic activity. There have been a few outbreaks caused by influenza B viruses; the most notable was a school outbreak in Portugal. In addition, China reported significant influenza activity cause by A($H_3N_{2)}$ viruses during December.

No influenza A(H_1N_1) viruses have been isolated in the US and very few were isolated world wide. No new antigenic variants have been identified and post vaccination serologic studies indicate that the current A/Texas/36/91 vaccine strain induces good cross protective antibody against the recently isolated viruses. Some recent influenza B viruses show moderate drift from the B/Panama/45/90 vaccine strain. Post vaccination serologic studies indicate that the current B/Panama vaccine strain induces good cross reactive antibody to the recently isolated influenza B viruses that have been tested, with some exceptions.

Antigenic analysis of influenza A(H_2N_2) viruses has shown that some recently isolated strains have exhibited moderate antigenic drift from the current A/Shangdong/9/93 vaccine strain. The post vaccination serologic studies indicate that the current A/Shangdong/9/93 vaccine strain induces reduced antibody titers to one of the recent variants, A/Johannesburg/33/94, and this particular virus is a candidate vaccine strain.

A meeting of the FDA Vaccines and Related Biologicals Advisory Committee took place on January 27, 1995. At that meeting it was recommended that the U.S. retain the influenza A(H1N1) vaccine component, A/Texas/36/91. It was recommended that both the influenza A(H_3N_2) and B vaccine components be decided at a later date when additional information would be available. The WHO vaccine strain selection meeting will be held February 13-14, 1995 and the WHO recommendations will be issued at that time.

Influenza-Associated Morbidity During Pregnancy - Dr. Paul Glezen

Through the ACIP statement for the 1965-1966 season, recommendations of the ACIP included pregnancy as a high risk condition. The following years the format was changed. Pregnancy was not listed as high risk condition because, although excess deaths were recorded from 1957-1958, similar data were not available for subsequent years. The influenza vaccine was recommended only for pregnant women with chronic underlying conditions. Data and studies were examined which clearly show the link between pregnancy and influenza associated morbidity, particularly in the third trimester. Therefore, influenza vaccination of a pregnant woman who will be in the third trimester of pregnancy during the influenza season has the potential for protecting two individuals during a vulnerable

period in their lives.

Influenza immunization is safe during pregnancy. Administration of influenza vaccine in the third ttrimesterof pregnancy does not cause fetal priming. It is estimated over 100,000 pregnant women were immunized annually during the years following the Asian flu epidemic. The large collaborate perinatal project found no deleterious consequences of the administration of influenza vaccine during pregnancy.

The proposed influenza statement with regard to pregnant women is:

> Influenza-associated excess mortality among pregnant women has been documented during the pandemics of 1918-1919 and 1957-1958. Additional case reports and limited studies suggest women in the third trimester of pregnancy and early puerperium, including those without underlying risk factors, may be at increased risk of serious complications from influenza. Vaccine is considered safe for pregnant women regardless of the stage of pregnancy. Pregnant women who have medical conditions which increase their risks for complications from influenza should be vaccinated. In additional, physicians caring for pregnant women should consider giving influenza vaccine to all women who would be in the third trimester of pregnancy or early puerperium during the influenza season.

The committee asked about the implementation in terms of cost effectiveness. The cost is expected to be based on 1.3 million doses per year with the cost per dose under $3.00 per dose currently. The committee would like to see more safety data over a longer period of time.

Assessment of GBS Risk Associated with 1993-1994 and 1994-1995 Influenza Vaccination - Dr. Ray Strikas

Through the Vaccine Adverse Event Reporting System (VAERS), three clusters of Guillain-Barre syndrome (GBS) were reported after receipt of the 1993-1994 flu vaccine. This is a higher rate of VAERS reports than in the past seasons. During a conference call

with ACIP in May, 1994 just before publication of the 1994-1995 Influenza Vaccine Recommendations, a review was made of the results to date. There were some reports that influenza vaccine coverage may have increased at that time, although it did not appear to have doubled, the rate of reports of GBS had doubled. At that time it was decided any change in the recommendations would be premature and perhaps alarming, and additional information was needed. It was decided a rapid national vaccine coverage study should be conducted with results to be available before fall 1994. Once sufficient data were available, a review should be conducted to determine whether there is a need to amend the recommendations. The coverage study was done. The results showed higher influenza vaccine coverage during 1993-1994 than in past years, although not as much as needed to explain the doubling of GBS reports. There was some concern about how best to disseminate this information. The feeling was an MMWR notice would result in a kind of red flag rather than the desired yellow flag. Since vaccine information material was being prepared at that time, minor changes in emphasizing the risk/benefit of vaccination was an appropriate means of updating this information. In addition, it was decided that when the recommendations were to be revised this issue could be readdressed. Language proposed in May 1994, when this issue was first discussed, with a small number of minor modifications is as follows:

Proposed Wording on Influenza Vaccination of Persons with a history of GBS

> As a group, and independent of influenza vaccination history, persons with a history of GBS have a substantially (probably 10 to 100 fold) greater subsequent incidence of Guillain Barre syndrome (GBS) than comparable persons without such a history. Also, there is a paucity of data about whether influenza vaccinations not clearly associated with GBS is the general population would further increase the risk of a recurrence in persons with a history of GBS. For most persons with a history of GBS who are at high risk of severe complications from influenza, the known benefits of influenza vaccination probably should not be withheld because of this paucity of data on whether or not there is some incremental increase

in risk of recurrence associated with the vaccination. However, and although not based on any known increased risk, in most instances it would seem prudent to avoid a subsequent influenza vaccination is persons known to have developed GBS within 6 weeks after an earlier influenza vaccination.

Proposed Revision:

Side Effects and Adverse Reactions ACIP Influenza Vaccine Recommendations

Unlike the 1976 swine influenza vaccine, subsequent vaccines prepared from other virus strains have not been clearly associated with an increased frequency of Guillain-Barre syndrome (GBS). However, it is difficult to make a precise estimate to risk for a rare condition such as GBS. In 1990-1991, although there was no overall increase in frequency of GBS among vaccine recipients, there may have been a small increase in GBS cases in vaccinated persons 18-64 years of age, but not in those aged >65 years. In contrast to the swine influenza vaccine, the epidemiologic features of the possible association of the 1990-1991 vaccine with GBS were not as convincing. Compared with the previous 3 seasons (1990-91, 1991-92, 1992-93) and the season since (1994-95), about twice as many reports of suspected GBS cases after influenza vaccination were passively reported to the Vaccine Adverse Event Reporting System (VAERS) in 1993-1994; cases were more likely to be in the 18-64 year old age group than >65. Whether this represents a real risk or not awaits further study. If GBS is a true side effect, the very low estimated risk of GBS is far less than that of severe influenza which could be prevented by vaccine.

To assist in making a comparison of associated risk complications in the high risk group, it was recommended to state, "the real risk is less than 1 in 100,00." Staff and Committee members were asked to provide comments within 2 weeks.

Optimal Needle Length for IM Injection Into the Deltoid-
Dr. Mark Miller

influenza vaccination is recommended as an IM injection because subcutaneous injection has been found to produce greater local reaction and may not be as immunogenic. However, data to support this route of injection are sparse. The optimal needle length to ensure a IM deltoid injection was discussed. Manufacturers licensed to produce influenza vaccine provide vaccine-filled syringes with 5/8" to 3/4" needles. Although this length would seem adequate to provide an IM injection in all but the most obese persons, a literature search has failed to find any studies to ascertain a standard skin to muscle measurement fro the deltoid in the US adult population. Nursing journals recommend needle lengths from 5/8" to 1 1/2" but provide no data to support their recommendations. Current ACIP general recommendations refer to the ideal needle lengths for intramuscular vaccinations to be 7/8" to 1" for infant anterolateral thigh injections, 5/8" to 1 1/4" for toddler and older children deltoid injections, and 1" to 1 1/2" for adult deltoid injections. The maximum length was determined to avoid accidental injection of nerve and bone and the minimum lengths were recommended to insure IM injection to minimize subcutaneous injections with associated local adverse reactions. The recommendations for children are based on previous studies which assess the ideal needle length for IM DPT injection in the thighs of infants and children. However, a literature review revealed no data to support the recommendations for adult deltoid injections. Because incongruity exists between ACIP recommendations and the vaccine manufacturer's labeling the following options may be considered:

1. Perform ultrasongraphic or some other diagnostic imaging study to assess the minimal and maximum needle lengths necessary to assure appropriate IM injections. An update to the ACIP general recommendations on immunizations would be based on these findings.

This would provide a simple rapid study, however, it would not provide any data on immunogenicity or rate reactivogenicity.

2. Sponsor studies comparing the immunogenicity of manufactures influenza vaccine in pre-filled syringes with 5/8" to 3/4" needles to syringes with a 1"-1 1/2" needle.

This would provide a definitive study, however, it would be quite expensive and would take about two to three years to complete.

3. Revise the general recommendation working to reflect the uncertainty of the needle length necessary to adequately assure IM deltoid injections in adults. Working may be included about manufacturers providing pre-filled syringes with smaller length needles which may be adequate for appropriate immunogencity in some populations.

This would allow for latitude for the practitioner, however, it is indefinite and not based on any data.

4. Change the general recommendation wording to allow a more liberal interpretation for providers to judge adequate needle length for an IM injection in adults. Any wording change adopted may also be included in the 1995-1996 Influenza Vaccine Recommendations.

Dr. Halsey questioned the need to specify the gauge of needle. The length of the needle was discussed in terms of patients needs, particularly obese patients who may require a non-standard needle length to ensure IM injection and reduce the chance of a local reaction due to a subcutaneous injection. The possibility that manufacturers may have immunogencity data regarding 5/8" needles was mentioned. It was suggested that industry may be able to present definitive data regarding this issue.

Comments on the proposed draft recommendation are to be returned within two weeks.

National Estimates of Influenza Vaccination Rates -Dr. Ray Strikas

Data from the US Immunization Survey (USIS) from 1973-1985, the National Health Interview Survey (NHIS) 1989, 1991, 1993, and Medicare Surveys were combined to present a comprehensive overview of information. Analysis of subsets by race (1985-1991) in the USIS and the NHIS found a profound discrepancy between races in vaccine coverage, especially in high risk populations. Influenza vaccination levels overall have significantly improved in persons 65 and older and we may be close to achieving the year 2000 objective for this subpopulation. However, vaccination

levels have not substantially improved in persons 18-64 years of age with high risk medical conditions. And we have no national data to estimate vaccination coverage levels in children, high risk children specifically. Based on conversations and discussions with people in the field, we feel there has been better acceptance by the public of preventative health measures. There has been an increasing delivery of vaccine by non-physicians such as visiting nurses and home health agencies. Part of the increase in coverage may have been due to Medicare reimbursement for influenza vaccine, but that became effective in May, 1993 and had some impact in the Fall 1993. Targeted programs are probably needed to continue to improve the vaccination levels in all persons 65 and older, particularly in some groups. There is also a need to improve levels in persons less than 65 years of age and to obtain better national estimates of influenza vaccination coverage in children.

The committee discussed the critical nature of the issue of vaccination for influenza and agreed to include this item on the agenda for the next meeting of the ACIP.

A suggestion was made to change the wording on page 6 of the current recommendation to create the opportunity for physicians caring for pregnant women to administer influenza vaccine to them.

A group of volunteers was enlisted to draft a proposal for this wording and report back to the committee later in the meeting.

Summary of Influenza - Dr. Nancy Arden

Because of the tight deadline from this meeting to publication of the recommendations in May finalization of package inserts cannot be made by manufacturers. The committee was asked to consider making comments on the influenza recommendations a priority. MMWR will do everything they can; however, it does generally take six weeks after the document ins finalized until publication. Dr. Davis stated that committee members should make comments about the possible risk of GBS and the statement on re-vaccination. These will be collected, drafted into another statement, and then resubmitted to the committee for additional comments. The GBS statement should be returned by February 17, 1995. There are no changes needed on the antiviral statement since it was published in December.

Minutes of Previous Meeting

Dr. Jeffrey Davis asked for any comments or concerns for accuracy of the previous meeting minutes. Dr. Edwards commented Dr. Halsey's name was spelled incorrectly. With no other corrections, a motion was made by Dr. Davis to accept the meeting minutes as written. The motion carried unanimously.

Miscellaneous

Committee members were asked to expedite comments on the statement for the MMWR regarding the Age 50 Vaccination Visit. The IOM Vaccine Safety Statement for the MMWR was distributed and comments are to be returned within two weeks.

Update on Schedule Simplification - Dr. Jacqueline Gindler

In January 1995 the Recommended Childhood Immunization Schedule was published in Pediatrics and in the MMWR as a notice to readers. It also appeared in the American Family Physician and other journals. In addition, it was circulated to CSTE, the Association of State and Territorial Health Officers, state immunization program managers, and is currently in the process of being sent out to pediatric department heads. Agreement and approval by ACIP as well as AAP, AAFP and their executive bodies must be reached before the next update is published. The timing of the next update regarding publication of the recommendation for adolescent hepatitis B vaccine, and also possible publication of Recommendations for Varicella zoster Vaccine, if it is licensed should be considered. The MMWR editorial staff will need 8-12 weeks after they receive the document to publish it. Some of the footnotes need changing and a contractor is currently working on evaluating the formate used along with other possible formats and will possibly be suggesting better ways to present this.

Recommendations for adolescent hepatitis B vaccination have been approved by AAP and ACIP, but the ACIP recommendations probably will not be published before May or June of 1995. Given the current schedule, how should the recommendations for hepatitis B vaccination of previously unvaccinated 11-12 year-olds appear on the schedule so as not to be construed as a booster dose?

A committee member suggested a clarification of the hepatitis B footnote be published in the MMWR before the next version of this schedule is published.

A suggestion of planning on a semi-annual publication of the schedule to allow users to anticipate a timely and regular update of information was also made.

Dr. Edwards made a motion to clarify the dosage of hepatitis B vaccine for HBsAg negative and positive mothers. The motion was seconded. The notion carried unanimously.

A motion was made by Dr. Halsey for the revision of the schedule to be published in July in the tree primary locations that have been stated, the MMWR, Pediatrics, and the American Academy of Family Practice Journal. The motion was not seconded. The chairman asked the committee for a counter motion.

A motion was made for annual publication of the schedule, with publication of recommendations for use of newly licensed vaccines as close to the time of licensure as possible.

With regard to footnotes, the current hepatitis B vaccine footnote specifies the volume and not microgram dose. In one particular instance (i.e. infants of HBsAg-positive mothers) this is confusing and potentially misleading. The current footnote does not state the dose of vaccine that infants of HBsAg negative mothers should receive. For infants born to HBsAg positive mothers, the problem is the footnote specifies that in addition to getting hepatitis B immune globulin (HBIG) they should receive 0.5 cc of hepatitis B vaccine. This dose (i.e. 0.5 cc) is appropriate for all routinely-used formulations except the Merck Recomivax HB pediatric formulation, which contains 2.5 micrograms of HBsAg per 0.5cc. This dose is too low for infants of HBsAg-positive mothers who are recommended to receive 5.0 micrograms of the Merck product.

The two manufacturers of hepatitis B vaccine recommend different microgram doses of vaccine depending on the surface antigen status of the mother. In addition, there are a number of formulations of vaccine currently available resulting in confusion about dosing. One possible solution which lengthens the footnote substantially, is to indicate the microgram dose rather than the volume. This could be included in the paragraph

on HBsAg negative mothers and HBsAg positive mothers or just on HBsAg positive mothers. The question of whether this proposed clarification can appear in the next scheduled update or whether it must be published immediately was discussed by the committee.

A suggestion was made by a committee member that rather than call some of these very important parts of additional information "footnotes" that they be called explanatory text as a way to emphasize these are important and they are not just traditional footnotes.

A suggestion was made by a committee member to provide the general recommendations of the schedule in their current format along with the statement that for certain conditions and situations one should refer to the package insert for additional dosing information. This would eliminate the need to constantly update this schedule and footnotes, etc.

Another committee member remarked that the footnotes are expanding rather than contracting and they may actually have created more confusion.

Regarding the recommendation for tetanus and diphtheria toxoid (Td) at 11-12 years of age, there is no mention of this at all in the footnote and there is no mention of whether there needs to be a minimal interval between this vaccine dose and the previous dose of DTP or DT. The suggested statement is:

> Td is routinely recommended at 11-12 years of age, provided at least five years have elapsed since the previous dose of diphtheria and tetanus containing vaccine.

With regard to MMR, when this information was presented at the State Immunization Program Managers Meeting in December, there was a lot of concern about the footnote stating MMR can be given either at entry to kindergarten or middle school. For states that have universal purchase and may be purchasing vaccine based on state and school requirements, it was felt the following information should be included in the footnote:

> A second dose of MMR vaccine should be administered either at 4-6 years of age, or 11-12 years of age, depending upon state school requirements.

State immunization program managers feel this statement would be helpful because if this were no included and physicians decided they wanted to give it at 4-6 years in a state where the law required the second dose at 11-12 years it could potentially cause problems with the vaccine supply.

The need for a footnote concerning polio vaccine was discussed. There is no footnote about polio vaccine in the current schedule and OPV is recommended at 2, 4, and 6 months of age. There has been some discussion about whether something should be included about certain situations when IPV is preferred or indicated. It was noted this was discussed earlier. Since this schedule was intended as something for routine use for normal infants and children, only the routinely-recommended vaccines would appear on the schedule. The situations where IPV is indicated are addressed in other sources.

Several committee members felt additional footnotes were unnecessary as this schedule is to serve as an overview. A more comprehensive review of available literature and recommendations should be made in other places.

Regarding the accelerated schedule, the major problem is that the minimal interval between doses of different vaccines are different (i.e. four weeks for DTP and Hib; six weeks for OPV). At the last ACIP meeting, the ACIP voted to accept a minimum interval of four weeks between the first and second, and second and third doses of OPV. There are plans to convene the working group to focus on the accelerated schedule.

Adolescent Vaccination - Dr. W. Williams

At the last meeting the committee adopted a set of recommendations to improve the delivery of vaccination services to adolescents and integrate recommendations for immunization with other preventive services provided to adolescents. Dr. Halsey and Dr. Ward catalyzed this working group. An early adolescent visit at age 11-12 years should be used to review immunization status and deliver necessary vaccines, including hepatitis B and MMR for adolescents not previously vaccinated. New recommendations might include giving an early Td booster dose at age 11-12, varicella vaccine, and influenza and pneumococcal vaccines, if indicated. At that visit other preventive services

would be provided as indicated. A draft was circulated to the committee for review which was developed with guidance from Dr. Halsey and reviewed by Dr. Arthur Elster, Director, Adolescent Health, AMA, who presented information to the group at the last meeting. It was also reviewed by CDC staff.

Dr. Halsey discussed the organizations that provide guidance about adolescent health in this country and include immunizations as part of those guidelines. These include the Committee on Infectious Disease of the American Academy of Pediatrics, the Department of Adolescent Health at the AMA, and the National and Child Health Bureau (Bright Futures Program). These programs and organizations have had an opportunity to review this draft and they are strongly supportive of proceedings with the concept. The American College of Physicians co-authored the statement of Adult and Adolescent Immunization. The US Preventive Services Task Force has come out with guidelines for providing care to adolescents. it had previously been proposed this would be a joint statement by the Committee on infectious Disease of AAP and the ACIP. What roles should the other organizations play? Almost all of them call for annual visits at around age 12 so anything we can do to help support this concept would be welcome.

Dr. Hector Izurieta presented data about the 187 tetanus cases reported to the CDC's Supplementary Surveillance System from 1991-1994. Fewer than 60 cases were reported per year, 66% were in persons age 60 or older, and only 14% were in persons under 30 years old, including 5 (3%) cases in 1-14 year olds, 19 (11%) cases in persons 15-20 years, and only one case was in a person younger than 10 years. Information on vaccination was available for all cases in persons under 15 years and for 79% of cases in persons 15 to 29 years old; 58% of cases in persons under 30 years had a history of three or more doses of tetanus toxoid prior to injury or onset of disease. (This does include the dose of tetanus toxoid given after injury.) The median interval between last vaccination and disease onset was nine years with a range of 3-25 years.

A committee member noted that a problem with the over 50 age group is those who have never received a primary immunization. This is the focus of the visit at fifty years of age that ACIP is considering. A routine immunization at that age would insure everybody at least has a primary immunization or a booster before they reach age 60.

Dr. Bob Chen presented data on the risk of adverse events with Td vaccinations in adolescents. Children 10-12 years old tend to have a 25% higher rate of hospitalization with or without vaccination. No significant increase was observed in the ER visits or hospitalizations within 7-14 or 30 days of Td vaccination in the children studied.

CDC's staff presented issues relevant to the adolescent immunization visit. The current policy for the timing of subsequent Td booster doses is every 10 years after the booster dose given at 14 to 16 years of age, that is at age 25, 35, etc.

Other options include:

> Moving the booster dose for the 14-16 year olds to age 20 and then giving booster doses every ten years thereafter, 30, 40, etc.
>
> Another possible option would be to give the booster dose at age 25 and then every ten years.

The committee discussion emphasized the importance of making sure everybody gets their primary immunization. The real problem with tetanus is that some 60 year olds never got immunized in the first place or for those that did get fully immunized they did not get a mid-life booster.

The next issue discussed was Td administered after the 4-6 year dose but before the adolescent visit at 14-16 years of age. The issue of timing is important since many people will have received a dose at 4-6 years of age and receiving another booster at 11-12 years of age may be too soon.

The consensus of the committee was to recommend the next dose be given after five years, i.e. at 11-12 years of age. This preserves the internal consistency of the current recommendation for a dose to be given at the first adolescent visit.

Adverse events associated with a Td booster at age 11-12 years was the next issue discussed. The proposed wording for the recommendation is:

> Available data suggests there should be no increased

> risk of serious side effects when the first booster dose is administered at five to six years of age rather than at eleven to twelve years of age.

The next issue was hepatitis B vaccination of adults which requires three visits and the need for special strategies to assure completion. Currently the ACIP does not recommend restarting the series when a child is not on schedule. General guidelines for infant immunization state that the second dose should be given at least a month after the first dose, and the third dose should be given at least four months later. A committee member suggested that similar guidelines would be appropriate for adolescents and the statement should state that there is no need to start over if the intervals between doses is longer. The Committee accepted this as a workable solution.

The issue of simultaneous administration of hepatitis B, MMR, Td, varicella, and other vaccines at the adolescent visit was then discussed. The issues are of the risk for adverse events and interference with the immune response. The ACIP general recommendations from January 28, 1994, state:

> Experimental evidence and extensive clinical experience has strengthened the scientific basis for administering certain vaccines simultaneously. Many of the commonly used vaccines can safely and effectively be administered simultaneously.

The committee concurred this statement should apply to the adolescent recommendations with the clarification that experimental evidence was not available for the adolescent population and furthermore several new vaccines, which were not in existence when this earlier recommendation was made, have not been studied.

The adolescent visit and provisions for seasonal influenza vaccination were considered. Influenza vaccine needs to be received in the fall. Approximately 2.2 million persons 10-18 years of age should receive the influenza vaccine about 500,000 age 11-12 years. The proposed working for this recommendation is:

> Adolescents at high risk seen by health care providers for routine care or the adolescent visit should be

offered influenza vaccine. Adolescents at high risk sen at times during the years when influenza vaccine is not indicated may be scheduled to return at an appropriate time to receive the vaccine.

The next issue discussed was persons without documentation of vaccinations. What is to be done if there is no immunization record or no documentation? Some of the options are: offer all the vaccines, offer no vaccines and reschedule a visit when the vaccination status of the adolescent can be determined, or use the language ACIP has set forth in the general recommendations.

Committee members noted it would be reasonable to consider school immunization laws and factor those laws into this decision and model any language based on that.

The next issue discussed was the public sector role in the adolescent visit at age 11-12 years. This is not currently addressed in the document. If the public sector takes a prominent role, does this possibly conflict with the concept of a medical home of all children? Does it create problems regarding record keeping and transfer of care to the usual provider? Another issue is the burden on the public sector. Should these things be addressed in the document somewhere?

A summary of the recommendations adopted during the last meeting was presented. This included the visit itself, the Td booster, hepatitis B vaccination, MMR dose 2, varicella vaccine, recommendations for both influenza and pneumococcal vaccination, and a recommendation regarding the delivery of other indicated preventive services. Comments, if any, regarding the specific wording of those recommendations are solicited from the committee to insure they reflect the intent of the committee regarding the direction to be taken.

Regarding the issue of endorsement or a joint statement with other groups, guidance is needed from the committee on how to proceed. It was recommended that the next draft be sent out to other groups for comments, but if it were to be a joint statement of the American Academy of Pediatrics (AAP) and the ACIP, the AAP would be responsible for deciding which of their committees get involved.

Dr. Davis stated the document with comments should be returned by

March 3, 1995.

Acellular Pertussis Vaccine Trials Update - Dr. Peter Strebel

The progress made so far in the eight acellular pertussis vaccine efficacy trials was summarized for the committee. Three trials are being conducted in Sweden, three in Germany, one in Italy, and one in rural West Africa. The start dates have all been since 1990 and they are all large studies, especially the Italian trial with 15,000 children and the Stockhom trials with 10,000 and 83,000 children respectively. Investigations in two studies have reported results, results of five of the remaining six trials are due in mid 1995.

The SmithKline Beecham study was conducted in Germany. The study was designed to look at the secondary attack rate in households of cases. The case definition for pertussis was the recommended World Health Organization case definition which is greater than or equal to 21 days of paroxysmal cough plus laboratory confirmation of pertussis (either a culture, serology, or a case that is epidemiologically linked to a culture positive case in the household). Three vaccines were used. The result obtained for absolute vaccine efficacy, that is comparing the attack rate in children who received acellular vaccine with those who received no acellular product was 89.9%. The 95% confidence interval was 76%-96%. They were also able to calculate vaccine efficacy for whole cell DPT and that point estimate was 97%. There was no statistically significant difference between the two point estimate.

The other study with announced results was the study funded by the NICHD, NIH conducted in Sweden. This was a randomized double blind placebo controlled clinical trial with an objective to determine absolute vaccine efficacy. The WHO case definition was used and administered in a three dose schedule at three, five, and twelve months of age. 3450 children were enrolled with 1725 in each of the study groups. The provisional result from this study reported a vaccine efficacy of 71%.

A trial sponsored by Lederle-Praxis Biologicals with a primary objective to determine relative vaccine efficacy and compare the vaccine efficacy of the Lederle acellular vaccine which is a four component vaccine with the Lederle whole cell vaccine. A secondary objective of the study is to estimate absolute vaccine

efficacy by comparing those who received the acellular vaccine with a group that received DT only. However, this latter group was not part of the randomization. There was a four dose schedule. This study involved 10,000 children, 4000 in each of the two study groups, and 2000 in the DT group. Results are expected in spring 1995.

Connaught Labs is sponsoring a prospective case-control study in Germany which involves surveillance for pertussis cases in 60 pediatric practices. The vaccines under study are the Connaught DTaP that is licensed in the US as a fourth and fifth dose and the Behring Werke DTP. The schedule is the same as the US schedule with doses given at 2, 4, and 6 months of age. Results are expected mid 1995.

The Senegal Study, the only study being done in a developing country, is sponsored by Pasteur-Merieux. The two vaccines under study are the two component Merieux acellular vaccine and their whole cell product administered in a three dose schedule at 2, 4, and 6 months of age; 3600 children are enrolled in the study and results are expected in mid 1995.

The Italian trial is one of the larger trials funded by NIAID and the manufacturers. This is a randomized clinical trial with an objective to determine both absolute vaccine efficacy and relative vaccine efficacy. The trial includes two acellular products which are both tri-component products, a whole cell vaccine and a DT "placebo" group. To date about 252 cases of confirmed pertussis meeting the WHO case definition have been documented in this study. The expected announcement of vaccine efficacy results is June 1995. Later in 1995, possibly December, the relative vaccine efficacy results will be announced.

The study with the largest sample size is the Stockhom trial which has two phases and is funded by NIAID. The study design is a randomized placebo controlled trial with an objective to estimate both absolute and relative vaccine efficacy. In phase 1, two acellular products are under study, the Connaught five component vaccine, and the SKB two component vaccine. In addition, Connaught whole cell DTP, and a placebo (a European formulation of DT) are being used. The schedule is 2, 4, 6 months. Just under 10,000 children are enrolled in 4 equal sized study arms. The overall attack rate so far in this study is nearly 7%. Results from this study are expected in June, 1995.

Phase two of the Stockhom trial is being sponsored by the manufacturers. The objective of this study is to determine relative vaccine efficacy. The vaccines under study are the Connaught five component vaccine (at a slightly higher dose), the SKB two component vaccine, the Biocine tri-component vaccine, and the Evans-Medeva whole cell vaccine. The schedule here is a 3, 5, and 12 month doses and 83,000 children have been enrolled in this study. Results are expected in mid-1996.

NIH is sponsoring immunogencity studies of acellular pertussis vaccine among adults in the US. These results are also due in late spring 1998. The purpose is to look at the immunogenicity and safety of acellular products in adults in the US. There are five acellular products under study as well as a saline placebo. These studies are being done through the vaccine evaluation units with 30 adult volunteers per group. Each vaccine is going to be used at either full strength, at half log dilution or whole log dilution. Blood for serologic testing is being obtained before vaccination, one month post vaccination, and one year post vaccination. These results are due in last spring 1995.

Report of a Meeting Regarding Conflicting Immunization Guidelines - Dr. Neal Halsey

The AAP volunteered to sponsor an informal workshop to discuss these issues with the intent to try to identify the relative roles and responsibilities of the different agencies and organizations, to find ways to work together to resolve some of the conflicts and to prevent future conflicts with regard to the use of the vaccines. The workshop was held in Baltimore at Johns Hopkins and there were participants from the AAP, the ACIP, and the National Vaccine Program Office, the CDC, the FDA, and some of the vaccine companies. The full minutes of that meeting were sent to each committee member. One of the most important things that came out of the workshop was a better understanding for the reason for some of the conflicting guidelines and that there are differing roles and perspectives for the advisory committees and for the FDA. The FDA usually requires data on a specific vaccine when setting requirements for the labeling. The advisory groups have a broader mandate, particularly the ACIP, in that there are societal perspectives that need to be brought into consideration. These include vaccine delivery systems and the impact of any changes that might occur in the systems, and the cost

effectiveness of how the vaccine may be used. The advisory groups are more willing to use expert opinion based on studies of similar vaccines when data are lacking. There have been differences of opinion between FDA and the advisory groups with regard to the value and the clinical significance of some data, e.g. geometric mean titers following a primary series. The ACIP and the Committee on Infectious Disease of AAP have in general been much more lenient with regard to simultaneous use of vaccines when data are lacking than the FDA has been.

From a manufacturer's or vaccine company perspective, there have been many problems in anticipating the use of the vaccines when they are under development. It was pointed out that many of the studies that are used toward ultimate licensure of a new products are designed several years before the results are actually presented to an advisory committee and things change in the meantime. For example, it is impossible to anticipate all the scheduling questions that will arise in the future, especially when new vaccines are added to the schedule during the time that companies have been developing other products and it was impossible fro the companies to anticipate this ahead of time. There is a general lack of input from advisory groups during the vaccine development process, particularly during the early phases of development. Because the ACIP meetings are public meetings, it has been difficult to offer the companies advise because of company reluctance to share proprietary information, particularly early in the development phase.

Some of the Labeling for vaccines has language that is in conflict with ACIP general guidelines on use of vaccines and occasionally in conflict with pre-existing statements about other vaccines made by other manufacturers. The requirements that the package inserts be based on the available data from clinical trials of that particular vaccine at the time of licensure limits the flexibility of FDA. The manufacturers would be reluctant to conduct additional studies that might slow down the licensure process even though the results of these studies would help the advisory groups base more of their recommendations of data rather than expert opinion or extrapolation from other studies. This is particularly true when it comes to listing adverse effects. The issue of how to obtain data for developing recommendations on a particular product that is already licenses or close otolicensure is difficult to resolve.

The FDA has encouraged the incorporation of ACIP guidelines in package labeling in recent times which seems to help alleviate the problems of the inconsistencies. But often times for new vaccines, either the AAP guidelines or the ACIP guidelines are not in final form at the time that the product is licensed and, therefore, that is not always possible.

There are also legal concerns. The legal counsel to the vaccine companies, and sometimes legal counsel to FDA, may perceive a conflict with the recommendations of advisory committees.

Potential solutions to the problem were discussed. However, we must recognize there are different roles and perspectives and responsibilities of the groups that are providing recommendations regarding the use of vaccine and the package labeling. We need to educate providers regarding these different missions and agency perspectives. Although we should make efforts to minimize these differences, we should not be creating the false expectation that the guidelines will always be completely consistent. The different perspectives represented in the decision making process are beneficial to society and often the perceptions of conflicts are greater than the real differences in the guidelines.

Proposed resolutions include:

Increased communication between the vaccine companies and the advisory groups at all stages of the development process. ACIP can facilitate this by encouraging additional presentations by the vaccine companies at its meetings.

The vaccine companies should actively seek out additional input from advisory committees regarding the wording of the package inserts with special attention being pad to the potential impact that the new vaccines might have on immunization schedules and the use of other vaccines that might be either already available or soon to be available.

Advisory groups could provide some additional guidance to the companies by providing the anticipated criteria that would likely lead to a recommendation for the use of the vaccine under different circumstances.

Advisory groups and the companies could have separate closed meetings to improve communication, particularly with regard to the confidentially issue.

The FDA has developed a series of points to consider regarding the development of new combination products; the FDA has not yet shared these with outside groups. The FDA has encouraged participation by ACIP and AAP members in their Vaccines and Related Products Advisory Committee meetings but the methods for more formal input from each of the major advisory committees in FDA deliberations should be sought. Possible inclusion of a representative from ACIP and/or AAP on the FDA Vaccine and Related Products Advisory Committee could be considered.

A number of specific recommendations focused on the advisory committees that we should consider include:

When seeking changes in the immunization schedule, the advisory committee should seek input from the vaccine companies and FDA.

ACIP could identify the conflicts between the advisory guidelines and the FDA package inserts and mechanisms for conflict resolution; however, the obligation to resolve the conflicts involves the advisory committees, the vaccine companies, and the FDA.

ACIP should encourage the vaccine companies to request package insert changes when ACIP identifies additional data that could lead to a resolution of the conflict.

The FDA can request that the manufacturers alter the package inserts based on new data.

The advisory groups need to determine a way to work with confidential information that might be provided by the companies.

The ACIP should indicate when the recommendations are based on expert opinion and not on definitive studies.

The companies should review the package inserts for discrepancies and initiate steps to change the package labeling.

Harmonization of ACIP/AAP Recommendations with FDA Labeling - Dr. Melinda Wharton

The ACIP and the FDA have recently reviewed the ACIP recommendations and compared them to the package inserts for specific vaccines from specific manufacturers. Although there are some differences in what individuals doing these reviews may consider worth noting, the two lists are remarkably similar.

In terms of general usage of vaccines it is apparent that the package inserts contain specific instructions not to administer by alternative routes of administration. Regarding simultaneous administration, the package inserts tend to be more restrictive than the ACIP. Regarding specific recommendations related to the use of vaccines, a difference between ACIP and the package insert has to do with the use of Hib conjugate vaccines where ACIP states that although it is preferable to use a single Hib conjugate vaccine for the entire series, the vaccines may be used interchangeably and the package inserts say that the same conjugate vaccines should be used for the entire series.

There are some discrepancies regarding the age of recommended use for some of the Hib conjugate vaccines and a difference related to the recommended immunization for persons who previously received inactivated measles vaccine.

For the measles, mumps, and rubella containing vaccines the package inserts state that a one month interval between administration of other vaccines is required, while the ACIP has stated that there is no interference with OPV or any killed vaccine.

For rubella containing vaccines, there is a recommendation in the package insert that for non pregnant adolescent and adult women, rubella susceptibility should be determined by serology prior to immunization. The ACIP has state that this is not necessary.

A difference exists for the period of time during which persons who receive OPV should not have contact with immunodeficient persons following the receipt of vaccine.
For the adverse events information there are many differences that could be identified, but generally most were related to the

package inserts tending to be very inclusive, including very long lists of minor adverse reactions which may or may not have any causal relationship with the vaccination and other events which are temporally related but not causally related. The ACIP recommendations tend to be much less inclusive and tend to focus on common reactions, reactions which are severe, and reactions which have been clearly demonstrated to be causally related.

There was a significant difference in information regarding contraindications to the use of vaccines, particularly regarding allergic reactions. Package inserts often refer to hypersensitivity or allergic hypersensitivity to any vaccine component was a contraindication, while the ACIP recommendations tend to be more focused on anaphylactic reactions.

The package inserts tend to include language discouraging product use or stating that the vaccines are contraindicated during any illness, or during febrile illness, or during acute illness or some variation of that theme. The ACIP statements have included language that is much more permissive, recommending that vaccination be deferred during severe illness, or moderate to severe illness with or without fever.

A number of differences which were noted in the precautions listed in the package inserts and the ACIP recommendations. Again, the tendency was that the package inserts were somewhat more restrictive than the ACIP recommendations.

With regard to differences in schedules, the differences are well known and fairly minor. There was some difference in language regarding the timing of the fourth dose of DPT. There are differences in the recommendation for DTaP for the fourth dose for one of the products. There are many differences regarding the use of Hib conjugate vaccines related to scheduling. There are many small differences of a month or two in the recommended schedule for immunizations, e.g. the third dose of OPV, and some differences in the hepatitis B vaccine schedules.

A committee member suggested that the manufacturers could be asked to review their package inserts to see it differs from ACIP recommendations. If they have data to support their position, they could provide it. A letter to the FDA could be developed that would be signed by the Chair of the ACIP requesting that the consideration be given to a change of the wording to be

consistent with the ACIP guidelines. One committee member noted that a package insert is as much a legal document to defend the manufacturer as a source of information. Thus, it might be difficult to remove restrictive language that had previously been in an insert without risking litigation. The National Vaccine Advisory Committee (NVAC) scheduled in May a meeting of the Federal agencies. It is hoped that members of the ACIP can participate in the NVAC meeting. It was agreed that a measure of progress in this area is needed in light of all the difficulties and frustration that everyone involved is experiencing.

Recommendations for Immunization Linkage with WIC - Dr. E. Maes

A copy of a draft statement was reviewed by the committee with regard to linking WIC services to immunization programs. WIC has reviewed this statement and suggested several changes:

(a) deleting the line specifying "one to three months supply".

(b) taking out the phrase "when available" from the sentence, "Recognizing the need to maintain and strengthen the provision of routine preventive services, children preferably should be referred to their usual source of care when available".

(c) inserting "When feasible, programs are encouraged to consider a number of integrated service delivery strategies, including making the frequency of voucher issuance contingent on up to date immunization status".

(d) adding "The Immunization record of each WIC client should be carefully reviewed at each WIC visit and clients should be immunized at the WIC site if practical or referred to their usual source of care if on site immunization is not practical".

A motion was made to accept the document as modified. It was seconded. In favor 7, opposed 0, abstained 0, absent 3. The motion carried.

Revisiting the Influenza Statement Subsection on Pregnant Women

The proposed draft working to be voted on is:

Influenza associated excess mortality among pregnant women has been documented during the pandemics of 1918-1919 and 1957-1958. Additional case reports and limited studies suggest that women in the third trimester of pregnancy and early preparium, including those without underlying risk factors, may be at increased risk of serious complications from influenza. Influenza vaccine is considered safe for pregnant women regardless of the stage of pregnancy. Pregnant women who have medical conditions that increase their risk for complications from influenza should be vaccinated. In addition, physicians caring for pregnant women should consider giving influenza vaccine to all women who would be in the third trimester of pregnancy or early prepartum during the influenza season.

A motion was made to accept this proposed recommendation. The motion was seconded. In favor 7, opposed 0, abstained 0, absent 3. The motion carried.

Update on Meningococcal Recommendation - Dr. J. Wenger

Dr. Wenger reviewed changes suggested to the draft meningococcal recommendations distributed to the committee during the previous meeting. Changes suggested for the general recommendations sections include:

Update of the data on the vaccination reaction rates.
Revision of the section on experimental group B meningococcal vaccines.
The addition of a section on when revaccination should be timed.
The phrase "intimate contact" was changed to "close contact".

Changes suggested for the section on control of group C meningococcal outbreaks include:

The section regarding the need to evaluate the situation at a local level may require additional factors that need to be considered. In addition to the statement on page 14, "if the rate exceeds this threshold, vaccination should be considered" add, in the next sentence, a statement about the need to consider on a case by case basis some of the specific considerations that

are enumerated on page 16.

In the section regarding outbreak situations, the addition of a statement addressing the use of mass chemoprophylaxis was suggested as follows:

> The effectiveness of mass chemoprophylaxis to large populations has not been demonstrated in those settings in which community or organizational outbreaks occur. Widespread administration of chemoprophylaxis has several disadvantages including cost of the drug and administration, difficulty insuring simultaneous administration of chemoprophylaxis to a large population, short duration of activity, side effects of the drugs among recipients, and emergence of resistant organisms. In most outbreak settings these disadvantages outweigh the possible and unproven benefit in disease prevention. However, in small organizational outbreaks, administration of chemoprophylaxis to all persons within the organization may be considered. If mass chemoprophylaxis is undertaken, efforts should be made to administer chemoprophylaxis to all members at the same time.

This statement will be redrafted and distributed to the committee with the intent to ready the draft for publication. Committee members were asked by Dr. Davis to review and return the amended draft with final comments by March 3, 1995.

Discussion on Injury Compensation Update - Tom Balbier

The Division of Injury Compensation of HRSA has recently been charged with the responsibility for coordinating vaccine safety efforts throughout the public health service. Dr. Leslie Ball will be coordinating the activities of the Advisory Commission on Childhood Vaccines. There will be a subcommittee created with representatives from the ACCV as well as the National Vaccine Advisory Committee at the next meeting in March.
This week the President sent his budget to Congress which included a provision that would reduce the excise taxes coming into the trust fund. Currently the fund receives about $100 million each year to finance the Vaccine Compensation Program. The proposal, although not yet clearly defined, would reduce those revenues by half or about $50 million. This reduction in

the excise tax would produce savings of $25 million in CDC's Immunization Grant Program. The legislative proposals will be sent to Congress. The Advisory Commission on Childhood Vaccines has recommended a reduction to a flat rate of fifty cents per antigen or disease prevented. This was endorsed by the National Vaccine Advisory Committee during its last meeting.

There is a continuing decline in the number of claims filed for vaccine injury compensation. Progress is being made in adjudication of the pre-1988 claims and the post-1988 claims have been adjudicated within fourteen months of submission. During fiscal year 1994, the post-1988 payments exceeded the pre-1988 awards; virtually half of that increase is the result of two awards under the program. One pertussis related award that cost $3 million was a very difficult award, and the other was an award of $7.5 million for a polio claim for a child that had very serious disabilities. This trend is not expected to continue through the rest of the fiscal year. The culmination of a four year effort resulted in the publishing in the Federal Register of a final rule implementing changes to the Vaccine Injury Table for the pertussis and rubella vaccines.

Dr. Geoffrey Evans presented the revised Vaccine Injury Table to the committee along with an update on some of the current litigation in vaccine injury cases.

An overview of the organizational and administrative processes that developed the current Vaccine Injury Table was presented. The following are the revisions to the Vaccine Injury Table:

Shock collapse and hypertonic hyperresponsive episode (HHE) have been removed under DTP vaccine.

Anaphylaxis has been changed from 24 hours to 4 hours for pertussis, DPT, MMR in any combination, and IPV.

There is also a new category created under measles-mumps-rubella vaccines in any combination that includes rubella to include the injury of chronic arthritis with an onset within 0-42 days after vaccination.

In the Aids to Interpretation of the Injury Table, several changes were noted:

The inclusion of a definition for anaphylaxis and anaphylactic shock.

The inclusion of a definition for acute and chronic encephalopathy.

The inclusion of a definition of a significantly decreased level of consciousness.

The process for determining that a child has not returned to a normal neurological state.

Criteria for residual seizure disorder making the temperature standard more consistent with the threshold for febrile seizure-changed from 102^0 F to 100^0 F with the additional provision that the 2 post vaccination seizures need to be separated by at least 24 hours.

The inclusion of a definition for sequelae.

The inclusion of a definition for chronic arthritis.

This is hopefully a very positive vaccine safety statement. This amended table goes into effect on March 10, 1995 and any claim filed after that date will be subject to the rules in the new table. Any claim filed prior to that date will be subject to the old table and any person who believes he/she has suffered an injury that is being added to the table has eight years to file a claim.

Vaccine Safety - Dr. B. Chen, Dr. P. Rhoades, and Dr. S. Rosenthal

The report will be deferred until the next meeting in the interest of time. It was proposed by the committee that it be put first on the next agenda.

National Vaccine Program Update - Dr. Roy Widdus

The National Vaccine Program Office (NVPO) had a considerable reduction in its appropriation and FTE's for 1995 to about one-third of what it was previously. The statutory responsibilities of general oversight remain very much the same despite the

reduction in resources. Those are general oversight of vaccine development and integration of immunization efforts both in the public and private sectors. The responsibilities for the National Vaccine Advisory Committee (NVAC) and the National Vaccine Program Interagency Group, consisting of NIH, CDC, FDA, US Agency for International Development, DOD, HRSA, and HCFA, will continue to be supported out of the NVPO. The NVAC met recently and addressed the relationship of immunization data needs to overall health data collection. It also looked at the question of using schools as immunization sites. The NVAC will have three subcommittees during the next year. One will be on expanding immunization coverage, particularly looked at the issues of immunization coverage in managed care programs and other insurance issues. The second will be on Vaccine Safety (jointly with the ACCV). The existing subcommittee that is looking at future vaccine development will be continued. Because of the reduction in funding, the subcommittees will be supported in the future by whichever public health service agency is most relevant. For Vaccine Safety-HRSA, for Immunization Coverage Expansion-CDC, and for Future Vaccine Development-NIH.

In addition, the NVPO continues to coordinate federal activities, following up on the NVAC report on Adult Immunization and working closely with HCFA and CDC on those activities. The next meeting of the National Vaccine Advisory Committee is scheduled for May 11-12, 1995. Three major issues will be discussed at that meeting: (1) the study of the economic picture of the US vaccine industry, (2) a discussion of the various facets of insuring consistency between recommendations for use and labeling, and (3) a report to NVAC on an interagency activity to develop a plan for coping with pandemic influenza.

Dr. Davis thanked the committee members for a very productive meeting. Committee members will be contacted regarding the specific dates for comments on the draft recommendation. He then asked for public comment on issues and concerns. There was none.

The meeting was adjourned at 4:15 p.m.

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

Jeffrey P. Davis, MD,
Chairman, ACIP

Date: _____