CENTERS FOR DISEASE CONTROL
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
OCTOBER 21-22, 1992
Auditorium A

Desk Copy

WEDNESDAY

9:00 8:30	Issues Regarding Reversion of Oral Polio Vaccine Virus Following Inactivated Polio Vaccination	Dr. Olen Kew
9:15	Danish Experience with an IPV\OPV Vaccination Schedule	Dr. Olen Kew Dr. Ivor Heron Statens Seruminstitut
10:20 9:30	Environmental Sampling for Wild Poliovirus	Dr. Jim Alexander Dr. Jon Andrus PAHO Dr. Rebecca Prevots
10:30 10:00	Polio Outbreak in the Netherlands	Dr. Frick Van Loon
10:10	BREAK	
10:30	Summary of WHO Meeting on Safety of High Titer Measles Vaccines	Dr. Samuel Katz Dr. Lauri Markowitz Dr. Ted Mortimer
11:00	Variation in Immunogenicity of Merck Hib Conjugate Vaccine	Dr. Jay Wenger Dr. Carl Frasch FDA ~~Dr. Pamela Adkins~~ Gary Calava Merck & Company Inc.
11:45	Update on BCG	Dr. Pierce Gardner Dr. Robin Huebner
12:00	LUNCH	
~~1:00~~ 1:30	General Recommendations for Immunization	Dr. Sonja Hutchins Dr. Charles Lebaron Dr. John Watson Dr. Walt Williams
2:30	Immunization in Bone Marrow Recipients	Dr. Bob Chen
2:45	BREAK	
3:00	Postexposure Prophylaxis for Hepatitis C	Dr. Miriam J. Alter 3:50 Thompson left
3:30	Change in Sensitivity of Test Kits for Anti-HBs: Implications for Pre- and Post Hepatitis B Vaccination	Dr. Miriam J. Alter
4:15	Low Serological Response Following Rabies Preexposure Intradermal Vaccination	Dr. James Childs Dr. Robin Ikeda NYS Dept. of Health
4:45	Proposed Changes in ACIP Recommendations Regarding Ferrets and Rabies	Dr. James Childs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL

MINUTES OF MEETING

Advisory Committee on Immunization Practices
October 21-22, 1992
Atlanta, Georgia

COMMITTEE MEMBERS PRESENT

Dr. Samuel L. Katz, Chairman
Dr. Mary Lou Clements
Dr. Kathryn Edwards
Dr. Neal Halsey
Dr. Gregory Istre
Dr. Rudolph Jackson
Dr. Carlos Ramirez-Ronda
Dr. Fred Thompson
Dr. Joel Ward

Ex Officio Members

Dr. Carolyn Hardegree (FDA)
Dr. John LaMontagne (NIH)

Liaison Representatives

Dr. Marvin Amstey (ACOG)
Dr. Keith Clark (NASPHV)
Dr. Pierce Gardner (ACP)
Dr. Caroline B. Hall (AAP)
Dr. Edward Mortimer, Jr. (AMA)
Dr. Georges Peter (AAP)
Dr. Michael Peterson (DOD)
Dr. William Schaffner, II (AHA)
Dr. Susan E. Tamblyn (NACI)
Dr. Ronald C. Van Buren (AAFP)

Executive Secretary

Dr. Claire V. Broome

NAVY ENVIRONMENTAL HEALTH CENTER

Capt. S. William Berg
Capt. Robert Brawley

HHS STAFF PRESENT

NATIONAL INSTITUTES OF HEALTH

Pamela McInnes, NIAID
Dr. Regina Rabinovich, NIAIP

CENTERS FOR DISEASE CONTROL

Office of the Director

Amanda Tarkington
Kevin Malone

National Center for Infectious Diseases

Dr. Miriam Alter
Dr. Michael Beach
Dr. Nancy Cox
Dr. Mitch Cohen
Dr. Carmen Deseda
Dr. Martin Favero
Dr. Laura Fehrs
Dr. Brian Mahy
Dr. James Hughes

National Center for Prevention Services

Dr. Stephen L. Cochi
Dr. Bob Chen
Ms. Rosamond Dewart
Dr. Steve Hadler
Dr. Lain Heath
Dr. Kimberly Heath
Dr. Sandra Holmes
Dr. Mary Hutton
Dr. Arthur Manohara
Dr. Laurie Markowitz
Dr. Anne Mellinger
Dr. Walter Orenstein

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
OCTOBER 21-22, 1992
Auditorium A

THURSDAY

	H Flue conjugate	Dr. Ward
8:30	National Vaccine Program Update Influence on Vaccine Research and and Development of Possible "Sole Source" Contract for Public and Private Vaccine	Dr. Steve Sepe
8:45	Suspension of Use of Urabe Mumps Strain in the United Kingdom	Dr. Walt Orenstein Dr. David Salisbury Dept. of Health, London
9:15	Risk of Guillain-Barre Syndrome Following Influenza Vaccination 1990-91	Dr. Bob Chen
9:45	BREAK	
10:00	Immunization Schedule	Dr. Samuel Katz
10:30	Vaccination Recommendations for Health Care Workers	Dr. Ray Strikas
11:00	Summary of FDA Workshop on Package Inserts and Warnings for Use of Vaccines	Dr. Steve Hadler
11:10	Update on Research Priorities of Division of Immunization	Dr. Lauri Markowitz Dr. Steve Hadler
11:45	Update on Immunization Action Plans	Dr. Roger Bernier
12:00	National Vaccine Injury Compensation Program Update - Changes in Injury Compensation Table	Dr. Vito Caserta National Vaccine Injury Compensation Program Dr. Steve Sepe
12:20	Public Comment	
12:45	ADJOURN	

Adjourn 12:10

National Center for Prevention
Services Continued

Dr. Mark Papania
Dr. Stephen Sepe
Dr. Robert Snyder
Dr. Peter Strebel
Dr. Raymond Strikas
Dr. Roland Sutter
Dr. Frederik Van Loon
Dr. John Watson
Dr. Melinda Wharton
Dr. Alan Hinman

OTHERS PRESENT

Paul Albrecht, FDA
Dr. Jon Andrus, PAHO
Dr. Marvin S. Amstey, Highland Hospital
Dr. Julia Barrett, FDA
Patricia Beshak, Plainsboro, NJ
Robin Biswas, FDA
Gary Calandra, Merck Research Laboratories
Dr. Vito Caserta, DVIC
Jill W. Chamberlain, Medical Communications Services
Dr. S. J. Cryz, Swiss Serum and Vaccine Institute Berne
Dr. Barbara Ann DeBuono, Rhode Island Department of Health
Corry Dekker, Chrion Corporation
Dr. J. Michael S. Dixon, Edmonton, Alberta, Canada
Anne Marie Duliege, Chiron Corporation
Craig Engesser, Lederle-Praxis
Dr. Ian Furminger, Medeva International
Dr. Carol Frankel, Medeva International
Dr. Anne A. Gershon, Columbia University
Dr. Karen L. Goldenthal, FDA
Dr. Hilda Grey, Cytel Corp.
Jill Hackell, Lederle-Praxis Biologicals
Dr. Iver Herow, Staten Serum Institute
Cynthia Howe, Institute of Medicine
Barbara Howe, SmithKline Beecham
Dr. RoseMary Hoy, Merck Vaccine Division
Susan Hummel, Sandler Communications
Dr. Robin Ikeda, NYSDOH (EIS Officer)
Byron Jordan, Organon Inc.
Sany Kaufman, Connaught Labs
Robet Kohberger, Lederle-Praxis Biologicals
Dr. Saul Krugman, New York University Medical Center
Kevin G. Lokay, Merck Vaccine
Sharon Mates, North American Vaccine
Frank Malinoski, Lederle-Praxis Biologicals
Sheldon Mazursky, Organon Tekriya Corporation
Carlton Meschievitz, Connaught Labs

OTHERS PRESENT CONTINUED

D.K. McClintock, Lederle-Praxis
Andrew Murdin, Connaught Labs Ltd.
Dr. Michael Olson, Statens Serum Institute
Paul Percheson, Health and Welfare Canada
Georges Peter, Brown University
Dr. Stanley A. Plotkin, Pasteur-Merieux-Gonnaught
Dr. Gregory A. Poland, Mayo Clinic
Valerie Randolph, Lederle-Praxis Biologicals
Timothy T. Rice, Biogen
Marie Rosenthal, Infectious Diseases in Children
Dr. Michael J. Roy, MedImmune, Inc.
Robert L. Scott, Lederle Laboratories
Judith Shindman, Connaught Laboratories Ltd.
Dr. Keith Sikes, NASPHV
Howard R. Six, Connaught Lab Inc.
Dan Soland, Connaught Laboratories
Dr. Mary Ann Sprayer, Indiana State Department of Health
Steve Sternberg, Atlanta Constitution
Kathleen Stratton, Institute of Medicine
Dr. David Strause, SmithKline
Joanne Tatem, Lederle-Praxis Biologicals
Dr. Linda G. Teague, FDA
Charles Trimarachi, NYS Department of Health
Carolyn Weeks-Levy, Lederle-Praxis Biologicals
Eric Whitman, Tech Management Group
John Zahradnik, Alliance Pharmaceutical Inc.
Dr. Barbara A. Zajac, Wyeth-Ayerst Research
Chris Zurawsky, Infectious Disease News

Executive Summary

On October 21-22, 1992, the ACIP convened at the Centers for Disease Control (CDC) to discuss the status of numerous vaccine-preventable diseases and vaccine-related issues. Dr. Samuel Katz presided as Chairperson; Dr. Claire Broome was Executive Secretary.

Dr. Sam Katz, Chairperson, opened the meeting by welcoming members, particularly new members Dr. Fred E. Thompson Jr. and Dr. Joel Ward, and a consultant, Dr. Barbara De Buono, Director of Health from Rhode Island.

Dr. Katz then asked those present to introduce themselves. In attendance were representatives of the pharmaceutical industry, the media, academia, and interested groups, as well as members of national government agencies.

Dr. Katz reminded members that the next ACIP meetings were February 9-10 (slated to begin at 1:00 p.m. on the 9th), 1993, and June 16-17 (usual schedule). However, there might be a conflict with the June 1993 ACIP meeting dates and an immunization conference. Calendars were to be dispersed for members to indicate dates they are not available so a new ACIP meeting date can be chosen.

Dr. Katz then introduced Dr. Claire Broome, the Executive Secretary of the ACIP Committee, who said that the Association of State Veterinarians has proposed a liaison person, Dr. Keith Clark, who will be attending ACIP meetings, with particular interest in the session on rabies. Dr. Broome also expressed thanks to Dr. Hernandez, who resigned from ACIP since the last meeting. Then Dr. Broome reminded members of the importance of indicating any actual or potential conflicts of interest.

Issues Regarding Reversion of Oral Polio Vaccine Virus Following Inactivated Polio Vaccination

Dr. Olen Kew, DVRD, NCID, revisited the issue of whether or not prior immunization with eIPV is associated with increased excretion of neurovirulent revertants when the child is subsequently immunized with OPV. Concern had been raised that if revertants were excreted at significantly higher rates, this might cause an increase in vaccine-associated disease were the United States to switch to a sequential schedule. He summarized virologic studies, which showed that the virologic research of Ogra et al[17] suggesting increased neurovirulence, is at variance with previous studies.

Danish Experience with an IPV\OPV Vaccination Schedule

Dr. Kew then introduced Dr. Ivor Heron, Statens Seruminstitut, Denmark, to explain the Danish experience with the sequential IPV/OPV schedule. Since 1968, the country has had four cases of

paralytic polio. One was definitely vaccine associated; one was possibly associated; two were imported cases.

Since 1986, the wild-type poliovirus has been isolated only three times in stool surveys: two from imported cases and one from a paralyzed child.

Dr. Kew summarized both presentations by saying that neither the virologic nor the epidemiologic evidence shows any basis for serious public health concern about the use of a sequential schedule. In subsequent discussion, it was pointed out that Israel also uses a combined IPV/OPV schedule.

Environmental Sampling for Wild Poliovirus

Dr. Kew then introduced Dr. Jon Andrus, from the Pan American Health Organization, who said that the Polio Eradication Initiative is on the verge of eradicating polio in the Americas. Dr. Andrus's presentation focused on surveillance of wild poliovirus. Sewage testing was done in Cartagena, Colombia--at a site where three culture-confirmed cases had been reported during the 3 months prior to the initiation of the study in mid-April, 1991. Some 240 children <5 years old who had not received vaccine within the last 30 days were enrolled in the study.

All wild polioviruses isolated in this study were type 1. Such poliovirus was detected in 8% of all children enrolled in the study (all inapparent infections) and 22% of sewage samples.

Three methods of sewage water collection were evaluated--two grab sample techniques (Buchner and millipore filter techniques) and one continuous sample technique (gauze pads left in sewage 48 hours); no differences were found. For purposes of PAHO's certification efforts, the cheaper and easier-to-use gauze pads for sewage collection may thus be sufficient, Dr. Andrus concluded.

Next, Dr. Rebecca Prevots, IM, NCPS, and Dr. Jim Alexander, VR, NCID, discussed system sensitivity and resource requirements for environmental sampling. They concluded that stool surveys have known sensitivity but are logistically difficult and expensive. Environmental sampling is logistically easier and less expensive, but researchers are still in the process of identifying and defining factors that affect sensitivity.

Polio Outbreak in the Netherlands

Dr. Frederick Van Loon, IM, NCPS, next reported on the ongoing outbreak of polio in the Netherlands. Since September 17, 1992, 11 cases have been reported, all among unvaccinated population (the same community that had a polio outbreak in 1978) and all caused by wild poliovirus type 3; the strain is from S. Asia. Dr. Van Loon also summarized CDC's responses to this outbreak.

Variation in Immunogenicity of Merck Hib Conjugate Vaccine

Next, Lauri Markowitz, IM, NCPS, summarized a recent meeting of the World Health Organization (WHO) on the safety of high-titer measles vaccines in infants. The meeting was held in Atlanta June 16-17, 1992. The meeting summarized studies in Guinea Bissau, Senegal, Haiti, The Gambia, Mexico, and the Philippines on this subject, presented modeling commissioned by WHO to look at the impact of these findings, and had an expert panel charged with making recommendations. The conclusions of the panel were as follows:

--Significant associations between high-titer measles vaccine and increased mortality were noted in several studies.
--The effects associated with high-titer vaccines are multiplicative and not additive, i.e., the negative effect multiplied background death rate, rather than adding an absolute risk.
--Female infants were at high risk after high- titer vaccine.
--The dose of the vaccine appeared to be a major factor associated with delayed mortality.

The panel recommended that: 1) high-titer measles vaccines ($>10^{4.7}$) not be used in immunization programs; 2) further field trials with high-titer vaccines not be conducted; 3) continued studies to develop measles vaccines that can be given to infants as early in life as possible be endorsed; 4) post-licensure field trials of new measles vaccines be designed to be capable of identifying late mortality; 5) biologic and virologic response after receipt of measles vaccine be studied.

Variation in Immunogenicity of Merck Hib Conjugate Vaccine

Dr. Jay Wenger, BD, NCID, introduced this subject and two speakers, Dr. Gary Calandra, from Merck & Company Inc. and Dr. Carl Frasch from FDA.

Dr. Calandra gave a thorough detailing of Merck's large-scale investigation initiated once the NIH alerted the manufacturer in June, 1992, that one of its studies showed a lower than expected titer with Merck Hib conjugate vaccine (PEDIVAXHIB). Merck has prepared a letter to physicians, in collaboration with CBER, recommending an additional dose of PedivaxHib for any infant or child who received at least one dose of a lot in question. The Merck Vaccine Division can track 99% of the doses and will notify physicians. Merck will supply an 800 number to provide help and answer all questions. Merck will also supply vaccine to replace vaccine, give credit, or give cash payment.

Dr. Ward, an ACIP member who is doing post-licensure safety evaluations of the vaccine at UCLA, spoke briefly about the

differences in antibody levels and the possible increase or lack of increase in disease risk for children who received one or more doses of suboptimal Hib vaccine. He summarized UCLA's study of vaccine failures throughout the country (there are a total of 15 cases of disease known in children who had received 1 or more doses of PRP OMP vaccine). Given the fact that we don't have geographical breakdown, age breakdown, or a dose breakdown, Dr. Ward said that he doesn't know if children who received the vaccine are at increased risk or not.

Next, Dr. Frasch of the FDA summarized FDA's role in this situation. He also noted that on September 17, the FDA approved Connaught's Hemophilus b conjugate vaccine as a booster to be given at 12-15 months of age after primary vaccination with any approved infant immunization series.

Dr. Wenger noted that a number of groups have reported drastic decreases in Hib disease, and that, since early 1990, 32 million doses of this vaccine have been distributed. Thus, the involved lots represent about 1% of the vaccine distributed. Therefore, the impact of the questionable lots on disease in the United States should be minimal.

Dr. Ward asked if the ACIP wanted to prepare a paragraph for the MMWR to acknowledge the problem and offer reassurance. Dr. Carolyn Hall said that the Red Book committee has already met and felt that there were a number of questions that couldn't be answered in the Merck/FDA letter and that a letter should be drafted to all the members of the AAP to answer some of these questions.

In subsequent discussion, members pointed out grave concerns--in terms of feasibility--about the impact of Merck's strategy on physicians, who theoretically would need to go through every record to check it against 16 lot numbers. A simplified approach was urged.

Dr. Ward reiterated his concerns, namely that, from a public health standpoint, a full-scale alert might only catch one or two cases and that 50% of the children couldn't be reached now. Because of all of the questions raised by this issue, Dr. Katz asked Drs. Wenger, Ward, Calandra, Mortimer and Hall to meet and report back some recommendations to the group later.

Update on BCG

Dr. Pierce Gardner reported that the BCG Subcommittee continues to wrestle with the issues of 1) efficacy of BCG in preventing tuberculosis in adults and 2) concerns about immunizing children born to mothers that are HIV- and TB-positive. He then introduced Dr. Robin Huebner, TB, NCPS.

Dr. Huebner said that since the last ACIP meeting a CDC BCG working

group was formed, composed of Dr. Frederick Van Loon, Dr. Ida Onorato, Larry Geiter, Michael Cantwell, and Dr. Huebner. Several activities have been planned:

1. $105,000 has been awarded to the Harvard School of Public Health to preform a quantitative meta-analysis of existing BCG data.
2. The subcommittee has contacted investigators in the United Kingdom, Sweden, the Netherlands, and Canada to see if they have databases which CDC could use to determine the efficacy of BCG in adults or health care workers (HCWs). All of these countries use BCG in HCWs. However, the working group found that these countries don't keep good statistics in this area.
3. The Hospital Infection Program at CDC is doing follow-up on some of the hospitals in New York that experienced outbreaks.
4. The Surveillance and Epidemiologic Investigations Branch is going to conduct two studies looking at TB in children.
5. CDC is providing technical assistance to Organon Technica, the company that has the licensed BCG vaccine for immunization in the United States. This company has developed a surveillance program to collect follow-up information on HCWs who received their vaccine.

Next, Dr. Katz asked a visitor, Dr. Ian Furminger, Medeva Evans, if he could give the Committee any insights about the United Kingdom's experience with BCG in HCWs. Dr. Furminger said that in the U.K., they've been using BCG in approximately 12-year-old children for about 30 years. The children are vaccinated at school, and coverage is very high. Very few efficacy studies have been done, but the public health service monitors an area in Redding, where they look at tuberculin conversion postvaccination. Over the last 20 years, checking 2,000 children a year, the conversion rate has been about 95%.

General Recommendations for Immunization

Dr. John C. Watson, IM, NCPS, led a one-hour-plus discussion of changes to the ACIP "General Recommendations on Immunization." All members received handouts with underlined changes, which Dr. Watson reviewed. Subsequent discussion focused on multiple vaccinations; jet injectors; immune globulin; vaccination of persons with hemophilia; and Table 4.

Postexposure Prophylaxis for Hepatitis C

Dr. Miriam J. Alter, VR, NCID, reviewed the studies that have attempted to assess prophylaxis with immunoglobulin (Ig) against non-A, non-B hepatitis and that led to the lukewarm ACIP recommendation. Virtually all the studies assessing IM prophylaxis

with Igs were done in transfusion recipients. All the studies did seem to suggest a positive prophylactic effect for Ig.

Dr. Alter also gave current data on the risk of HCV infection from needle-stick injuries. A review of three studies shows that there is a risk of acquiring HCV from needle-sticks, she said.

Dr. Michael Beech, a molecular virologist from CDC's Hepatitis Branch, then reviewed current data on immune response to HCV. The studies he briefly reviewed suggested that HCV infection does not elicit protective immunity against reinfection with either homologous or heterologous strains. In a subsequent question and answer period, it was noted that, since last spring, the FDA has been recommending screening whole plasma donors for anti-HCV; that one-half of HCWs tested may be false positive, based on results of supplemental assays; and that supplemental tests are under review at the FDA.

Following these presentations, Dr. Alter asked the ACIP if they felt there were sufficient data to modify the current ACIP recommendations. No conclusion was reached.

Change in Sensitivity of Test Kits for Anti-HBs: Implications for Pre-and Post-Hepatitis B Vaccination

Next, Dr. Alter discussed test kits for detection of antibody to hepatitis B surface antigen (Anti-HBs). Such kits, licensed by the FDA, can be used for several reasons. Of concern in this discussion was when they are used to evaluate immunity prior to or following hepatitis B vaccination. Since March 1986, manufacturers of these test kits have altered commercially available kits to increase their sensitivity. In 1991, the FDA conducted studies on currently distributed ones to determine the lower limits of their detection relative to the World Health Organization Anti-HBs Reference Preparation. These studies estimated the lower limits of detection to be below 5 mIU/mL.

Accordingly, a positive result determined by any current licensed anti-HBs test kit (EIA or RIA) could mean that the actual quantity of anti-HBs present may be less than 10 mIU/mL and not indicative of immunity. CDC did some tests to assess the potential impact of this increased sensitivity on the rate of false-positive tests results. Their data are consistent with earlier studies showing that in some persons, low-level anti-HBs may occur along with anti-HBc, indicating prior infection with HBV; in others, low level isolated anti-HBs may indicate prior exposure to HBV and immunity from reinfection.

This information and proposed FDA labeling changes for these test kits may cause concern among those who, by virtue of a single anti-HBs test since 1986, have been told they are immune either pre- or post-vaccination. However, CDC feels that the positive predictive

value of tests is extremely high, and routine re-testing of persons on whom either pre- or post-vaccination screening has been done is not warranted.

Immunization in Bone Marrow Recipients

Dr. Bob Chen, NCPS, revisited the subject of an ACIP statement for immunization of bone marrow recipients. He has shared the draft ACIP statement with the Advisory Committee on Bone Marrow Transplant Registry as well as with 10 bone marrow transplant experts for their comments. He has received some feedback, to date, all good. The deadline for comments is December 1.

Monovalent Tetanus Toxoid and Tetanus Immune Globulin

Dr. Katz brought up two issues, not on the agenda, for discussion. The first was the amount of monovalent tetanus toxoid (TT) being used instead of tetanus diphtheria toxoid (TdT). Dr. Ted Mortimer said that, in talking with FDA, he found that enormous amounts of TT are still being sold, even though there are very few indications for its use. It was suggested that the reason some hospitals are still using TT is because it costs less than TdT.

Secondly, someone reported that Connaught had a problem with its last batch of tetanus immune globulin. It failed FDA testing and is back ordered. There are no other manufacturers of this product. In response to this comment, Dr. Walt Orenstein, IM, NCPS, said that, when notified of this problem, CDC contacted FDA and was told they had released three lots recently, and that the FDA was unaware of the shortage.

Finally, Dr. Katz noted that since the last ACIP meeting, a second acellular DTP vaccine was licensed, Tripedia.

Low Serological Response Following Rabies Preexposure Intradermal Vaccination

Dr. Robin Ikeda, from the New York State Dept. of Health, summarized two studies undertaken in New York to determine the prevalence of and risk factors for low serologic response following primary preexposure rabies vaccination by intradermal route. Low serologic response occurred in both cohorts. Subjects who were older and those with increased body mass index tended to be at greater risk. These studies raise the question, Dr. Ikeda said, of whether routine serologic testing should be recommended following intradermal vaccination.

Accordingly, the New York State Health Department has made the following recommendations: 1) preexposure immunization be done by the intramuscular route; 2) if the intradermal route is used, follow-up serologic testing should be done; 3) if these recommendations are implemented on a widespread basis, increased

rabies serologic testing needs to be made available throughout the United States.

Dr. James Childs reminded ACIP members that ID vaccine is not recommended for persons postexposure or for those taking immunosuppressant drugs. He said that 2%-10% of vaccinees may have inadequate titers by some definition within one year of ID immunization. The problem is that most serologic tests of vaccinees are not done within 2 weeks after immunization, as recommended by the ACIP. Data do indicate anamnestic response to IM booster, even if titer is <1:5. Finally, the data are unclear for timing or the type of antibody response following booster, especially when the titer was unacceptable at 2-4 weeks postimmunization.

Based on these findings, CDC is currently recommending the following: 1) no change in current ACIP recommendations; 2) a study of booster (ID and IM) response of individual seronegative 2-4 weeks after primary ID immunization be initiated; 3) the wording of the ACIP statement regarding serologic testing be examined.

Proposed Changes in ACIP Recommendations Regarding Ferrets and Rabies

Next, Dr. Childs proposed two changes to the ACIP rabies statement regarding ferrets to synchronize them with the Compendium of Rabies Control, by the National Association of Public Health Veterinarians. Subsequent discussion and a vote of the members determined that the facts (and lack of them; for example, details on the course of rabies disease in ferrets are unknown) need to be spelled out in the ACIP statement and that Dr. Childs' recommended changes not be accepted as is but first be simplified and clarified.

Dr. Katz adjourned the meeting for the day at 5:35 p.m. The meeting reconvened on October 22 at 8:05 a.m.

Calendars were passed out to all members, who were asked by Dr. Katz to sign them and X-out the days they were not available in June 1993 and submit them to Gloria Kovach.

Ad Hoc Committee Report on Variation in Immunogenicity of Merck Hib Conjugate Vaccine

Joel Ward discussed the Merck HIB lot potency issue. He said the ad hoc committee had met twice and received a copy of the proposed letter that has been submitted to FDA for approval. He read excerpts from it to the ACIP committee. He said that the ad hoc committee, which included both AAP and ACIP members, was concerned that implementation was not possible. They also suggested additions or changes to the letter.

A Merck representative was asked if the manufacturer would change the letter. She said she could not answer; that, obviously, there are legal and ethical concerns for Merck, which dictate an approach that is not necessarily practical for others. However, she would bring that message back to Merck. Dr. Peter then asked if a conference call between the ACIP ad hoc group and the AAP committee on infectious diseases (the Red Book Committee) could be arranged. She said she thought that was a valuable suggestion and she thought it could be arranged to develop a consensus. Dr. Katz designated Dr. Ward to represent ACIP; Dr. Hall will represent the Red Book at such a meeting.

National Vaccine Program Update

Dr. Steve Sepe, NCPS, explored the advantages and disadvantages of federal purchase of all vaccines. He also announced that CDC and the National Vaccine Program Office have developed a scope of work and have negotiated a contract with Mathematica Policy Research, Inc. (MPR) to examine the economic and commercial underpinnings associated with alternatives to supplying vaccine. MPR will begin by developing a background paper, based on a literature review and interviews with experts. Then a panel of economists will be appointed.

Dr. Katz said this was a major issue and asked Dr. Sepe to distribute a copy of his presentation to the Committee. He said the ACIP needs the opportunity to review the document and have an impact, at least through providing data, before the issue is turned over to the panel of economists.

Dr. Pierce, representing the Adult Immunization Committee, asked if the panel would extend the analysis to include at least the two major adult vaccines--influenza and pneumococcus.

Suspension of the Use of Urabe Mumps Strain in the United Kingdom

Next, Dr. Orenstein introduced Dr. David Salisbury, Director, Department of Health, London, United Kingdom. Dr. Salisbury described a unique laboratory surveillance technique for adverse events which led to the United Kingdom's making the purchasing decision not to buy any more Urabe vaccine once it was found to be associated with meningitis. (The United Kingdom has a unifying purchasing and distribution policy for all vaccines.)

In subsequent discussion, Dr. Tamblyn noted that Canada had similar problems with Urabe vaccine and its license was suspended in that country. Dr. Plotkin said that French data also indicate that this vaccine is associated with meningitis.

Risk of Guillain-Barre Syndrome (GBS) Following Influenza Vaccination 1990-1991

Dr. Robert Chen then updated the ACIP on the risk of GBS following flu vaccination in 1990-91. Restricting the analysis to definite GBS cases only results in the following relative risk (RR) for 18- to 64-year-olds in the primary sites, depending on the risk window: 6 weeks: RR = 2.1; 12 weeks: RR = 4.1. Otherwise, there is no clear association between GBS and flu vaccination, and it was decided that no changes in the current recommendations were warranted.

Vaccination Recommendations for Health-Care Workers

Dr. Ray Strikas, IM, NCPS, distributed a preliminary draft and a handout of "points for discussion" of an ACIP statement for HCWs. In subsequent discussion, Committee members suggested changes regarding polio vaccine; said CDC should come to grips with whether postimmunization serologies on HCWs who are immunized with hepatitis B vaccine should be routine; acknowledge OSHA's requirements in the document; add a section on immunocompromised HCWs; and mention diphtheria and tetanus. Dr. Katz reminded Committee members to review the ACIP statements on general immunization and HCWs and to submit comments about them by Nov. 20th.

Summary of FDA Workshop on Package Inserts and Warnings for Use of Vaccines

Dr. Steve Hadler, IM, NCPS, next reported on results of an FDA workshop on package inserts, held on September 18, 1992, in which CDC and the ACIP were asked to participate. He summarized differences--usually not major--between package inserts and ACIP recommendations. He said that CBER of FDA will be having an internal meeting on November 19 to review the revised package inserts and return them to manufacturers for further revision. The docket will be open for comment through December 18. The final rule is to be published in January.

Update on Research Priorities of Division of Immunization

Next, Dr. Lauri Markowitz gave an overview of future research plans of the Division of Immunization. In all, 11 studies are pending, under way or recently completed on measles; 1 on tetanus; 8 on domestic or international polio issues; 2 on rubella; 2 on varicella; 3 on pertussis; 2 on pneumococcal vaccine; 2 on influenza; 1 on hepatitis B vaccine; and 2 on vaccine safety. (See minutes for details.)

Update on Immunization Action Plans

Dr. Roger Bernier, IM, NCPS, reminded the ACIP that six cities had been funded one year ago to develop immunization action plans. In August, Congress made an additional $45 million available for immunization; CDC decided to use it to extend these plans.

Accordingly, in August, DHHS Secretary Louis Sullivan, MD, announced the disbursement of the $45 million to assist 87 areas around the country in implementing local immunization action plans. Dr. Bernier outlined how the funds were awarded and what they were awarded for.

National Vaccine Injury Compensation Program Update--Changes in Injury Compensation Table

Dr. Vito Caserta, Division of Vaccine Injury Compensation, HRSA, next outlined the changes that Secretary Sullivan recently proposed making in the Federal Vaccine Injury Table, as outlined in the Federal Register of August 18, 1992. Dr. Sepe handed out copies of the old and proposed tables, as well as a summary of proposed changes to it and the Aids to Interpretation. He said that public and written comments will be accepted for 6 months. A public hearing will be held on December 3, and, in February, HHS will publish a final rule in the Register.

Following Dr. Caserta's presentation, Dr. Katz tabled discussion of examination of immunization schedules until the next meeting. He also reminded members that Dr. Ken Bart has sent a fax, which was distributed, reviewing the National Vaccine Program activities. He reminded members to that Gloria Kovach needs their calendars to schedule an alternative date for the June 1993 meeting.

Dr. Katz then adjourned the meeting at 12:10 p.m.

Note: For a "reminder" listing of agreed-upon actions, see the last page of the complete minutes.

The ACIP convened in Auditorium A of the CDC, Atlanta, Georgia, on October 21, 1992, at 8:35 a.m. Samuel Katz, MD, Wilburt C. Davison Professor, Duke University Medical Center, presided as Chairperson.

In attendance were representatives of the pharmaceutical industry, media, academia, and interested groups, as well as members of national government agencies.

Welcome and Opening Remarks

Dr. Sam Katz, Chairperson, opened the meeting by welcoming members, particularly new members Drs. Fred E. Thompson, Jr., and Joel Ward and consultant Dr. Barbara De Buono, Director of Health, Rhode Island.

Dr. Katz then asked those present to introduce themselves. In attendance were representatives of the pharmaceutical industry, the media, academia, and interested groups, as well as members of national government agencies.

Dr. Katz reminded members that the next ACIP meetings were February 9-10 (slated to begin at 1:00 p.m. on the 9th), 1993, and June 16-17 (usual schedule). However, there might be a conflict with the June 1993 ACIP meeting dates and an immunization conference. Calendars were to be dispersed for members to indicate dates they are not available so a new ACIP meeting date can be chosen.

Dr. Katz then introduced Dr. Claire Broome, the Executive Secretary of the ACIP Committee, who said that the Association of State Veterinarians has proposed a liaison person, Dr. Keith Clark, who will be attending ACIP meetings, with particular interest in the session on rabies. Dr. Broome also expressed thanks to Dr. Hernandez, who resigned from ACIP since the last meeting. Then Dr. Broome reminded members of the importance of indicating any actual or potential conflicts of interest.

Issues Regarding Reversion of Oral Polio Vaccine Virus Following Inactivated Polio Vaccination

Dr. Olen Kew, DVRD, NCID, revisited the issue of whether or not prior immunization with eIPV is associated with increased excretion of neurovirulent revertants when the child is subsequently immunized with OPV. Concerns had been raised that if revertants were excreted at significantly higher rates, this might cause an increase in vaccine-associated disease if the United States were to switch to a sequential schedule. He summarized virologic studies, which showed that the virologic research of Ogra et al[1] suggesting increased neurovirulence, is at variance with previous studies. The reason for this variance, Dr. Kew said, could be because Ogra used a virologic technique (plaque) not usually used for characterization of clinical isolates, and, more importantly, that the times at which samples were taken for virus isolation were

inconsistent within the study and were not as favorable for detecting revertants as the methods used by other researchers. (In subsequent discussion, a representative from Lederle Praxis said that Ogra also used a slightly different formulation of OPV, though the strain was theoretically the same, than did other studies.)

Danish Experience with an IPV\OPV Vaccination Schedule

Dr. Kew then introduced Dr. Ivor Heron, Statens Seruminstitut (SSI), Denmark, to explain the Danish experience with the sequential IPV/OPV schedule. Dr. Heron explained that Denmark uses IPV with subsequent OPV; some 55,000-63,000 doses are administered yearly in a combined schedule that requires 9 different vaccinations. IPV is manufactured by the SSI. Since 1988, the country has used e-IPV. Dr. Heron said that, unfortunately, the data he was presenting were derived from use of the weak IPV, in use before 1988.

Since 1968, the country has had four cases of paralytic polio. One was definitely vaccine associated; one was possibly associated; two were imported cases.

Denmark also does stool surveys each year from 1,000-2,000 hospitalized persons to check for circulation of wild poliovirus strains. In the last 23 years, 30,000 feces samples have been examined. Since 1986, the wild-type poliovirus has been isolated only three times, two from imported cases and one from a paralyzed child.

Dr. Kew summarized both presentations by saying that neither the virologic nor the epidemiologic evidence shows any basis for serious public health concern about the use of a sequential schedule. In subsequent discussion, it was pointed out that Israel also uses a combined IPV/OPV schedule.

Environmental Sampling for Wild Poliovirus

Dr. Kew then introduced Dr. Jon Andrus, from the Pan American Health Organization, who said that the Polio Eradication Initiative is on the verge of eradicating polio in the Americas. Last year, there were only nine cultured-confirmed cases reported--8 from Colombia and 1 from Peru. That last, Peruvian, case is the last reported case, and it occurred more than 1 year ago. In July, 1990, the International Certification Committee met for the first time, and mandated criteria to be used for certification that fall under two general headings: surveillance of acute flaccid paralysis and surveillance of wild poliovirus.

Dr. Andrus' presentation focused on one of these criteria, absence of wild poliovirus, as documented by surveys. Surveillance for wild poliovirus can focus on surveys of normal children or on environmental sampling. PAHO elected to evaluate the usefulness of

school surveys of healthy children and testing of sewage in tropical communities for detecting wild poliovirus. The study site, Cartagena, Colombia, with a population of 80,000, situated on the Atlantic Coast, was chosen because three culture-confirmed cases had been reported from there during the 3 months prior to the initiation of this study in mid-April, 1991. All cases were from a section of the city located along a large, stagnant tropical lagoon. Open canals, easily accessible to children and domestic animals, carry raw sewage from homes within the high-risk study area to the lagoon. Sewage samples were collected from three sites located in each of the four large canals. Some 240 children <5 years of age who had not received vaccine within the last 30 days were enrolled in the study.

All wild polioviruses isolated in this study were type 1. Such poliovirus was detected in 8% of all children enrolled in the study (all inapparent infections) and 22% of sewage samples.

Three methods of sewage water collection were evaluated--two grab sample techniques (Buchner and millipore filter techniques) and one continuous sample technique (gauze pads left in sewage 48 hours); no differences were found. For purposes of PAHO's certification efforts, the cheaper and easier-to-use gauze pads for sewage collection may thus be sufficient, Dr. Andrus concluded.

However, questions still remain about the system's sensitivity of community surveillance and the interpretation of negative results. Because of these concerns, PAHO recommends the following:

--such studies should be done during the high season of transmission in risk areas where polio outbreaks typically occurred in the past.
--efforts to improve sensitivity of sewage collection techniques be encouraged.
--strict adherence to the reverse cold chain must not be overlooked, otherwise the probability of isolating wild poliovirus decreases even when it is present.
--laboratory concentration and purification steps need further evaluation to improve sensitivity, particularly when some of the more transitional reagents may interfere with the polymerase chain reaction (PCR).

Next, Dr. Rebecca Prevots, IM, NCPS, and Dr. Jim Alexander, VR, NCID, discussed system sensitivity and resource requirements for environmental sampling. Dr. Prevots said that the development of highly sensitive diagnostic techniques, such as the PCR, has raised the possibility that direct detection of wild poliovirus might be able to replace detection of disease. The presence of virus in communities could theoretically be detected by stool surveys of asymptomatic children or environmentally sampling of waste waters and solids. However, the feasibility, sensitivity, and cost-effectiveness of these alternative approaches need to be assessed

to see if they could become a useful adjunct to case surveillance.

She presented some preliminary estimates of system sensitivity and resource requirements for a single stool survey of a random sample of children <5 years old and an environmental sampling survey conducted in one city. The hypothetical study site selected was a U.S.-Mexico border city, population 500,000, including 50,000 children under 5 years old. Vaccination coverage rate was 75% for those children.

Dr. Alexander said that the field costs for such a 250-specimen stool survey would be $30 per specimen, for a total of $7500. The laboratory costs, at $500 per specimen, would be $125,000; thus, a stool survey for one city would cost an estimated $132,000.

The environmental sample would be based on collection of a 2-liter sample of sludge, which would contain 100 g of solids. For low rates of infection, such as 1/10,000, the probability of detecting wild poliovirus from one or more sludge samples would be 60%-70%. As infection rates increase, detection probabilities tend to approach 100%.

An environmental sampling survey, as described, would cost approximately $32,000, Dr. Alexander said.

In conclusion, Dr. Alexander said, stool surveys have known sensitivity but are logistically difficult and expensive. Environmental sampling is logistically easier and less expensive, but we are still in the process of identifying and defining factors that affect sensitivity.

The Polio Laboratory at CDC is participating with PAHO in environmental sampling field studies in the Americas. To address the unresolved issues, both for the Americas and the global eradication effort, CDC is initiating collaborative studies with the University of North Carolina to determine optimal concentration techniques for environmental samples and to compare sensitivity of virus isolation and PCR. Secondly, the molecular virology section is developing combined biological and molecular detection methods for identification of unknown wild poliovirus genotypes. Third, CDC proposes to conduct field studies in polio-endemic countries to compare environmental sampling's and stool surveys' sensitivity for wild poliovirus detection.

Polio Outbreak in the Netherlands

Dr. Frederick Van Loon, IM, NCPS, next reported on the ongoing outbreak of polio in the Netherlands. Since September 17, 1992, 11 cases have been reported, all in an unvaccinated population (the same community that had a polio outbreak in 1978) and all caused by wild poliovirus type 3; the strain is from S. Asia.

Why is this outbreak important to the United States? In 1978, the Netherlands had 80 cases among these members of the Reformatory Church. The outbreak spread to Canada, which had 6 cases, to the Amish population in the United States, which subsequently had 15 cases, including 10 of paralysis.

In the Netherlands, OPV is only used to control outbreaks. The following steps have been undertaken to prevent a polio outbreak among Amish in the United States:

1). CDC has informed all State Epidemiologists and Immunization Program Managers in states with Amish (Pennsylvania, Ohio, Indiana, New York).
2) An MMWR article has been published[2] and articles have been sent to newspapers and to the Amish bishops
3) Immunization efforts are being intensified in certain communities
4) CDC is trying to set up surveillance systems in the areas at risk, including school stool surveys.

Since the Committee is supposed to decide if there is justification for changing the U.S. schedule to a combined schedule, Dr. Katz asked if there were any questions. There were none. Dr. Katz then asked Dr. Susan Tamblyn, Medical Officer of Health with the Canadian National Advisory Committee on Immunization (and a liaison representative)to give the committee a run-down on the Canada experience. She said that a couple of provinces are using IPV; a large number of provinces using only OPV; Ontario, which was using IPV had to switch suddenly to OPV in 1990, when there was a shortage of vaccine; (there have been on cases of vaccine-associated polio in the subsequent 3-year period.)

Dr. Katz said that what struck him most about the Danish presentation was their extraordinary compliance and efficacy of their health programs. He asked Dr. Walt Orenstein, to address that. Dr. Orenstein said that most child in the United States get some vaccination in their first year of life; the big fall-off occurs in the second year of life. In inner cities, the estimated complete immunization rate for DTP, 3 OPV and 1 MMR by the second birthday, is 40%-60%, and as low as 10%. If the United States went to a schedule of IPV early, with OPV administered in the second year of life, there would be substantial concern about the ability to deliver OPV in inner-city populations.

Variation in Immunogenicity of Merck Hib Conjugate Vaccine

Next, Lauri Markowitz, IM, NCPS, summarized a recent meeting of the World Health Organization (WHO) on the safety of high-titer measles vaccines in infants. The meeting was held in Atlanta June 16-17, 1992. The meeting summarized studies in Guinea Bissau, Senegal, Haiti, The Gambia, Mexico, and the Philippines on this subject, presented modeling commissioned by WHO to look at the impact of

these findings, and had an expert panel charged with making recommendations. The conclusions of the panel were as follows:

> "Associations between high-titer measles vaccine and increased mortality were noted in several studies. The combined analysis suggested a relative risk of about 1.24, a difference which was significant at a p-value of 0.05.
>
> "Other studies which had a far lower overall mortality in the vaccinated and control cohorts did not show increased mortality, suggesting that the effects associated with high-titer vaccines were multiplicative and not additive, i.e., the negative effect multiplied background death rate, rather than adding an absolute risk.
>
> "Of seven analyses that studied the interaction of vaccine effect with gender, six were consistent with the hypothesis that female infants were at high risk after high titer vaccine. Combined analysis of the Senegal and Haiti studies showed an increased delayed mortality relative risk in females of 1.8 ($p<0.02$).
>
> "The dose of the vaccine appeared to be a major factor associated with delayed mortality. Definitive conclusions could not be made about the impact of age of vaccination with high titer vaccine or the strain used."

The recommendations of the panel were as follows:

- High-titer measles vaccines ($>10^{4.7}$) should not be used in immunization programs.
- Further field trials with high-titer vaccines are not recommended.
- Endorsement of continued studies to develop measles vaccines that can be given to infants as early in life as possible
- Post-licensure field trials of new measles vaccines must be designed to be capable of identifying late mortality.
- Biologic and virologic response after receipt of measles vaccine should be studied.

In subsequent discussion it was revealed that the increased mortality observed was not immediate, but 2 years later; the most common causes of death are diarrhea, malaria, and malnutrition. The increased mortality in females is not a question of prejudicial treatment for males for the particular countries studied, Dr. Markowitz said, and there were no difference in the nutritional status of girls and boys, except that the girls were <u>better</u> nourished in the Senegalese study. Some ACIP members hypothesized that the high-titer vaccines were mimicking what has been confirmed in several underdeveloped countries, namely, that increased

mortality is observed up to years later after acute measles. It was also noted that WHO and FDA will probably set a maximum titer that will be allowed. Dr. Katz reminded everyone present that this is not a problem in the United States, since we don't use a high-titer vaccine.

Variation in Immunogenicity of Merck Hib Conjugate Vaccine

Dr. Jay Wenger, DBMD, NCID, introduced this subject and two speakers, Dr. Gary Calandra, from Merck & Company Inc., and Dr. Carl Frasch from FDA.

Dr. Calandra said that in June 1992, Merck initiated a large-scale investigation after the NIH alerted Merck that one of its studies showed a lower than expected titer with Merck Hib conjugate vaccine (PEDIVAXHIB).

On June 15, Merck sent a letter to investigators initiating collection data at numerous sites and alerted and met with CBER. Immunogenicity data were available for several lots showing decreased levels of antipolysaccharide antibody. A chemical test that may be a marker for lots with reduced immunogenicity was also identified. Lots with demonstrable reduced immunogenicity or abnormal values on this test were characterized as having questionable immunogenicity. Numerous lots produced before and after the lots in question had expected immunogenicity. Surveillance of disease is ongoing in two large sites and thus far shows no apparent increase in disease in children receiving lots in question.

Important considerations in assessing the public health impact of this matter include distribution and releases data. All of the lots in question expired by 5/92, and most by 12/91. Approximately 350,000 doses from questionable lots were distributed in the United States. Overall, about 2 million doses of PEDIVAXHIB were distributed. Many of the lots in question were sent to the private sector. Initial distribution was in August 1990; last distribution was in August 1991. Finally, because there was a shortage of the vaccine, most was used very quickly, usually within a couple of months. Merck thinks at least 90% of the vaccine was used before 1992. Good antibody response has been seen in some children who got the lots in question.

Merck has prepared a letter to physicians, in collaboration with CBER, recommending an additional dose of PEDIVAXHIB for any infant or child who received at least one dose of a lot in question. (One caveat to this: if they received a lot not in question at 15 months or older, they would not receive an additional dose.) The Merck Vaccine Division can track 99% of the doses and will notify physicians. Merck will supply an 800 number to provide help and answer all questions. Merck will also supply vaccine to replace

vaccine, give credit, or give cash payment.

Joel Ward, an ACIP member who is doing post-licensure safety evaluations of the vaccine at UCLA, spoke briefly about the differences in antibody levels and the possible increase or lack of increase in disease risk. They distributed approximately 150,000 doses of the Merck vaccine, about half of it of the lots in question. Dr. Ward also has computerized tracking records that were able to determine and call back children who had received known lots of vaccine.

UCLA had conducted five different immunogenicity studies on hundreds of children; the researchers were able to get blood specimens from them within 6 weeks of learning of the problem with the Merck vaccine. The antibody levels were significantly less with the lots in question after a first dose, second dose, and third dose; however, if you give a subsequent "good lot" (as a second or third dose) intermediate levels of antibody response were noted.

He added that Kaiser Permanente has eradicated Hemophilus disease in their population. Before the immunization program, it had 20-30 cases per year, consistently; last year, 2 cases were identified. Both of the children had received questionable lots of vaccine (one after 1 dose, which is not a complete immunization schedule; one after 2 doses of a questionable lot).

UCLA also looked at vaccine failures throughout the country; there are a total of 15 cases of disease known in children who had received 1 or more doses of PRP OMP vaccine. There was a larger number of vaccine failures in children who received only one dose. A few children developed disease a few days after vaccination, when few would expect a vaccine to be protective.

Given the fact that we don't have geographical breakdown, age breakdown, or a dose breakdown, Dr. Ward said that he doesn't know if children who received the vaccine are at increased risk or not.

Next, Dr. Frasch of the FDA told how it first learned that some of the Merck lots were not immunogenic in mid-June. Since then, he said, FDA has had several meetings and conference calls with the manufacturer and received a large amount of data for its analysis. Two weeks after learning of the problem, FDA had an inspection team at Merck and a follow-up inspection two months later. It was the FDA's decision that a "Dear Dr." letter should be sent out to physicians who had used the suspect lots. The letter has undergone several revisions and a final version should be submitted to the FDA for its approval this week or next. Based upon FDA's analysis, it agrees with Merck in its observation that the subpotent lots were all produced during a very confined time period and were therefore not randomly distributed. However, FDA does not believe that the cause of the poor immunogenicity has been determined.

Finally, on September 17, the FDA approved Connaught's Hemophilus b conjugate vaccine as a booster to be given at 12-15 months of age after primary vaccination with any approved infant immunization series.

Dr. Wenger noted that a number of groups have reported drastic decreases in Hib disease. This trend has continued through the early part of this year, so it is clear that Hib disease has responded to the introduction of conjugate vaccines, despite a potential problem with a portion of those vaccines. Since early 1990, 32 million doses of this vaccine have been distributed; thus, the involved lots represent about 1% of the vaccine distributed. Therefore, the impact of the questionable lots on disease in the United States should be minimal.

Dr. Ward asked if the ACIP wanted to prepare a paragraph for the MMWR to acknowledge the problem and offer reassurance. Dr. Carolyn Hall said that the Red Book committee has already met and felt that there were a number of questions that couldn't be answered in the Merck/FDA letter, for a number of reasons, and that a letter should be drafted to all the members of the AAP to answer some of these questions. (Executive Committee approval for this has not yet been obtained.) She said that she has not yet seen the Merck letter. Dr. Ted Mortimer, liaison for the AAP, said that he had to voice concern on behalf of physicians that this letter had been delayed this long.

In subsequent discussion, members pointed out that the long lists of lot numbers and the large window of time involved are going to create a "nightmare" for physicians, who theoretically would need to go through every record to check it against 16 lot numbers, which would be almost impossible, and handle a lot of phone calls. A simplified approach was urged. Merck acknowledge how difficult their strategy might be, but said, not being able to calculate the risk, the most conservative thing to do is to try to determine risk for individual children. Merck knows where 99% of the vaccine went. Two weeks after the letter goes out to all physicians, Merck will call those physicians who received questionable lots, tell that them replacement vaccine will be mailed. (note: FDA pointed out that any licensed product can be used. Also, Dr. Frasch noted that the issue of a recall is moot, since all the lots in question had expired before the issue became known.)

Dr. Ward reiterated his concerns, namely that, from a public health standpoint, a full-scale alert might only catch one or two cases and that 50% of the children couldn't be reached now. Because of all of the questions raised by this issue, Dr. Katz asked Drs. Wenger, Ward, Calandra, Mortimer and Hall to meet and report back some recommendations to the group later.

Update on BCG

Dr. Pierce Gardner reported that the BCG Subcommittee continues to wrestle with the issues of 1) efficacy of BCG in preventing tuberculosis in adults and 2) concerns about immunizing children born to mothers that are HIV- and TB-positive. He then introduced Dr. Robin Huebner, TB, NCPS.

Dr. Huebner said that since the last ACIP meeting (as a result of the controversy on this subject), CDC had a meeting to determine what issues were important and additional information was needed to make an informed decisions about BCG. A CDC BCG working group was formed, composed of Dr. Van Loon, Dr. Ida Onorato, Larry Geiter, Michael Cantwell, and Dr. Huebner. Several activities have been planned:

1. $105,000 has been awarded to the Harvard School of Public Health to preform a quantitative meta-analysis of existing BCG data. In January, they will be reporting back to the subcommittee to indicate whether such an analysis is feasible. If so, they will preform it. Results should be available in May or June. They are being asked to identify the efficacy in adults and in children. They will also do subanalyses on the efficacy of different vaccine strains.

2. The subcommittee has also contacted investigators in the United Kingdom, Sweden, the Netherlands, and Canada to see if they have a database with which we could determine the efficacy of BCG in adults or HCWs. All of these countries use BCG in HCWs. What we have found is that they don't keep any statistics on who gets or doesn't get BCG. There are also no denominator data.

3. The Hospital Infection Program at CDC is doing follow-up on some of the hospitals in New York that experienced outbreaks. There were several foreign-born individuals who might have been vaccinated with BCG that were exposed during those outbreaks. CDC is hoping to get some information on the vaccine status of those HCWs.

4. The Surveillance and Epidemiologic Investigations Branch is going to conduct two studies looking at TB in children. The first is going to identify all the cases of TB in children in Atlanta and then go back and look at how the case was identified, whether or not an infectious adult contact was involved in transmission, and then if there were such an adult, look at that adult in terms of what risk factors (including HIV status) may have promoted transmission. The second study is aimed at determining what impact the AIDS epidemic has had on childhood cases of TB.

5. CDC is providing technical assistance to Organon

Technika, the company that has the licensed BCG vaccine for immunization in the United States. This company has developed a surveillance program to collect follow-up information on HCWs who received their vaccine.

Next, Dr. Katz asked a visitor, Dr. Ian Furminger, Medeva Evans, if he could give the Committee any insights about the United Kingdom's experience with BCG in HCWs. Dr. Furminger said that in the U.K., they've been using BCG in approximately 12-year-old children for about 30 years. The vaccine has also been used in other places, such as Finland and Hong Kong, where they vaccinate neonates. The U.K. also supplies vaccine to UNICEF for use in neonates. There have also been a few cases where the U.K. has used it in neonates, e.g., in small, inner-city Asian populations, where there is a TB problem.

The children are vaccinated at school, and coverage is very high. Very few efficacy studies have been done, but the public health service monitors an area in Redding, where they look at tuberculin conversion postvaccination. Over the last 20 years, checking 2,000 children a year, the conversion rate has been about 95%. Asked about TB rates of late, Dr. Furminger said that TB rates have come down, as with every other country, but that they are not that much lower than in the U.S. per population. In the last year, when the United States has seen an increase, U.K. has had a leveling off, that is, cases are not decreasing as much.

Dr. Stanley Plotkin said that in France, in principle, all children are given BCG when they enter day care or school. Coverage rates are reasonably high. The data from two not very well controlled trials suggest that the vaccine is at least 80% effective. The trends of TB are going down in that country, though it's difficult to say whether it's due to the vaccine or improved sanitation.

Members of the group also told Dr. Huebner that it would be very useful to have data on whether or not children vaccinated at infancy lose skin-test positivity. Dr. Huebner said several studies had looked at that issue and that, in general, between 5 and 10 years after vaccination, the individual's skin test will wane, although it is dependent upon the age when the child is vaccinated and how many times they've been skin tested in the interim. Repeated PPDs have a tendency to maintain a positive test. Nutritional status of the child may also affect sensitivity.

Update on Subcommittee re Hib Conjugate Vaccine

Dr. Katz, learning that the ad hoc committee on Hib conjugate vaccine, had not reached consensus, asked them to meet again that night and give the group an update the next day.

General Recommendations for Immunization

Dr. John C. Watson, IM, NCPS, led a one-hour-plus discussion of changes to the ACIP "General Recommendations on Immunization." All members received a hefty handout with underlined changes, which Dr. Watson reviewed. The key changes or new sections are as follows:

1. An updated listing of vaccines and other immunobiologics available in the United States by type and recommended routes
2. Advice on the proper storage and handling of immunobiologics
3. An updated section on the recommended routes for administration of vaccines
4. Discussion of the use of jet injectors
5. Updated schedules for immunizing infants and children
6. Clarification of the guidelines for spacing administration of immune globulin preparations and different vaccines
7. An updated discussion of hypersensitivity to vaccine components
8. An updated section on the immunization of immunocompromised persons
9. An updated discussion of vaccination during pregnancy including a statement on vaccination and breast-feeding
10. Recommendations for the immunization of premature infants
11. Recommendations for immunization of hemophiliacs
12. Discussion of the "Standards for Pediatric Immunization Practices," including contraindications and precautions to vaccination
13. Information on the National Vaccine Injury Compensation Program, the Vaccine Adverse Events Reporting System, and Vaccine Information Pamphlets.
14. Guidelines for vaccinating persons without documentation of immunization
15. A section on reporting of vaccine-preventable diseases, and
16. A section on future vaccine development.

Subsequent discussion focused on the following areas:

1. multiple vaccinations (discussion about how far apart DTP and another vaccination should be, when given on the same limb; current draft says 2". It was decided to share the draft with the person revising The Red Book so that ACIP and that group have as similar as possible recommendations. It was also noted that the draft should emphasize not delaying a vaccination.)
2. jet injectors (This is a new section, pp. 14-15 of handout. Discussion centered around the risk of transmission of bloodborne pathogens, on proper handling of these devices, and on how deep they give vaccine. Dr. Katz took the Chairman's prerogative and stopped the

discussion, for reasons of time.)

3. immune globulin (Dr. Halsey presented data from an in press manuscript on the suggested intervals between receipt of immunoglobulin (BPIG) at different doses and receipt of live measles vaccination. He said that suppression of response to measles vaccine is dose dependent and time dependent. The larger the dose, the longer will be suppression of the antibody response to vaccine. See Table 5. Any minor differences between Dr. Halsey's data and the ACIP statement will be worked out before the next meeting. The Committee decided to work out wording and add it to this ACIP statement and to the next draft of the measles ACIP statement.)
4. vaccination of persons with hemophilia. (pp. 36-37 in the draft. CDC found an apparent lack of consensus on this subject among the different organizations polled, including the Red Book, Canada, and the National Hemophilia Foundation (NHF). The NHF recommends intramuscular vaccination for hepatitis B with fine needle and firm pressure. The options suggested to the ACIP were to defer making a statement or to go with the recommendations of the NHF. Again, Dr. Katz apologized to ACIP members and to Dr. Watson for the lack of time for further discussion, but urged them to read over this material and respond by mail.)
5. Tables. There was concern about how impractical it is to recommend four vaccinations at once.

Postexposure Prophylaxis for Hepatitis C

Dr. Miriam J. Alter, VR, NCID, said that the last ACIP statement states that for parenteral exposure to non-A, non-B hepatitis it may be reasonable to administer immune globulin in a dose of 0.06 mg as soon as possible after exposure.

In May 1990, the first test for antibody to hepatitis C virus was licensed; since that time, CDC has received repeated inquiries regarding the specific recommendations for needle-stick exposures to a patient who is positive for hepatitis C virus.

Dr. Alter reviewed the studies that have attempted to assess prophylaxis with immunoglobulin (Ig) against non-A, non-B hepatitis and that led to the lukewarm ACIP recommendation. Virtually all the studies assessing IM prophylaxis with Igs were done in transfusion recipients. All the studies did seem to suggest a positive prophylactic effect for Ig.

Dr. Alter also gave current data on the risk of HCV infection from needle-stick injuries. A review of three studies shows that there is a risk of acquiring HCV from needle-sticks, she said. In one recent prevalence study conducted by CDC, 1% of HCWs at a California hospital who participated in a hepatitis B vaccine study

were found to be anti-HCV positive. These studies suggest that there is a need for pre- or post-exposure prophylaxis to prevent occupationally acquired hepatitis C.

Dr. Michael Beech, a molecular virologist from CDC's Hepatitis Branch, then reviewed current data on immune response to HCV. The studies he briefly reviewed suggested that HCV infection does not elicit protective immunity against reinfection with either homologous or heterologous strains. In a subsequent question and answer period, it was noted that, since last spring, the FDA has been recommending screening whole plasma donors for anti-HCV; that one-half of HCWs tested may be false positive, based on results of supplemental assays; and that supplemental tests are under review at the FDA.

Following these presentations, Dr. Alter asked the ACIP if they felt there were sufficient data to modify the current ACIP recommendations. No conclusion was reached.

Change in Sensitivity of Test Kits for Anti-HBs: Implications for Pre-and Post-Hepatitis B Vaccination

Next, Dr. Alter discussed test kits for detection of antibody to hepatitis B surface antigen (Anti-HBs). Such kits, licensed by the FDA, can be used for several reasons. Of concern in this discussion was when they are used to evaluate immunity prior to or following hepatitis B vaccination. In the ACIP statements for use of hepatitis B vaccine issued in 1987 and 1990, a protective level of anti-HBs was defined as ≥10 mIU/ml, approximately equivalent to 10 sample ratio units by radioimmunoassay or positive by EIA.

However, since March 1986, manufacturers of these test kits have altered commercially available kits to increase their sensitivity. In 1991, the FDA conducted studies on currently distributed ones to determine the lower limits of their detection relative to the World Health Organization Anti-HBs Reference Preparation. These studies estimated the lower limits of detection to be below 5 mIU/mL.

Accordingly, a positive result determined by any current licensed anti-HBs test kit (EIA or RIA) could mean that the actual quantity of anti-HBs present may be less than 10 mIU/mL and not indicative of immunity. CDC did some tests to assess the potential impact of this increased sensitivity on the rate of false-positive test results. Of >400 samples tested, only 2% were false positives, i.e., ≥10 SRU by RIA or positive by EIA but <10 mIU/ml. In addition, their data are consistent with earlier studies showing that in some persons, low-level anti-HBs may occur along with anti-HBc, indicating prior infection with HBV; in others, low level isolated anti-HBs may indicate prior exposure to HBV and immunity from reinfection.

This information and proposed FDA labeling changes for these test

kits may cause concern among those who, by virtue of a single anti-HBs test since 1986, have been told they are immune either pre- or post-vaccination. However, CDC feels that the positive predictive value of tests is extremely high, and routine re-testing of persons on whom either pre- or post-vaccination screening has been done is not warranted. In only one setting, does CDC recommend a change. This concerns postexposure prophylaxis in which a previously vaccinated individual is exposed to HBsAg-positive blood or body fluids containing blood. If that person has no quantitative determination of anti-HBs following vaccination since 1986, he or she should receive postexposure prophylaxis. Finally, Dr. Alter noted that, to date, there have been no cases of hepatitis B reported in individuals previously considered to be hepatitis B vaccine responders.

Immunization in Bone Marrow Recipients

Dr. Bob Chen, NCPS, revisited the subject of an ACIP statement for immunization of bone marrow recipients. He said that, as requested, he has shared the draft ACIP statement with the Advisory Committee on Bone Marrow Transplant Registry as well as with 10 bone marrow transplant experts for their comments. He has received some feedback, to date, all good. The deadline for comments is December 1.

Monovalent Tetanus Toxoid and Tetanus Immune Globulin

Dr. Katz brought up two issues, not on the agenda, that he wanted to discuss with the Committee. The first was the amount of monovalent tetanus toxoid (TT) being used instead of tetanus diphtheria toxoid (TdT). Dr. Ted Mortimer said that, in talking with FDA, he found that enormous amounts of TT are still being sold, even though there are very few indications for its use. (Biologic surveillance data show that 4 million doses of it were sold in 1991, vs 12 million of Td. This is down from 8 million in the early eighties.) It was suggested that the reason some hospitals are still using TT is because it costs less than TdT.

Secondly, someone reported that Connaught had a problem with its last batch of tetanus immune globulin. It failed FDA testing and is back ordered. There are no other manufacturers of this product. In response to this comment, Dr. Orenstein said that, when notified of this problem, CDC contacted FDA and was told they had released three lots recently, and that the FDA was unaware of the shortage. Dr. Orenstein described the situation as "evolving."

Finally, Dr. Katz noted that since the last ACIP meeting, a second acellular DTP vaccine was licensed, Tripedia.

Low Serological Response Following Rabies Preexposure Intradermal Vaccination

Dr. James Childs, NCID, introduced Dr. Robin Ikeda, from the New York State Dept. of Health. She summarized two studies (one retrospective cohort; the other, prospective cohort) undertaken in New York to determine the prevalence of and risk factors for low serologic response following primary preexposure rabies vaccination by intradermal route. Low serologic response occurred in both cohorts. Subjects who were older and those with increased body mass index tended to be at greater risk. These studies raise the question, Dr. Ikeda said, of whether routine serologic testing should be recommended following intradermal vaccination.

Accordingly, the New York State Health Department has made the following recommendations:

1. Preexposure immunization be done by the intramuscular route.
2. If the intradermal route is used, follow-up serologic testing is recommended.
3. If these recommendations were to be implemented on a widespread basis, increased capability for rabies serologic testing would be needed in the United States.

Before Dr. James Childs gave his presentation, there was some discussion. Dr. Stanley Plotkin said that if two IM doses are given at 1-dose intervals, he expected that an immune response would be obtained. Dr. Bill Schaffner said the studies pointed out the relative unreliability of intradermal inoculations. But he underlined Dr. Ikeda's comments about the limited capacity in this country for serologic testing for antibodies. It would be much easier to follow Dr. Plotkin's suggestion for two intramuscular doses. However, there was concern by another Committee member that two doses would just not get done in many veterinary clinics. Asked about cost, Dr. Childs said that an ID unit dose is $39.30 versus $90.75 for an IM dose.

Dr. Childs reminded ACIP members that ID vaccine is not recommended for postexposure or for persons taking immunosuppressant drugs. He said that 2%-10% of vaccinees may have inadequate titers by some definition within one year of ID immunization. The problem is that most serologic tests of vaccinees are not done within 2 weeks after immunization, as recommended by the ACIP. Data do indicate anamnestic response to IM booster, even if titer is <1:5. Finally, the data are unclear for timing or the type of antibody response following booster, especially when the titer was unacceptable at 2-4 weeks postimmunization.

Based on these findings, CDC is currently recommending the following:

--No change in current ACIP recommendations.
--A study of booster (ID and IM) response of individual seronegative 2-4 weeks after primary ID immunization be initiated.

--The wording of the ACIP statement regarding serologic testing may be confusing and should be examined.

Proposed Changes in ACIP Recommendations Regarding Ferrets and Rabies

Next, Dr. Childs proposed two changes to the ACIP rabies statement regarding ferrets to synchronize them with the Compendium of Rabies Control, by the National Association of Public Health Veterinarians. There are several law suits in progress across the country, and ACIP guidelines are being brought up in court. At issue is whether the ACIP is misrepresenting facts about pen-raised ferrets. One issue is that ferret owners feel the ACIP classification of ferrets as "exotic" or "wild" rather than as "domestic" requires pet ferrets to be unnecessarily sacrificed when they bite someone. By contrast, dogs and cats (which are classified as domestic) are quarantined to see if rabies develops. There are, according to the National Ferret Association, 10-14 million pet ferrets are in the United States. There have been 10 reported rabid ferrets since 1980 in the United States--all domestic.

Subsequent discussion and a vote of the members determined that the facts (and lack of them; for example, details on the course of natural rabies disease in ferrets are unknown) need to be spelled out in the ACIP statement and that Dr. Childs' recommended changes could not be accepted as is but needed to be simplified and clarified, such as follows:

--Even though a ferret vaccine was approved in 1990, even a vaccinated ferret that has run wild cannot be trusted.
--we do not know enough about the incubation period of ferrets or the length of time in which they may shed rabies virus.

Dr. Katz adjourned the meeting for the day at 5:35 p.m. The meeting reconvened on October 22 at 8:05 a.m.

Calendars were passed out to all members, who were asked by Dr. Katz to sign them and X-out the days they were not available in June 1993 and submit them to Gloria Kovach.

Ad Hoc Committee Report on Variation in Immunogenicity of Merck Hib Conjugate Vaccine

Joel Ward discussed the Merck HIB lot potency issue. He said the ad hoc committee had met twice and received a copy of the proposed letter from Merck to all medical practitioners that has been submitted to FDA for approval. He read excerpts from it to the ACIP committee. He said that the ad hoc committee, which included both AAP and ACIP members, was concerned that implementation was not possible. They also decided that an MMWR article should be prepared, mentioning that Merck will be contacting pediatric

practices that received lots of the suspect vaccine.

Dr. Frasch, FDA, clarified that FDA has final approval of this letter and that the letter is an issue between Merck and FDA. Once the letter is approved, Merck is required to send it. He also said he needed ACIP input ASAP so that the letter could get out. Dr. Katz responded that it was not the Committee's intent to rewrite the Merck letter, but to ensure that the MMWR article that the ACIP drafted was consistent with the letter. Dr. Ward pointed out that there had not been a discussion of risk until last week and no consultation with ACIP or AAP until this week. Further, he thought it very important for the letter and the MMWR article to recommend the same things. He therefore urged one more week of dialogue to coordinate messages and urged Merck and FDA to use the ad hoc committee's messages regarding three doses being sufficient (vs. the letter's message requiring another dose for all children). Dr. Halsey added that anything that could be done to simplify the letter would be appreciated by physicians. Dr. Georges Peter, liaison member from the AAP, asked a Merck representative if the manufacturer would change the letter. She said she could not answer; that, obviously, there are legal and ethical concerns for Merck, which dictate an approach that is not necessarily practical for others. However, she would bring that message back to Merck. Dr. Peter then asked if a conference call could be arranged between the ACIP ad hoc group and the AAP committee on infectious diseases (the Red Book Committee) to develop a consensus. She said she thought that was a valuable suggestion and she thought it could be arranged. Dr. Katz designated Dr. Ward to represent ACIP; Dr. Hall will represent the Red Book at such a meeting.

National Vaccine Program Update

Dr. Steve Sepe, NCPS, explored the advantages and disadvantages of federal purchase of all vaccines (i.e., sole source contract for public and private vaccine) as a means of improving all children's access to immunization. Recently the high costs of vaccines, especially in the private sector, has been a further catalyst to such discussions. (In 1982, 5 doses of DTP, 3 OPV, and 1 MMR cost $6.69 in the public sector, and $23.39 in the private sector; in 1992, the price of vaccines is $122.28 and $244.10, respectively.)

Advantages of universal federal vaccine purchase are that:

- it could avoid fragmentation of care by allowing immunizations to be delivered without the need for extra visits by eliminating referral of children from the private sector to the public sector.
- population-based immunization registries could be developed
- tracking and follow-up systems could be developed to monitor children for coverage

However, the impact on price, competition and incentives for manufacturers to continue to develop new or improve existing vaccines needs to be assessed.

CDC and the National Vaccine Program Office have developed a scope of work and have negotiated a contract with Mathematica Policy Research, Inc. (MPR) to examine the economic and commercial underpinnings associated with alternatives to supplying vaccine. MPR will begin by developing a background paper, based on a literature review and interviews with experts. Then a panel of economists will be appointed, chaired by an economist, to 1) develop alternative models for the purchase of vaccine; 2) describe the effect of scientific advances on research, development, and production of vaccine (particularly the megashot vaccine); 3) analyze the economics of the vaccine market; 4) assess the impact of state policies on childhood immunization; and 5) evaluate the implications for increased offshore purchase of vaccine. A public conference will be convened to discuss policy papers resulting from this panel. As far as they are aware, Dr. Sepe said, this is the first time rigorous economic theory has been applied in an attempt to answer such an important public health question. Dr. Sepe closed by inviting input from the ACIP.

Dr. Katz said this was a major issue and asked Dr. Sepe to distribute a copy of his presentation to the Committee. He said the ACIP needs the opportunity to review the document and have an impact, at least through providing data, before the issue is turned over to the panel of economists. He said that there are state examples that Dr. Sepe did not mention, and asked Dr. Orenstein whether states that make all vaccine available to everyone have better immunization rates than others. Dr. Orenstein said CDC would have data, hopefully in the next few months from retrospective surveys, from which they will be able to assess coverage rates.

Dr. Pierce, representing the Adult Immunization Committee, asked if the panel would extend the analysis to include at least the two big adult vaccines--influenza and pneumococcus. Dr. Sepe said he was hopeful that the final analysis they end up with will be applicable to any vaccine. Dr. Pierce persisted, and Dr. Sepe said CDC could certainly discuss this point with the contractors.

Suspension of Use of Urabe Mumps Strain in the United Kingdom

Next, Dr. Walt Orenstein introduced Dr. David Salisbury from the Department of Health, London, United Kingdom. Dr. Salisbury said that the United Kingdom has not suspended licensure of the Urabe vaccines, but rather, has made the purchasing decision not to buy any more. The U.K. does have a unifying purchasing and distribution policy for all childhood vaccines, he said.

MMR was introduced in the U.K. in 1988. There is a yellow card

system for reporting adverse events, wherein physicians anonymously fill out and send in yellow cards to the Committee on Safety of Medicine, which analyzes the data. However, the cards may lack discriminatory details. The U.K. set up a new form of surveillance using the British Paediatric Surveillance Unit, involving pediatricians. Every month they receive a card on which are listed 12 rare conditions, including any neurologic events within 42 days of MMR immunization. This very effective system is also used for Reye syndrome, congenital rubella syndrome, among other conditions.

All neurologic events associated with MMR immunization are followed up by a research fellow for 12 months. Classification of cases was definite (vaccine virus isolated from CSF), probable (no virus, but lymphocytes in the CSF), and rejected cases. The preliminary analysis from the BPSU was 71 cases; 15 were definite virus cases; 34 were probable; and 22 were rejected. They added 6 definite cases they had detected before the BPSU was set up, giving 55 definite cases; follow-up has been completed on 53.

Of the 21 cases with virus isolates, 16 were Smith Kline, 5 were Pasteur Merieux; the rate for both vaccines was exactly the same, in terms of their distribution. This is a virus positive rate of 1 case per 233,000 doses distributed; the rate of probable and definite cases came down to nearly 1/100,000. When they looked at the distribution of cases, it was quite clear there was a problem and that it was occurring around 21 days.

The Department of Health then learned that the Nottingham District had a cluster of four virus-positive cases. The cluster was not in time, but in place, and occurred over a 4-year period. The Communicable Disease Surveillance Centre, on behalf of the Department of Health, then undertook a very detailed, retrospective analysis of that laboratory and four others. Each lab went through its records, looking for all children 1-2 years old who had had a lumbar puncture. They categorized these children by CSF with mumps virus, CSF with lymphocytes, and both negative CSFs and bacterial-positive CSFs as controls. These children were tracked in the district's computer records to determine when they had received MMR immunization; they became the numerator. Using the same computer system, the children who had received MMR vaccine in the same time periods could be identified (thus, the denominator).

It turned out to be a "novel and highly precise surveillance of adverse events," Dr. Salisbury said. The Nottingham analysis showed that they had three virus-positive cases, for a rate of 1/11,000 immunized children. There were 5 lymphocyte-positive children. When these two groups were combined, the overall rate was 1/4,000 immunized children.

When they looked at these cases, all were found to be Urabe recipients. All had presented to hospital with fever; 12 of the 13 had presented with febrile seizures. Only one had a symptom of

meningism.

The conclusions of the reactogenicity data were that 1) laboratory-based surveillance detected likely and definite cases at far higher frequency than the yellow card system of physician reporting; 2) high detection rates, as in Nottingham, probably correlate with lumbar puncture rates; thus, there is probably a bias correlated with lumbar puncture rates, but the bias is toward the truth; 3) cases occurred with equal frequency with either Smith Kline or Pasteur/Merieux, but did not appear to be the same rate for Jerryl Lyn; and 4) the Department of Health wishes to extend this technique of laboratory surveillance in the future.

He also said that antibody tests using ELISA had not been particularly good for determining protection; neutralization tests were much better.

In short, the U.K. had learned how important it is to link laboratory data with the immunization computer database. Dr. Katz, in thanking Dr. Salisbury for his presentation, noted that it was "a model for immunization surveillance we'd love to emulate in this country."

Dr. Tamblyn noted in subsequent discussion that Canada had similar problems with Urabe and the license was suspended there. Again, meningitis was a late presentation. "You have to extend the observation period long enough to capture this sort of event," she said.

Dr. Plotkin said that French data indicate that there is no question that Urabe is associated with meningitis. Rates calculated by relatively passive surveillance are 1/60,000 and with some corrections, the rate might be 1/20,000.

Risk of Guillain-Barre Syndrome Following Influenza Vaccination 1990-1991

Dr. Robert Chen then updated the ACIP on the risk of GBS following flu vaccination in 1990-91. Since updating the Committee on this subject 1 year ago, the data have been double entered, edited, validated, and re-analyzed. On September 29, 1992, a conference call with three external reviewers and almost all members of the ACIP was held. The minutes of this conference call detailed the 1/2 hour-long discussion. The group felt that the data presented were not compelling enough to change the current recommendations, which state that for years subsequent to swine flu, there is no clear association between GBS and flu vaccination.

Vaccination Recommendations for Health-Care Workers

Dr. Ray Strikas, IM, NCPS, noted that the CDC has published vaccination recommendations for HCWs twice in the past, in 1987 and

1989; these were not ACIP recommendations. The next revision--which is a compilation of existing recommendations--will be an ACIP statement. He distributed a preliminary draft and a handout of "points for discussion." Among the points he discussed were:

--Immunobiologics indicated for all or some adults, which are not specifically recommended for HCWs are not discussed (e.g., tetanus/diphtheria toxoids, pneumococcal vaccine).
--The current format lists diseases and their vaccines which are grouped based on whether protection of HCWs is felt to be strongly recommended or not. Immunization recommendations follow the background discussion for each group of disease.
--The discussion of BCG vaccine reflects published recommendations only. The content will be revised, pending any new ACIP recommendations on use of BCG. Thus, this ACIP statement will not be used until the one on BCG comes out.
--Acellular pertussis vaccine has not been included. Eventually, this should be an important issue, but it will not be included now.
--Varicella vaccine is not discussed in detail.
--The use of immune globulin to prevent hepatitis A infection in health care settings is not discussed. The committee should decide whether they wish to include this subject. Dr. Peter asked if something on immunoglobulin for hepatitis C and some data and references could be included, since this frequently comes up in hospital infection control committees.
--Work restrictions for non-immune workers exposed to vaccine-preventable diseases were adapted from existing CDC Hospital Infection Control guidelines and are included for completeness.
--Since there is no polio in the Western Hemisphere, does the Committee see problems with a discussion of polio vaccination of HCWs in this document?

In subsequent discussion, Committee members made following comments:

--There seemed to be consensus that, since polio eradication has not yet been certified, the treatment on p 24 of the draft seemed appropriate.
--CDC urged to come to grips with issue, and make a recommendation, concerning whether postimmunization serologies on HCWs who are immunized with hepatitis B vaccine should be routine. Dr. Broome and Dr. Hadler agreed to contact the Hepatitis Branch about this matter.
--The document ought to acknowledge that OSHA is the driving force in hepatitis B vaccination in hospitals. Thus, OSHA's requirements ought to be listed first. Our additional recommendations or considerations should follow.
--A new section should be added on immunocompromised HCWs for whom immunization is contraindicated.
--Diphtheria and tetanus should at least be mentioned.

--Review of an upcoming JAMA article on acellular pertussis vaccine trial among adults was recommended before entirely discounting including discussion of this vaccine in these recommendations.
--CDC evaluate the utility of including a discussion of hepatitis A vaccines, which will soon be licensed in the United States, in these recommendations.
--Some discussion should be included on the use of rubella serology as a screening measure before vaccination of HCWs.

Dr. Katz reminded Committee members to review 2 ACIP statements (general immunization and HCWs) and to submit comments about them by Nov. 20th.

Summary of FDA Workshop on Package Inserts and Warnings for Use of Vaccines

Dr. Steve Hadler next reported on results of an FDA workshop on package inserts, held on September 18, 1992, in which CDC and the ACIP were asked to participate. Differences--usually not major--between package inserts and ACIP recommendations were found in the following areas:

Measles, Mumps, Rubella Vaccines:

- Recommendation for timing of second dose of measles vaccine
- Use of monovalent or trivalent vaccine during measles outbreaks (children <12 months and children >/= to 12 months)
- Serologic testing of women of childbearing age prior to rubella immunization
- Use of MMR in children with active untreated tuberculosis
- Use of MMR in individuals with symptomatic HIV infection

Oral Poliovirus Vaccine

- Use of OPV in children with diarrhea
- Use of Acetaminophen

DTP Vaccines

- Use of DTP in children with evolving neurologic conditions; family history of convulsions; inconsolable crying; seizures

Common Issues

- Simultaneous administration of vaccines
- Immunization during illness

Commentary on each of these issues was prepared by the Division of

Immunization with the assistance of Dr. Kathy Edwards of the ACIP; copies of all commentaries were made available to all attendees of the meeting.

Dr. Hadler said that parents groups, present and vocal at the workshop, did bring up a number of issues that FDA will be considering, among them: assuring that package inserts discuss the true vaccine efficacy data, not just pre-licensing data, and reporting and analysis of adverse events reports to VAERS.

CBER of FDA will be having an internal meeting on November 19 to review the revised package inserts and return them to manufacturers for further revision. The docket will be open for comment through December 18. The final rule is expected to be published in January.

In subsequent discussion, an ACIP member pointed out that the Committee did not get the polio commentary; Dr. Hadler agreed to mail them.

Dr. Gardner noted his disappointment that this review was just for childhood vaccines, not all vaccines, including those for adults. Dr. Katz agreed, though noting that package inserts fall under the purview of FDA. Dr. Gardner said that at least ACIP could identify the issues and ask FDA to study them.

Update on Research Priorities of Division of Immunization

Next, Dr. Lauri Markowitz gave an overview of future research plans of the Division of Immunization. In all, 11 studies are pending or under way on measles; 1 on tetanus; 8 on domestic or international polio issues; 2 on rubella; 2 on varicella; 3 on pertussis; 2 on pneumococcal vaccine; 2 on influenza; 1 on hepatitis B vaccine; and 2 on vaccine safety. These are outlined below:

Domestic Measles Research

Primary measles vaccine failure study (to determine response to primary vaccination at 15 months of age and response to revaccination of non-responders. Nearing completion - HMOs in MN and WI).

Vaccination at 9, 12, 15 months of age (to compare seroconversion rates after MMR vaccination at 9, 12, and 15 months of age and response to revaccination of non-responders. Ongoing - HMO in MN.)

Measles Vaccine/URI studies (To compare seroconversion rates in children with and without illness at the time of vaccination; ongoing GA, MN, WI).

Changing levels of maternal antibody (To determine if younger mothers are transferring lower levels of measles antibody to their infants/response to vaccination; CA, MN).

EZ/Moraten measles vaccine trial (To compare immunogenicity of two vaccine strains at different doses and ages, long-term antibody persistence, vaccine safety; immunogenicity study completed - HMO in Los Angeles).

AIK-C/Moraten measles vaccine trial (To compare immunogenicity of two vaccine strains at different ages, long-term antibody persistence, vaccine safety; planned).

Measles vaccine in HIV-infected children and adults (To determine immunogenicity of measles vaccine in HIV-infected children--NYC; to determine safety and immunogenicity of measles vaccine in HIV-infected adults--CA).

Survey of prematriculation immunization requirements (PIRs) in colleges and universities (To determine percentage of colleges and universities implementing PIRs and impact on measles disease; completed).

International Measles Research

EZ/AIK-C measles vaccine trial (To compare immunogenicity of two vaccine strains at different doses and ages; Completed - Zaire).

Demonstration project of EZ vaccine at 6 months of age (To assess impact of introduction of EZ vaccine administered at 6 months of age; Kinshasa, Zaire).

Follow-up laboratory studies of high-dose measles vaccines (To investigate biologic hypotheses for differences in survival between children who received standard and high-dose measles vaccines;ongoing).

International Tetanus Research

Potency testing of tetanus toxoid (TT) (Collaboration with WHO to evaluate potency of TT produced in developing countries and factors causing failure of TT to prevent neonatal tetanus; ongoing).

Domestic Polio Research

Seroprevalence of antibody against poliovirus types 1, 2, and 3 among inner-city preschoolers (To determine seroprevalence in vaccinated and unvaccinated children and importance of secondary spread; completed - Houston and Detroit).

OPV/eIPV studies (To evaluate humoral and secretory antibody response following sequential schedules of eIPV and OPV; ongoing - Johns Hopkins, Baltimore).

International Polio Research

OPV formulation study (To evaluate immunogenicity of different formulations of OPV; Gambia, Brazil).

Supplemental dose of polio vaccine. (To evaluate additional dose of different OPV formulations or eIPV given at the time of measles vaccination; Oman, Cote d'Ivoire).

Combined schedules of OPV/eIPV (To evaluate OPV, eIPV and simultaneously administered OPV and eIPV at 0, 6, 10 and 14 weeks; ongoing - Thailand, Oman, Gambia).

Vaccine-associated paralysis in Romania (A case-control study to determine reasons for high rate of vaccine-associated paralysis in Romania; ongoing).

Stool and environmental sampling surveys (To establish environmental reservoirs and excretion in high-risk areas; Mexico, Oman).

Acute flaccid paralysis (AFP) investigation (To investigate non-polio causes of AFP; China - China paralytic syndrome).

Rubella Research

Persistence of antibody after vaccination (To determine the persistence of rubella antibody 20 years after vaccination; completed - Hawaii).

Rubella serosurvey (To determine seroprevalence of rubella antibody in different age/ethnic groups using NHANES-III sera; ongoing).

Varicella Research

Modeling of impact of varicella vaccine (To determine changes in age distribution, morbidity and mortality predicted after introduction of varicella vaccine; completed).

Varicella serosurvey (to determine seroprevalence of varicella antibody in different age/ethnic groups using NHANES-III sera; ongoing).

Pertussis Research

Acellular vaccine trials (To compare immunogenicity and

efficacy of acellular vaccines with WCV [consultants to studies in Italy (NIH), Senegal (Merieux), Germany (Lederle)])

Case definition for Pertussis (Survey of states to ascertain the case definition/laboratory methods used for pertussis investigation and reporting).

New diagnostic tests (Collection of specimens from suspected pertussis patients for evaluation of PCR and other immunodiagnostic assays; ongoing).

Pneumococcal Vaccine

Vaccine effectiveness (Retrospective case-control study of effectiveness of vaccine against pneumonia with and without bacteremia--Ohio, Hawaii).

Vaccine cost-effectiveness study (Cohort study of medicare beneficiaries--Hawaii).

Influenza Vaccine

HCFA/Medicare demonstration project (To determine the effectiveness of influenza vaccine in preventing hospitalizations for pneumonia during the flu season; completed--OH and PA. There is also a cost-effectiveness analysis ongoing through HCFA).

Cost-effectiveness study in HMO. (To determine the cost-effectiveness of influenza vaccine during 1981-1989; completed - OR).

Hepatitis B Vaccine

Enhanced surveillance of Perinatal Hepatitis B Surveillance Project (To assess efforts to screen women and deliver vaccine, identify risk factors for compliance failure, immunogenicity under field conditions--Dallas, Detroit, Minneapolis, Atlanta).

Vaccine Safety

Large linked databases (To determine adverse events occurring post-vaccination with childhood vaccines through linkage of records of vaccination, pharmacy, and medical care; 60,000 births per year; HMOs in OR, CA, and WA).

Chronic arthropathy following rubella vaccination (A retrospective case-control study to determine risk of developing chronic arthropathy; HMO in Northern California).

Update on Immunization Action Plans

Dr. Roger Bernier, IM, NCPS, reminded the ACIP that six cities had been funded one year ago to develop immunization action plans. In August, Congress made an additional $45 million available for immunization; CDC decided to use it to extend the planning process nationwide. Accordingly, in August, HHS Secretary Louis Sullivan, MD, announced the disbursement of the $45 million to assist 87 areas around the country in implementing local immunization action plans. In awarding these funds, renewed emphasis was placed on the merit of the proposed plan rather than only on an assessment of need. A second unique feature is that CDC is trying to introduce a greater degree of accountability in the grantee activities than has heretofore been the case.

National Vaccine Injury Compensation Program Update--Changes in Injury Compensation Table

Dr. Vito Caserta, Division of Vaccine Injury Compensation, HRSA, said that DHHS Secretary Sullivan recently proposed amending the Federal Vaccine Injury Table, as outlined in the Federal Register of August 14, 1992. Dr. Caserta handed out copies of the old and proposed tables, as well as a summary of proposed changes to it and the Aids to Interpretation. He said that public and written comments will be accepted for 6 months. A public hearing will be held on December 3 at 1:00 in the Parklawn Building. In February, HHS will publish a final rule in the Register. Dr. Caserta also said that these revisions would have no effect on cases already in the system. Dr. Caserta said that there are two ways to change the table--that proposed, or an Act of Congress. There have been some positive signs in the latter direction just recently; Congress has included in the legislation for the reauthorization of CDC's health block grant program (HR3635) a provision that would increase the authority for FY 1993 appropriations for pre-1988 awards by $30 million to a level of $110 million.

The changes are as follows:

For DTP; P; DTP/Polio Combination, or any other vaccine containing whole-cell pertussis bacteria, extracted or partial-cell bacteria, or specific pertussis antigens; DT; Td; or Tetanus toxoid:

- The time frame for the onset of anaphylaxis/anaphylactic shock (a condition of hypersensitivity to proteins or other substances, caused by previous exposure resulting in shock or other physical reactions) is narrowed. To be eligible as a Table injury, the onset must occur within 4 hours of vaccination, instead of the earlier 24 hours.
- Shock-collapse or hypotonic-hyporesponsive collapse is removed from the table. This is a "shock-like" condition that occurs infrequently with pertussis immunization, but is considered transient with no proven permanent

necessarily an indication of seizure activity."

- Adds criteria for the diagnosis of chronic arthritis, including guidelines for the onset and continued signs of both acute and chronic arthritis following vaccination with a vaccine containing rubella. The Aids to Interpretation will contain a list of nonvaccine-related musculoskeletal disorders that would be considered conditions not related to vaccine injury.

Following Dr. Caserta's presentation, Dr. Katz tabled discussion of examination of immunization schedules until the next meeting. He also reminded members that Dr. Ken Bart has sent a fax, which was distributed, reviewing the National Vaccine Program activities. He reminded members to that Gloria Kovach needs their calendars to schedule an alternative date for the June 1993 meeting.

Dr. Katz then adjourned the meeting at 12:10 p.m.

Summary of Actions Requiring Follow-Up:

- All members to review ACIP statements on HCWs and General Immunization and submit comments by November 20th.
- All members to submit June calendars to Gloria Kovach so that she can arrange an alternative date for the June 1993 meeting.
- Dr. Hadler arranged to mail polio and diphtheria package inserts to Committee members.
- Dr. Markowitz agreed to send copies of her handouts on CDC's research projects to all members. (These are included in these minutes.)
- Dr. Sepe agreed to discuss inclusion of influenza and pneumococcus (adult) vaccines in the background paper for the National Vaccine Program Office and CDC. He also agreed to send a copy of his presentation on the advantages and disadvantages of federal purchase of vaccine and CDC's contract with MPR to the ACIP.
- Merck, Dr. Carolyn Hall, and Dr. Joel Ward were to see about having a conference call to develop a consensus about the letter to physicians re. Merck's Hib conjugate vaccine.
- Dr. Childs agreed to simplify and clarify the ACIP rabies statement about ferrets.

References

1. Ogra PL, Faden HS, Abraham R, et al. Effect of prior immunity on the shedding of virulent revertant virus in feces after oral immunization with live attenuated poliovirus vaccines. J Infect Dis 191;164:191-4.
2. CDC. Poliomyelitis--Netherlands, 1992. MMWR 1992;41:7758.

I hereby certify that, to the best of my knowledge, the foregoing

summary of minutes is accurate and complete.

Samuel L. Katz, MD, Chairperson

Date: 9 February 1993

complications.

- Residual seizure disorder would be removed from the Table. (This is a seizure occurring with 72 hours of vaccination, followed by two more seizures within the next year, each with a documented fever less than 102 degrees F.)

For MMR alone or in any combination:

- Narrows the time for the onset of anaphylaxis or anaphylactic shock from 24 hours to 4 hours.
- For residual seizure disorder, narrows the time frame for the initial postvaccination seizure from zero-5 days to 5-15 days.
- For encephalopathy, narrow the time frame of onset from 0-15 days to 5-15 days.

For MMR, Measles, Rubella (MR), or Rubella vaccines only:

- Add chronic arthritis to the Table, with the onset of signs within 42 days of vaccination with a vaccine containing rubella.

For IPV:

- Narrows the time for the onset of anaphylaxis or anaphylactic shock from 24 hours to 4 hours.

There were also fairly extensive changes to the Aids to Interpretation, outlined below:

- The definition for anaphylaxis and anaphylactic shock is added.
- Definitions for infantile spasms and sudden infant death syndrome (SIDS) are added with language specifying them as conditions not covered under the Table.
- Clarifies the definition of encephalopathy by:
  --Defining acute encephalopathy by age-group (less than 24 months of age versus 24 months of age or older).
  --Defining chronic encephalopathy which must follow the acute encephalopathy and continue for greater than 6 months
  --Specifying the clinical signs that are not consistent with acute encephalopathy.
- Clarifies the definition of residual seizure disorder by:
  --Removing "Petit Mal and Absence of Seizures."
  --Specifying that the two additional postvaccination afebrile seizures required over the next 12 months be separated in time by at least 24 hours.
  --Changing the temperature standard for defining "afebrile" from 102 degrees F to 101 degrees F (rectally) and 100 degrees F (orally).
  --Adding "Jerking movements or staring episodes alone are not

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL

MINUTES OF MEETING

Advisory Committee on Immunization Practices
June 9-10, 1992
Atlanta, Georgia

The Immunization Practices Advisory Committee (ACIP) met in Auditorium A at the Centers for Disease Control, Atlanta, Georgia, on June 9-10, 1992 Those in attendance are listed below:

COMMITTEE MEMBERS PRESENT

Dr. Samuel L. Katz, Chairman
Dr. Mary Lou Clements
Dr. Katherine Edwards
Dr. Neal Halsey
Dr. Gregory R. Istre
Dr. Carlos Ramirez-Ronda
Dr. Rudolph Jackson
Dr. Mary E. Wilson

Ex Officio Members

Dr. Carolyn Hardegree (FDA)
Dr. John R. La Montagne (NIH)

Liaison Representatives

Dr. Kenneth Bart
Dr. Pierce Gardner (ACP)
Dr. Caroline B. Hall (AAP)
Dr. Edward A. Mortimer, Jr. (AMA)
Dr. Georges Peter (AAP)
Dr. Michael Peterson (DoD)
Dr. William Schaffner, II (AHA)
Dr. Susan E. Tamblyn (NACI)
Dr. Ronald C. Van Buren (AAFP)

Executive Secretary

Dr. Claire V. Broome

NAVY ENVIRONMENTAL HEALTH CENTER

Capt. S. William Berg

ARMED FORCES EPIDEMIOLOGY BOARD

Capt. W.M. Parsons, MSC, USN

HHS STAFF PRESENT

NATIONAL INSTITUTES OF HEALTH

Dr. David Klein, NIAID
Dr. Regina Rabinovich

CENTERS FOR DISEASE CONTROL

Office of the Director

Ms. Marymal Dryden
Ms. Amanda Tarkington

Office of the General Counsel

Mr. Kevin M. Malone

Office of Health and Safety

Dr. Naima Abd Elghany
Mr. John Richmond

Epidemiology Program Office

Center for Environmental Health and Injury Control

Ms. Debbie Combs

Center for Infectious Diseases

Dr. William Adams
Mr. John Becher
Dr. Nancy Cox
Dr. Martin Favero
Dr. Robert Good
Dr. Kenneth Herrmann
Mr. Jim McAuley
Dr. Ted Tsai
Dr. Jay Wenger

CENTERS FOR DISEASE CONTROL (Cont'd)
Center for Prevention Services

Dr. William Atkinson
Dr. Robert Chen
Dr. Stephen Cochi
Dr. Susan Davis
Ms. Rosamond Dewart
Dr. Vance Dietz
Dr. Sam Dooley
Ms. Judy Gantt
Dr. Mark Grabowsky
Dr. Robin Huebner
Ms. Sonja Hutchins
Ms. Mary Hutton
Mr. Robert Keegan
Dr. Alan Kendall
Dr. Charles LeBavor
Mr. Arthur Manoharan
Dr. Lauri Markowitz
Dr. Bernard Moriniere
Dr. Walter Orenstein
Mr. Mark Papania
Dr. Peter Patriarca
Dr. Dixie Snider
Dr. Raymond Strikas
Dr. Peter Strebel
Mr. Roland Sutter
Dr. Steve Wassilak

OTHERS PRESENT

Mr. Paul Albrecht, FDA
Ms. Jill Chamberlain, Vaccine Bulletin
Dr. Pinya Cohen, Connaught Labs
Dr. George Comstock, Johns Hopkins University
Mr. Victor Corderas, Emory University, School of Public Health
Dr. Gerard ten Dam, WHO
Dr. Albert Donnenberg, University of Pittsburgh, School of Medicine
Dr. Juhani Eskola, National Public Health Laboratory, Finland
Dr. Paul Fine, London School of Tropical Public Health
Mr. Thomas R. Flippen, Lederle-Praxis
Ms. Carol Frankel, Medeva International
Dr. Jill Hackell, Lederle-Praxis
Ms. Rose Mary Hoy, Merck Vaccine Division
Dr. David Krause, SmithKline Beecham
Mr. Dace Madore, Lederle-Praxis Biologics
Mr. Sheldon Mazursky, Organon Tekriya Corp.
Mr. Carlton Meschievitz, Connaught Labs
Mr. David McClintock, Lederle-Praxis
Mr. Daid Novack, Lederle-Praxis Biologicals
Dr. Michele Puryear, Division of Vaccine Injury Program
Ms. Lorraine Radick, Lederle Laboratories
Dr. Mary L. Rorabaugh, Emory University
Mr. B.A. Rubin, DCOM
Ms. Jane Scott, Lederle Laboratories
Mr. Irwin Shapiro, Tanabe USA
Dr. Judith Shindman, Connaught Laboratories, Ltd.
Mr. Howard R. Six, CLI
Mr. Michael Speidel, Lederle-Praxis Biologicals
Ms. Barbara Sweeney, National Association of Pediatric Nurse Practitioners
Dr. Ed Thompson, CSTE
Ms. Lin Wenlii, AMVAX, Inc.
Dr. Jo White, Merck Sharpe & Dohme Research Labs
Mr. Walter Woods, Connaught Labs
Dr. John Zahradnik, Biologics Response
Mr. Chris Zurawsky, Infectious Disease News, SLACK, Inc.

Executive Summary

On June 9-10, 1992, the ACIP convened at the Centers for Disease Control (CDC) to discuss the status of numerous vaccine-preventable diseases and vaccine-related issues. Dr. Samuel Katz presided as Chairperson; Dr. Claire Broome was Executive Secretary.

Dr. Katz opened the meeting by welcoming members, particularly Dr. Marvin Amstey, a new member of the Committee. He then introduced Dr. Broome, who asked all ACIP members and liaisons who have potential conflict of interest to make them known. She then disclosed several consultation arrangements of Dr. Kathryn Edwards and Dr. Neal Halsey.

Dr. Broome then announced that the Committee's name had been returned to its original one so that its acronym (ACIP) now matches its designation as the Advisory Committee on Immunization Practices.

Dr. Katz then asked all the approximately 70 people present to introduce themselves. Those present included representatives of vaccine manufacturers, state health departments, the media, FDA, industry (Amjet), the Department of Defense, parent groups, and staff of CDC.

An update on acellular pertussis vaccine trials was the first subject for discussion. CDC's Dr. Steven Wassilak reported that Connaught is still awaiting FDA licensure on its acellular pertussis vaccine. He then briefly reviewed large-scale clinical efficacy studies that are already under way and others that are planned.

Next, CDC's Dr. Steve Cochi briefly summarized his and others' 2-hour review of research on polio vaccines (presented at the February 12-13 ACIP meeting) that needed to be considered to re-evaluate the ACIP's polio vaccination policy. Dr. Cochi reiterated for the Committee three questions he had posed to them at the February meeting and asked them to consider: 1) Have the research questions raised by the Institute of Medicine (IOM) been adequately addressed? 2) Are there issues other than those raised by the IOM that still need to be addressed? and 3) If DTP-IPV is licensed, is the ACIP prepared to consider a change to a sequential IPV/OPV schedule?

Next, Dr. Carlton Meschievitz updated the ACIP on Connaught's randomized clinical trial using the combined eIPV-DTP vaccine. The trial was initiated in late December of 1990; enrollment was completed in February 1992, with a total of 422 infants enrolled. A preliminary safety analysis on 148 infants shows that the addition of IPV did not increase local reactions; systemic reactions were often higher with the combined vaccine except for

diarrhea. He then summarized monkey studies using this vaccine. Dr. Meschievitz said he expects a final report on the trial to be submitted to FDA in October, 1992.

Next, Dr. Neal Halsey summarized a report he had given at the Immunization Conference the week before on the need to simplify vaccine schedules. He went over the current immunization schedule to illustrate how complex it has become and then made several suggestions to simplify it: eliminate ranges; eliminate extra visits; don't give more than two injections at any visit except for children behind on schedule; when combination products become available, simplify and give instructions about compatibility and mix-'n-matching.

Dr. Katz then restated the IOM questions raised by Dr. Cochi. Several members expressed concern about the subject of possible increased reversion to neurovirulence in people challenged with OPV after having previously received IPV. Members were unclear whether this is an issue or not. Dr. Katz asked ACIP members whether they were willing to vote or wanted more information on neurovirulence. The group voted unanimously that neurovirulence needed to be examined further before the Committee would vote for a change. The subject was added to the agenda for the fall meeting, again by unanimous vote.

CDC's Dr. Ted Tsai reviewed the ACIP statement on Japanese encephalitis vaccine. Before going over the draft statement with the Committee, he briefly reviewed one case of Guillain-Barre syndrome (GBS) temporally associated with JE vaccination that had occurred since the Committee last met. The GBS case occurred in a 25-year-old soldier, who developed weakness about 8-14 days after receiving the first dose of JE vaccine. He made an uneventful recovery without therapy. This is the first GBS case reported in temporal relationship with JE vaccination among 30,000 U.S. vaccinees.

The Committee was then led through a review of changes in the ACIP statement since members had last seen it. Then Dr. Meschievitz went over the indications and usage, contraindications, immunization schedule, and warnings contained in the package insert for JE-VAX.

The Committee then voted that the statement was "sufficiently definitive about restrictions in its use" to be published. It will now go to CDC's editors to be published.

Dr. Katz then announced meeting dates for the ACIP in 1993. They are: February 9-10, June 16-17, and October 6-7.

Next, Dr. Pierce Gardner, Chairperson of the BCG subcommittee, explained that interest in this vaccine is heating up considerably because of the threat of multiple-drug-resistant tuberculosis

(MDRTB). He went over the six documents given to members that related to this one-hour discussion. Then CDC's Dr. Robin Huebner updated the Committee on six hospital outbreaks of MDRTB. IN one of these, she said that between May-July 1991, approximately 50 health-care workers (HCWs) had PPD skin-test conversions following exposure to prison inmate-patients with TB.

Regarding use of BCG in HIV-infected individuals, the draft document distributed to members is as comprehensive a review as they could obtain of side effects of BCG use in HIV-infected persons. CDC's Dr. Sam Dooley was asked by a Committee member what suggestions were made for HCWs who are PPD positive and exposed to MDRTB. He said that CDC's recommendations are to: 1) Make an assessment how certain you are that the person is newly infected with TB; 2) If he or she is newly infected, determine the likelihood that it's MDRTB; 3) If you do think the HCW is newly infected with MDRTB, what are that persons's personal characteristics that might make him or her more or less likely to progress to more active disease. If the person is newly infected with MDRTB and is immunocompromised, the recommendation is to use a multi-drug preventive therapy.

Next, Dr. John Bass, Chairperson of the Advisory Committee for Elimination of TB (ACET), summarized the ACET's reactions to the ACIP draft BCG document. He said that recent studies show no efficacy in adults. The ACET's two biggest concerns are: 1) lack of scientific data to back up a recommendation for adults and 2) a more practical concern: if a relatively simple intervention is recommended with any degree of certainty, then the more difficult interventions above that will tend to get ignored. Thus, people in administrative positions will "just give everybody BCG." In short, the consensus of the Council would be to be even more conservative, rather than to enlarge the BCG recommendations.

Dr. Gardner pointed out that if BCG is used and doesn't work, there's actually a negative side-effect: we lose the skin-test surveillance, which has been the backbone of our attempt to control TB. He asked the Committee if it could agree that BCG is of no use so that the paper can be published. This suggestion met with considerable resistance, by members who were uncomfortable accepting zero efficacy as dogma without hearing more data. Dr. Broome also raised the question of whether HCWs, as individuals who have recently acquired infection, wouldn't be more analogous to children, for whom efficacy has been demonstrated. After discussion, it was agreed that the take-home message of the document about efficacy should be that its efficacy is "highly variable and unpredictable" not "highly questionable."

The final sense of the Committee seemed to be summed up by Dr. Halsey, who stated that the paper must do the following: 1) make sure HCWs are informed of potential negatives if they use BCG--including changing their skin-test results; and 2) not recommend

BCG as routine, with a statement to the effect that "data are inconclusive to recommend" BCG. There also seemed to be a "silent consensus" to "look harder" at existing studies, various strains, and studies of efficacy in adults before a "more definite statement" can be made.

Discussion then turned to use of BCG in children. Dr. Andre Nahmias, Emory University, was asked to comment about the recommendations regarding newborns. He said that the World Health Organization has recommended the use of BCG in newborns, and that over 60 countries require it, and over 100 strongly suggest it. Furthermore, 11 studies reviewed showed efficacy of 50%-90%. The recommendation he and others have come up with for the United States is to use it in newborns or young infants exposed perinatally to HIV-infected mothers.

Winding up this one- and one-half-hour discussion, Dr. Katz said it was clear that the ACIP had the least argument with recommendations about newborns, and the biggest problem with HCWs. He asked Dr. Gardner if, given more staff support, his Committee wouldn't find it useful to look again at primary exposure, reactivation, different strains, HCW data. Dr. Gardner agreed. It was also pointed out that the NIH was having a meeting the next day on research issues regarding BCG, and that a report of this would be given at the next meeting.

Discussion then turned to issues involved in implementing infant hepatitis B vaccination. CDC's Dr. Hal Margolis gave a brief background on hepatitis B in the United States. Some 22,000 HBsAg-positive women give birth each year. Most states have active perinatal prevention programs funded through the state immunization projects. About 4,500 antigen-positive infants born to antigen-positive mothers were reported through state immunization programs for 1991. Alaska has universal immunization at birth, and some states have started to require surface-antigen screening (and in some cases, reporting) in their administrative rules or state laws.

Regarding universal infant immunization, CDC has reviewed project grant proposals funded this month or early July. Ms. Donna Lazorik, Hepatitis B Coordinator for the State of Massachusetts Immunization Program, which began a universal immunization program in February, next presented information on that state's start-up of that project. The ACIP was very impressed with the Massachusetts project, and asked what plans existed for adolescent vaccination. Ms. Lazorik said they are seeing if any funding is available on the state level for pilot projects.

Before breaking for lunch, Dr. Broome emphasized that the ACIP clearly supports the new OSHA regulations for control of occupational exposure to blood-borne pathogens, issued in December 1991, which recommend hepatitis B vaccine for those with occupational exposure to potentially infectious materials.

Reconvening at 2:00 p.m., Dr. Margolis summarized the general and specific objections that universal hepatitis B infant immunization is likely to raise, as Ms. Lazorik's presentation demonstrated. In reference to alternative strategies for adolescents, he said that Minnesota, Wisconsin, Oregon and California are trying to put together adolescent demonstration projects. British Colombia is also launching an adolescent program this fall.

Next, CDC's Dr. Eugene Hurwitz presented data on reports of lower-than-expected response rates among adults to hepatitis B vaccination. He said published data on the immunogenicity of the vaccine show that 74%-97% of vaccinees have an adequate response. Factors that have been reported to affect the immune response are age (over 40), sex, obesity, smoking, and immunocompromised conditions. For example, a recent study of responses to Recombivax among firemen in Connecticut found that 73% of smokers responded adequately, versus 93% for nonsmokers. Obesity (over 200 lbs.) was also a factor, with only 77% of obese employees having an adequate response. Finally, Dr. Hurwitz described the types of studies CDC is conducting or planning on adult hepatitis B vaccination, including one on immunogenicity of HB vaccine in populations now being vaccinated and a planned one on the differences in immunogenicity between Engerix and Recombivax.

Next, Dr. Lauri Markowitz introduced several speakers who presented a variety of data on the issue of whether the recommended age for measles immunization should be lowered in the United States.

CDC's Dr. Bill Atkinson summarized recent measles epidemiology, which illustrates the changing age distribution of measles cases. Until 1988, most U.S. cases were in school-age children (5- to 19 years), but by 1990 the proportion of cases in pre-school-age children (under 5) exceeded those in school-age children. In 1991, pre-school cases accounted for 50% of all reported cases. The new low for median age of all reported cases is now 60 months; the highest increase is in those less than 16 months of age.

Next, Dr. Mark Papania, Immunization Division, NCPS, summarized a retrospective cohort study of a measles outbreak in New Jersey in 1991 to determine risk factors for children less than 16 months of age. The major implication of this study is that the risk for measles in exposed children in the United States less than 16 months of age will continue to increase as the proportion of mothers born since 1968 increases.

Next, four presentations were made documenting decreasing maternal measles antibody titers, three from the United States and one from Canada. First to speak was Dr. Henry Pabst of the University of Alberta, who reviewed a study of 328 mother-infant pairs that showed a significant difference between babies of mothers who were or were not vaccinated.

Dr. Markowitz summarized a CDC study conducted in a Los Angeles health maintenance organization (HMO). The data demonstrate decreasing measles antibody titers in U.S.-born women; decreasing seropositivity rates in their children; and higher seroconversion rates to measles vaccine in children born to younger women.

CDC's Dr. William Bellini reported CDC indirect antibody assay results demonstrating that children of younger (assumed to be vaccinated) mothers have significantly less measles antibody at 2, 4, and 7 months than children born of the older mothers (who presumably had natural disease). These data demonstrate that an approximate 8-month "window of susceptibility" may be present.

Next, Dr. Gail King summarized a review of U.S. birth certificate data of births from 1971-1988 to mothers between the age of 15-44 years of age. These data demonstrate that by the end of this decade or sooner, the vast majority of mothers in the birthing cohort will have been born during the measles vaccine era and will be delivering infants with lower levels of maternal measles antibodies. These data suggest that the increasing susceptibility at younger ages, due to falling maternal antibody, may be the reason for the rising proportion of measles cases in children less than 16 months of age during the most recent measles epidemic.

Following these presentations, Dr. Markowtiz said that CDC has initiated a three-arm, randomized study at an HMO in Minnesota to evaluate this question more directly. She said the ACIP could take three possible actions, based on these data: 1) to leave the recommendations the same as they are now; 2) to change the recommended age for MMR to 12 months; and 3) to alter the recommendation to allow a permissive vaccination between 12 and 15 months of age.

When Dr. Katz called for a formal vote of members, option #1 was decided upon.

CDC's Dr. Jay Wenger described two surveillance systems for cases of Hib disease used to evaluate the impact of the new Hib conjugate vaccine. Analysis of data from these surveillance systems shows that substantial decreases in Hib disease have occurred, that these have occurred in vaccine-eligible age-groups, and that these decreases were clearly associated with national vaccine distribution and administration to the public sector.

Dr. Donna Jones said that there was renewed anticipation that the varicella (chickenpox) vaccine, produced by Merck, Sharpe and Dohme, might become available. She introduced Dr. Jo White, Director of Research at Merck, Sharpe and Dohme to speak.

Dr. White said their varicella vaccine had a good safety profile in its use with over 9,000 children. The vaccine is highly immunogenic (at least 96%) and has excellent persistence (through

6 years). It's efficacious and the breakthroughs that follow vaccination are very mild disease.

Next, CDC's Dr. Robert Breiman introduced Dr. Jay Butler to summarize new data on pneumococcal vaccine efficacy and duration of protection. Dr. Butler said that, using surveillance and laboratory data, CDC has confirmed that the pneumococcal polysaccharide vaccine is efficacious for preventing serious pneumococcal infection in most immunocompetent persons. CDC found that the vaccine is efficacious in certain immunocompromised patients and that protection following a dose of this vaccine appears to last for 6 or more years. These findings support the current ACIP recommendation that routine re-vaccination is not indicated. However, until more data are available on duration of protection for patients with specific risk factors, re-vaccination should be considered for persons at highest risk of complications from pneumococcal infection, as is currently recommended.

Following Dr. Butler's presentation, the meeting adjourned at 5:55 p.m. It was called to order again the next day at 8:30 a.m.

Dr. Katz introduced Dr. Walt Dowdle, Deputy Director, CDC, who thanked all the ACIP members for contributing to making the Committee such a success and specifically Dr. Mary Wilson, who was leaving after 4 years on the Committee. Dr. Wilson was given a Certificate of Appreciation from Dr. Roper and a copy of *Sentinel for Health*, the newly released history of the CDC written by Elizabeth Etheridge. Dr. Katz noted that Dr. David Fraser was also leaving effective this meeting and recorded thanks to him for his contributions.

CDC's Dr. Mark Grabowsky was the first of the day's speakers. He briefly reviewed the draft of the ACIP statement on immunization of bone marrow transplant (BMT) recipients.

Dr. Albert Donnenberg, an expert of this subject from Pittsburgh's Montefiore Hospital, then answered technical questions about the statement. Dr. Katz asked that information on cytomegalovirus studies be made available for the next meeting. Other suggestions for the statements were made and noted. Dr. Katz said that any other comments about the statement should be mailed to Dr. Grabowsky by June 19. It was clarified that this statement is not an appendix to another immunization statement, but a separate document. Dr. Donnenberg said he would get together a list of the major BMT centers so that the statement could be mailed to them.

CDC's Dr. Steve Hadler then led a lengthy review of the safety of jet injectors. He reviewed a 1985 outbreak of hepatitis B in a California weight reduction clinic traced to jet injectors. He then summarized CDC's Hepatitis Branch studies of jet injectors, undertaken the same year. The conclusion of these studies was that, if artificially contaminated, both Med-E-Jet and Ped-O-Jet

injectors transfer serum on subsequent injection. The Med-E-Jet injector became contaminated on the exterior and also on the interior, requiring disassembly to disinfect. Second, the volume of serum transferred could contain infectious virus particles. The risk of serum transfer in the volume transferred was reduced by swabbing the injectors prior to the next injection.

Next, Dr. Glacus de Souza Brito from the Division of Immunization at the Sao Paulo, Brazil, State Department of Health, reported on three field studies in Brazil using human volunteers, undertaken after reports of Med-E-Jet hepatitis outbreak. Injectors are widely used in the military for most antigens and are used in the Amazon to administer yellow fever, measles and sometimes meningococcal vaccine. They are also planned for use in the National Measles Elimination Initiative.

Among almost 3,000 injections, results were: 1) The prevalence of visible blood at the injection site immediately after use of the injector varied from 2.2% to 23.3%, being much higher in Amazon studies; 2) Blood showed up in subsequent doses (determined by injecting it into vial and testing with a dipstick for occult blood) 1% of the time, but 6.6% in the Amazon. 3) In these studies, there was little to no correlation between visible bleeding and detection of occult blood in the successive vaccine doses; 4) Swabbing between doses using dry cotton seemed to reduced detectability of occult blood. Swabbing may also reduce residual blood content. However, these preliminary results need further confirmation.

Based on these results, the Technical Committee on Immunization of Brazil tried to quantify the risk of HIV transmission for its National Measles Campaign. It estimated the risk of such transmission by HCWs by needlestick was 0.3%. By contrast, the risk via jet injectors was estimated to be "in the range of 1 per 238 million to 1 per 476 million injections. Theoretical risk of hepatitis B transmission was determined to be in the range of 1 per 388 to 1 per 3,367 injections.

Based on these risk estimates, jet injectors are currently used in Brazil in the special vaccination campaigns, with the exception of areas with high hepatitis B prevalence, like the Amazon.

Dr. Grabowsky said that CDC has also attempted a model of the risk of HIV and hepatitis B transmission using jet injectors. He said it is likely to be less than 1 per 100,000 jet injections for either virus. In the worst case scenario, there would be approximately 5.1 transmissions of hepatitis B and about 2-3 transmissions of HIV per 100,000 injections. The risk is lower in populations with lower disease prevalence and when the jet injector is swabbed.

CDC's suggested recommendations are that, although jet injectors

can be used safely in low HBV/HIV prevalence areas, to minimize the risk of transmission of bloodborne pathogens the jet injector tip should be swabbed after each injection. If the jet injector is visibly contaminated with blood, it should not be used until decontaminated.

Dr. Hadler then asked liaison member Dr. Mike Peterson to summarize the military experience with jet injectors. He said that the military has used them since they were invented. Air Force uses them for 160,000 injections a year; the Army for 440,000 year; and Navy 560,000 year. Now all use Ped-O-Jet exclusively. The Army screens for HIV but not for Hepatitis B.

Dr. Grabowsky then asked if the ACIP should make an official recommendation about jet injectors. Dr. Katz asked if the Committee was in consensus that a recommendation on this subject was within the purview of the ACIP and should be drafted and added to the general immunization statement. The Committee agreed with this. Dr. Hadler agreed to have suggested wording ready for the next ACIP meeting if the Committee would give a sense of what should be in the recommendations about proper cleaning and disinfection of these instruments. (There had been some discussion, after the presentations, about the fact that acetone is preferred because alcohol is slower drying and leaves an oily film, causing chance of slippage.) A vote was taken to see if the recommendation should say something about swabbing. Only Dr. Carolyn Hardegree voted against it, saying that disposal of swabs would need to be spelled out and that she wanted to discuss the matter with FDA's device people. Dr. Hadler agreed to put together the overheads from the presentation and fax them up to FDA.

Next, CDC's Dr. Jay Watson presented a list of items being considered for revision of the ACIP General Recommendations on Immunization. He highlighted several areas that he particularly wanted input from the Committee on (immunobiologics; route, site and technique of immunization; combining vaccines; altered immunocompetence; and contraindications), and asked that written comments on these and other issues be submitted by July 1. (Gloria Kovach will send out worksheets on this; then the matter will be re-visited at the fall ACIP meeting.)

Mr. Thomas Balbier, Director of the National Vaccine Injury Compensation Program (VICP), updated the Committee on the NVIC. He said in the past 1-1/2 years a number of changes in the way the program operates have occurred. Dr. James Mason organized a task force to look at the VICP and charged it with coming up with a set of comprehensive legislative proposals for fixing it. The Task Force broke into two subcommittees. One subcommittee came up with some legislative proposals that were enacted last year that improved the overall operation of the program. The other looked at the vaccine injury table in the statute, with the expectation that the IOM report due out on the adverse effects associated with

pertussis and rubella vaccines would provide the impetus for proposing changes to that table. The subcommittee's recommendations were presented to Dr. Mason, and then reviewed by an independent group, under the auspices of the NVAC. Those recommendations were then sent to the Advisory Commission on Childhood Vaccines, the advisory commission for the VICP. That group has come to closure on this whole issue of changing the table. It will be sent to OMB this week and is expected to be published in the Federal Register very soon.

There has also been a change in the participation by the parents. Dr. Mason has met on two separate occasions with Ann Millan of Dissatisfied Parents Together to talk about some of the operating problems with the program and to discuss the changes to the table. This parents' group also identified an expert to serve on the subcommittee of the NVAC.

Mr. Balbier called attention to a recently developed publication, distributed to members, entitled *Commonly Asked Questions about the Vaccine Injury Compensation Program.* It will be part of a kit that CDC will be distributing which includes the new Standards for Pediatric Immunization Practices. He then reviewed the weekly status report of the VICP (see handout). He said that the Advisory Commission will meet again next week to try to develop new criteria for newly recommended or new vaccines. The Commission hopes to resolve these next week. Adding new vaccines will require legislation. Ultimately, VICP will suggest changes to the Department of Treasury, which sets the surcharges.

CDC's Dr. Vance Dietz updated the ACIP on what has happened with the standards since the February meeting. The final document was distributed to all ACIP members today. The comments of both NVAP and the ACIP were incorporated into the document. The standards were approved by NVAC and PHS and have been endorsed by the American Academy of Pediatrics and the Council of State and Territorial Epidemiologists. A task force has been created to take the necessary steps to implement the standards. CDC is now getting endorsements of all major working groups. Dr. Dietz asked the ACIP to endorse the standards at this time.

He then went over the changes made since February, which included adding the word *Pediatric* to the title; deleting one standard about who can give permission to vaccinate a child; and other, mostly minor changes. (See complete minutes.) Following his presentation, the ACIP unanimously voted to endorse the standards.

Dr. Ken Bart, Director of the National Vaccine Program, was unable to attend today's meeting. He gave a summary of his presentation to Dr. Broome, who distributed it to the Committee. (See handout.)

Next, Ms. Ann Millan, Director of the National Vaccine Information Center operated by Dissatisfied Parents Together, addressed the

ACIP. This center is a national, not-for-profit educational organization which serves as a clearinghouse for information on existing vaccines as well as vaccines still in development. A copy of her entire speech is attached for the record.

Following this presentation, Dr. Katz adjourned the meeting.

The ACIP convened in Auditorium A of the CDC, Atlanta, Georgia, on June 9, 1992, at 8:35 a.m. Samuel Katz, MD, Wilburt C. Davison Professor, Duke University Medical Center, presided as Chairperson.

In attendance were representatives of the pharmaceutical industry media, academia, and interested groups, as well as members of national government agencies.

Welcome and Opening Remarks

Dr. Sam Katz, Chairman, opened the meeting by welcoming members, particularly Dr. Marvin Amstey, a new liaison member of the Committee, who represents the American College of Obstetrics and Gynecology and is a faculty member at the University of Rochester.

Dr. Katz then introduced Dr. Claire Broome, the Executive Secretary of the ACIP Committee, who asked all ACIP members and liaisons who have potential conflict of interest to make them known. She said she had been given permission by Dr. Kathryn Edwards and Dr. Neal Halsey to mention several consultation arrangements that they have reported on their financial disclosure forms. Dr. Edwards has consulted with Institute Merieux on pertussis vaccine and with Connaught Laboratories on *Hemophilus influenzae* b (hib), and given lectures for Lederle Laboratories. Dr. Halsey has had a research grant from Pasteur-Merieux on measles vaccine adverse effects and from Merck-Sharpe and Dohme for a study of hepatitis B vaccine in infants of mothers positive for human immunodeficiency virus (HIV).

Dr. Broome then announced that the Committee had undergone a formal change, returning to its original name, so that its acronym now matches its designation: The Advisory Committee on Immunization Practices (ACIP).

Dr. Katz then asked all the approximately 70 people present to introduce themselves. Those present included representatives of vaccine manufacturers, state health departments, the media, FDA, industry (Amjet), the Department of Defense, parent groups, and staff of CDC.

Update on Acellular Pertussis Vaccine Trials

Dr. Steve Wassilak, Division of Immunization (IM), National Center for Prevention Services (NCPS), reported that Connaught is still awaiting FDA licensure on its acellular pertussis vaccine. He then briefly reviewed large-scale clinical efficacy studies that are already under way, and others that are planned.

Hopefully these studies can answer six questions: 1) are DTaP vaccines effective when given at 2, 4 and 6 months of age? 2) Are these vaccines at least as effective as whole-cell vaccines? 3) What mix/amounts of components provide an advantage in protection? 4) How do the DTaPs compare in protection against severe pertussis

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL
AUDITORIUM A
ATLANTA, GEORGIA
JUNE 9-10, 1992
AGENDA

June 9

8:30 am	Welcome and Opening Remarks	Dr. Samuel Katz Dr. Claire Broome
9:00 am	Update on Acellular Pertussis Vaccine Trials	Dr. Steve Wassilak
9:15 am	Poliomyelitis - eIPV/OPV Schedules Combined eIPV-DTP Vaccine	Dr. Steve Cochi Dr. Carlton Meschievitz Connaught Labs
10:15 am	Japanese Encephalitis Vaccine Statement	Dr. Ted Tsai Dr. Carlton Meschievitz Connaught Labs
10:30 am	**BREAK**	
10:45 am	Report of the BCG Working Group	Dr. John Bass Chairperson, ACET Dr. Pierce Gardner Dr. Robin Huebner
11:45 am	Issues in Implementing Infant Hepatitis B Vaccination: Occupational Use of Hepatitis B Vaccine	Dr. Harold Margolis Dr. Eugene Hurwitz Ms. Donna Lazorik State of Massachusetts Immunization Program
12:45 pm	**LUNCH**	
1:45 pm	Update on Measles Epidemiology - Maternal Antibody Influence on Infant Immunization	Dr. William Atkinson Dr. William Bellini Dr. Lauri Markowitz Dr. Mark Papania Dr. Henry Pabst University of Alberta
3:45 pm	**BREAK**	

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
AGENDA CONTINUED

June 9

4:00 pm	Impact of Haemophilus b Conjugate	Dr. William Adams Dr. Jay Wenger
4:30 pm	Varicella Vaccine	Dr. Donna Jones Dr. Jo White Merck, Sharp & Dohme
4:50 pm	Re-evaluation of Pneumococcal Vaccine Efficacy and Duration of Protection	Dr. Robert Breiman Dr. Jay Butler

June 10

8:30 am	Immunization in Bone Marrow Recipients	Dr. Mark Grabowsky Dr. Albert Donnenberg Montefiore Hospital
9:00 am	Safety of Jet Injectors	Dr. Mark Grabowsky Dr. Steve Hadler
9:45 am	**BREAK**	
10:15 am	Issues to Consider in Revising General Recommendations on Immunization	Dr. Jay Watson
10:35 am	National Vaccine Injury Compensation Program Update	Mr. Thomas Balbier Public Health Service
10:55 am	Standards for Immunization Practice	Dr. Roger Bernier Dr. Vance Dietz
11:10 am	National Vaccine Program Update	Dr. Ken Bart National Vaccine Program
11:30 am	Public Comment Period	Ms. Ann Millan Dissatisfied Parents Together
12:00 pm	**ADJOURN**	

disease? --against milder pertussis disease? 5) Would large-scale use avoid seizures and hypotonic-hyporesponsive episodes? 6) Can a serologic correlate of protection be identified?

Ongoing studies (details given in handout) are: 1) Senegal: a randomized, double-blind, cohort study of 3,600 children being conducted from May 1990 to December 1995 by Merieux; vaccine schedule: 2, 4,, 6 months; two vaccines: Merieux whole-cell DTP and Merieux PT, FHA +DT; 2) Germany: a randomized, double-blind cohort study of 6,000 children being conducted by Lederle from May 1991 to mid-1994; vaccine schedule: 2, 4, 6, 15-18 months; two vaccines: Lederle whole-cell DTP and Lederle PT,FHA, Pertactin, Fimbriae 2+DT; 3) Sweden: an NICHD study of 3,000 children, being conducted from September 1991 to July 1994; vaccine schedule: 3, 5, 12 months with two vaccines, Amvax PT + DT, and DT; 4) Germany: a prospective case-contact study of 20,000 children, being conducted (Phase II) by SmithKline Beecham from October 1991 to December 1992; vaccine schedule: routine 3,4,5, 15-19 months; vaccine: SmithKline Beecham PT, FHA, Pertactin+DT (Behringwerke DT) (Behringwerke whole-cell DTP); 5) Sweden: an NIAID randomized, double-blind, placebo-controlled, cohort study of 10,000 children, being conducted from March 1992 to September 1995; vaccine schedule: 2, 4, 6 months; 4 vaccines: Connaught whole-cell DTP; Connaught PT, FHA, Pertactin, Fimbriae 2 & 3/6+DT; SmithKline Beecham PT, FHA+DT; and DT; 6) Sweden: a planned randomized, double-blind, cohort study involving 50,000 children, sponsored by vaccine manufacturers, to be conducted from October 1993 to September 1995; vaccine schedule: 3, 5, 12 months; vaccines: Connaught whole-cell DTP; others not confirmed; 7) Italy: a NIAID plus manufacturers' randomized, double-blind, placebo-controlled cohort study of 11,000 children, planned for October 1992-April 1995; vaccine schedule: 2, 4, 6 months; four vaccines: a whole-cell DTP; Biocine PT, FHA, Pertactin+DT; SmithKline Beecham PT, FHA, Pertactin +DT; and DT.

Poliomyelitis Vaccines

Next, Dr. Steve Cochi, IM, briefly summarized his and others' 2-hour review of research on polio vaccines (presented at the February 12-13 ACIP meeting) that needed to be considered to re-evaluate the ACIP's polio vaccination policy. (See pages 25-31 of the last minutes.) Those presentations and subsequent discussion centered around five questions posed by the Institute of Medicine (IOM) in its last review of such policy in 1988, namely: 1) Is wild virus circulating in the country? 2) What are the levels of immunity in adults? 3) What are the levels of immunity in preschool children, especially those in inner cities? 4) To what extent in the United States today does OPV vaccine virus spread to contacts of recipients and 5) What mixtures in schedules of IPV and OPV would yield the maximum benefit?

Dr. Cochi reiterated for the Committee three questions he had posed

to them at the February meeting and asked them to consider: 1) Have the research questions raised by the IOM been adequately addressed? 2) Are there issues other than those raised by the IOM that still need to be addressed? and 3) If DTP-IPV is licensed, is the ACIP prepared to consider a change to a sequential IPV/OPV schedule?

Then Dr. Cochi asked Dr. Carlton Meschievitz of Connaught Laboratories, to give an update of the clinical trial using the combined eIPV-DTP vaccine. This randomized trial compares three lots of the vaccine with matched controls. The study compares eIPV+DTP vs. DTP-eIPV at 2 and 4 months, with a booster at 18 months. The booster, however, is not the combined vaccine; the children are randomized to receive either eIPV or OPV. The trial was initiated in late December of 1990; enrollment was completed in February 1992, with a total of 422 infants enrolled.

This vaccine comes in a prefilled, two-chamber syringe, isolating until the time of vaccination the eIPV from the DTP, because of the thimerasol contained in the latter vaccine. A preliminary safety analysis on 148 infants shows that the addition of IPV did not increase local reactions; systemic reactions were often higher with the combined vaccine except for diarrhea. He then summarized monkey studies using this vaccine. The protocol consisted of vaccine injected from the dual-chamber syringe into monkeys on days 0, 7, and 14, with serum obtained on days 0 and 21. Thirty-six monkeys (12 per lot of vaccine) were vaccinated and sera tested for potency to the three poliovirus types. In each case, with each lot and each serotype, the potency greatly exceeded the minimum standard. Dr. Meschievitz said he expects a final report on the trial to be submitted to FDA in October, 1992.

Next, Dr. Neal Halsey summarized a report he had given at the Immunization Conference the week before on the need to simplify vaccine schedules, based in part on an opportunity he had to review information on this subject prepared by the AMA. He found that the latter report on the U.S. routine immunization schedule for 1992--prepared by two experts using ACIP recommendations and the Red Book as sources--had five major errors. Dr. Halsey also reviewed plans for a simplified stamp that the AMA is preparing for parents so that they can mark their calendars about what vaccines are needed for each age. Again, he was struck that that's a difficult task, indeed. He went over the current immunization schedule for ACIP members to illustrate how complex it has become and then made several suggestions to simplify it: eliminate ranges; eliminate extra visits; don't give more than two injections at any visit except for kids behind on schedule; when combination products become available, simplify and give instructions about compatibility.

Dr. Katz then restated the IOM questions raised by Dr. Cochi. Several members expressed concern about the subject of possible

increased reversion to neurovirulence in people challenged with OPV after having previously received IPV. Members were unclear whether this is an issue or not. Dr. Katz took Dr. Halsey's suggestion that the data being generated from the Modlin study[1] on this subject be presented at the next meeting because of the group's consensus that this matter needed to be looked into more closely to make sure the ecology was not being changed by this policy decision.

Dr. Cochi then asked the ACIP members if they were willing to go on record for a change in the recommendations (Question #3, above). A member expressed concerned that the question of neurovirulence needed to be examined more thoroughly first. A representative of the licensee for eIPV in Denmark, which has been mixed with acellular DTP, offered to have someone speak at the next meeting about the Denmark experience. Dr. Katz said that if someone could speak about reversion--whether there have been any problems using this combined schedule in terms of the risk of vaccine-associated disease in unimmunized contacts--that would be very helpful. He also asked Dr. Susan Tamblyn to discuss Canada's experience. She said Prince Edward Island uses a combined schedule and has not had a reported problem. She said the Province of Ontario also had a "natural experiment" because it had to suddenly switch from using IPV to OPV in 1990. No cases of vaccine-associated paralysis have been reported to date.

Dr. Katz asked ACIP members whether they were willing to vote or wanted more information on neurovirulence. The group voted unanimously that neurovirulence needed to be examined further before the Committee would vote for a change. The subject was added to the agenda for the fall meeting, again by unanimous vote. Also, Dr. Stanley Plotkin from Connaught offered to talk with Dr. Katz on the subject before the next meeting.

Japanese Encephalitis (JE) Vaccine

Dr. Ted Tsai, Division of VectorBorne Infectious Diseases (DVBD), National Center for Infectious Diseases (NCID), reviewed the ACIP statement on Japanese Encephalitis vaccine, which he described as much-improved and ready for consideration. Before going over the draft statement with the Committee, he briefly reviewed one case of Guillain-Barre syndrome (GBS) temporally associated with JE vaccination that had occurred since the Committee last met. The GBS case occurred in a 25-year-old soldier who developed weakness about 8-14 days after receiving the first dose of JE vaccine. He made an uneventful recovery without therapy. This is the first GBS case reported in temporal relationship with JE vaccination among 30,000 U.S. vaccinees. There have been no cases in 85,000 Danish vaccinees, and in Japan there have been very few neurologic illnesses of any kind reported in temporal relation to JE vaccine. The rate of all such neurologic events has been about 1 per million.

The Committee then was led through a review of changes in the ACIP statement since they had last seen it. The primary points of consideration were statements that "a causal relationship between JE vaccination and temporally related neurologic events has not been established" (page 5) and that the vaccine be recommended only for a restricted group of travellers who genuinely are at risk. Dr. Tsai went over all changes and additions, which are double-underlined in the attached handout. Members made the following additional requests:

1. on pages 3 and 5, make sure the document is internally consistent regarding the myelin basic protein content.
2. on page 7, strengthen the statement that "JE vaccine is not recommended for all travellers to Asia." This was based in part on testimony by S. William Berg, Captain, Medical Corps, U.S. Navy, that 4% of those who react are hospitalized.
3. on page 9, be more explicit about what the statement that "Vaccinees should remain in areas where they have ready access to medical care in the 10 days after receiving a dose of JE vaccine" means.

Dr. Carlton Meschievitz of Connaught Labs then went over the indications and usage, contraindications, immunization schedule, and warnings contained in the package insert for JE-VAX. (See attachment.)

Dr. Katz asked for a show of hands on whether or not the ACIP statement, as submitted, is sufficiently definitive about restrictions in its use. All members except one voted that the statement was OK as is. Dr. Tsai said it would now go to CDC's editorial section.

1993 ACIP Meeting Dates

Following a break from 10:50 to 11:07, Dr. Katz announced meeting dates for the ACIP in 1993. They are: February 9-10, June 16-17, and October 6-7.

Report of the BCG Working Group

Next, Dr. Pierce Gardner, Chairperson of this work group, explained that interest in this vaccine is heating up considerably because of the threat of multiple-drug-resistant tuberculosis (MDRTB). He said Committee members had six documents that related to this one-hour discussion: a draft, dated early May, of the subcommittee on BCG; a document from the National Vaccine Advisory Committee (NVAC) containing suggestions regarding evaluation and future development; a letter to Dr. Caroline Hall regarding BCG use in children of HIV-infected mothers; a document on "Suggestions Regarding Use of BCG in High-Risk Newborns" by Dr. A. Nahmias; a decision-analysis paper that appeared in the *American Review of Respiratory Disease* that challenges the tenor of the ACIP BCG draft paper and raises the

fundamental issue of whether BCG works in adults (the authors conclude that BCG should be used to prevent TB in house officers and medical students); and a letter to the editor rebutting that decision-analysis and another letter answering it.

Dr. Katz informed members that the newly formed Hospital Infection Control Practices Advisory Group (HICPAC) had sent a letter to the ACIP highlighting two areas of prime concern to them that they wished to keep in contact with the ACIP about: nosocomial pneumonia isolation procedures and prevention and control of TB.

Next, Dr. Robin Huebner, NCPS, updated the Committee on six hospital outbreaks of MDRTB--five in New York City. The CDC definition of MDRTB is INH and Rifampin resistance, with or without resistance to any of the other anti-TB drugs. The vast majority of cases (from 82%-100%) have been HIV infected; the mortality has been between 72%-89%. The median interval between diagnosis and death has been as short as 4 weeks up to 16 weeks.

Preliminary data from a prison outbreak in upstate New York indicated seven cases in immunocompromised inmates; all have died. The outbreaks was linked to a nosocomial outbreak in a NYC hospital. Evidence suggests transfer of MDRTB from other prisons to this prison and the subsequent transmission within the affected prison.

Regarding one of the six hospital outbreaks, Dr. Huebner said that between May-July 1991, approximately 50 health-care workers (HCWs) had PPD skin-test conversions following exposure to these prison inmates with TB. One prison guard, who had been immunocompromised due to a malignancy, developed MDTTB after hospital duty guarding inmates with the disease; he died. Three non-inmate patients have also been reported to have MDRTB.

Regarding use of BCG in HIV-infected individuals, the draft document distributed to members is as comprehensive a review as they could obtain of side effects of BCG use in HIV-infected persons. Dr. Sam Dooley, DTBE, NCPS, was asked by a Committee member what suggestions were made for HCWs who are PPD positive and exposed to MDRTB. He said that CDC's recommendations, which will be published very soon, suggest: 1) Make an assessment how certain you are that the person is newly infected with TB; 2) If he or she is newly infected, determine the likelihood that it's MDRTB; 3) If you do think the HCW is newly infected with MDRTB, determine that person's personal characteristics that might make him or her more or less likely to progress to more active disease. If the person is newly infected with MDRTB and is immunocompromised, the recommendation is to use a multi-drug preventive therapy.

Next, Dr. John Bass, Chairperson of the Advisory Committee for Elimination of TB (ACET), summarized the ACET's reactions to the ACIP draft BCG document. He said that recent studies in Chingelput

and Malawi, using the most antigenic strains, show no efficacy; specifically, the efficacy in adults has not been shown. In short, it's even worse than not having any positive data suggesting efficacy; recent data actually suggest that the vaccine is not efficacious.

The ACET's two biggest concerns are: 1) lack of scientific data to back up a recommendation for adults and 2) a more practical concern: if a relatively simple intervention is recommended with any degree of certainty, then the more difficult interventions above that will tend to get ignored. Thus, people in administrative positions will "just give everybody BCG." In short, the consensus of the Council would be to be even more conservative, rather than to enlarge the BCG recommendations.

Discussion then centered around the statement in the BCG draft that BCG's efficacy is "highly questionable." Dr. Gardner asked Dr. John La Montagne, NIH, to comment further on the use of BCG in adults. Dr. La Montagne was a member of the NVAC, which forwarded six suggestions to Dr. James Mason on this subject, namely: 1) to assess TB infection rates among institutional staff caring for high-risk groups (this is now planned); 2) to determine if the strain of BCG in the vaccine licensed in the United States is the optimal strain available; 3) to review the safety and potential benefit of BCG vaccines for asymptomatic HIV-infected individuals; 4) to explore the feasibility of developing a BCG strain that could be safely administered to HIV persons; 5) to establish a research base to develop a more effective vaccine against TB; and 6) to reconsider the potential utility of BCG vaccine in individuals at high risk of acquiring MTRTB.

Dr. La Montagne said the genesis of this discussion stems from two Washington meetings: one in February, at the NIH, convened to discuss research issues related to TB. The use of BCG was discussed extensively. Two sobering facts came out of that meeting: 1) if we were going to develop a new vaccine, ideally it would not produce a skin test conversion to the PPD test; and 2) that's going to take a long time. The second meeting was at the NVAC, which expressed concern that the epidemiologic situation has changed dramatically in the last year or two.

Dr. Katz noted that the NIAID has established this as a high priority, and has made millions of dollars available to investigators.

Dr. Gardner pointed out that if BCG is used and doesn't work, there's actually a negative side-effect: we lose the skin-test surveillance, which has been the backbone of our attempt to control TB. He asked the Committee if it could agree that BCG is of no use so that the paper can be published. This suggestion met with considerable resistance by members who were uncomfortable accepting zero efficacy as dogma without hearing more data. Dr. Broome also

raised the question of whether HCWs, as individuals who have recently acquired infection, wouldn't be more analagous to children, for whom efficacy has been demonstrated. Dr. Dixie Snider, Assistant Director of Science, NCPS, was asked to comment. He said that sometimes BCG works and sometimes it doesn't and the reasons for this variation are not known. After discussion, it was agreed that the take-home message of the document about efficacy should be that its efficacy is "highly variable and unpredictable" not "highly questionable." It was also emphasized that HCWs need to know BCG may not work at all.

One CDC staff person pointed out that most studies have been in children, not adults. However, a member of the audience disagreed, noting that some 20 studies of adults are mentioned in the *Review of BCG Vaccine* by Rosenthall. Since several of those studies concerned medical students, Dr. Broome asked if they couldn't be examined to see what data could be obtained on efficacy.

The final sense of the Committee seemed to be summed up by Dr. Halsey, who stated that the paper must do the following: 1) make sure HCWs are informed of potential negatives if they use BCG--including changing their skin-test results; and 2) not recommend BCG as routine, with a statement to the effect that "data are inconclusive to recommend" BCG. There also seemed to be a "silent consensus" to "look harder" at existing studies, various strains, and studies of efficacy in adults before a "more definite statement" can be made.

Discussion then turned to use of BCG in children. Dr. Andre Nahmias, of Emory University, was asked to comment about the recommendations regarding newborns. He said that the World Health Organization has recommended the use of BCG in newborns, and that over 60 countries require it, and over 100 strongly suggest it. Furthermore, 11 studies reviewed showed efficacy of 50%-90%. The recommendation he and others have come up with for the United States is to use in newborns or young infants exposed perinatally to HIV-infected mothers.

Winding up this one- and one-half-hour discussion, Dr. Katz said it was clear that the ACIP had the least argument with recommendations about newborns, and the biggest problem with HCWs. He asked Dr. Gardner if, given more staff support, his Committee wouldn't find it useful to look again at primary exposure, reactivation, different strains, HCW data. Dr. Gardner agreed, though he pointed out that the ACIP was going to be under increasing pressure to make a recommendation. It was also pointed out that the NIH was having a meeting the next day on research issues regarding BCG, and that a report of this would be given at the next meeting.

Issues in Implementing Infant Hepatitis B Vaccination

Next Dr. Hal Margolis, NCID, gave a brief background on hepatitis B in the United States. Some 22,000 HBsAg-positive women give birth each year. Most states have active perinatal prevention programs funded through the state immunization projects. About 4,500 antigen-positive infants born to antigen-positive mothers were reported through state immunization programs for 1991--clearly underreporting. Alaska has universal immunization at birth, and some states have started to require surface-antigen screening (and in some cases, reporting) in their administrative rules or state laws. Any persons who want an information folder/teaching module on this subject should give this request to Gloria Kovach, the staff specialist for the ACIP.

Regarding universal infant immunization, CDC has reviewed project grant proposals that will be funded some this month or early July. Ms. Donna Lazorik, Hepatitis B Coordinator for the State of Massachusetts Immunization Program, which began a universal immunization program in February, next presented information on that state's start-up of that project.

Massachusetts has a history of universal distribution of vaccine for children, in both public and private sectors; funding is provided through a state vaccine trust fund, established by the state legislature and funded with a cigarette tax. Additional funding comes from a federal immunization grant. Hepatitis B vaccination is now provided to all children in the state born since January 1, 1992.

Once funding was secured, the next step was to solicit input from the state immunization advisory committee on the development of state recommendations regarding infant hepatitis B immunization. Members of the committee were sent drafts of the proposed ACIP recommendations. A majority of members preferred the schedule in which the first dose of vaccine was administered to the infant prior to discharge from the hospital. This schedule was adopted.

The next step was to approach the hospitals. An advisory was developed and mailed to the medical director, chiefs of obstetrics and pediatrics, maternity nurse manager, pharmacist, and infection-control nurse at each of the 56 maternity hospitals in the state. She found that implementing this schedule in the hospital required a lot of personal attention by immunization program staff, who made visits to most of the hospitals. In-service programs on hepatitis B screening and immunization were conducted at many of the hospitals. (Massachusetts currently has no law requiring prenatal hepatitis B screening.)

She estimates that less than 1% of the women giving birth in Massachusetts each year are surface antigen positive, though the rate in some communities, such as populations of immigrants from

endemic countries, is much higher. Seroprevalence of HBsAg among pregnant women at three community health centers serving large numbers of newcomers ranged from 5.6% to 15%.

Despite such rates, the hepatitis project found that hepatitis B is not generally perceived as a pediatric problem because pediatric care providers do not usually see it in their practices. Because of this, the project really emphasized the likelihood of developing chronic infection when infection occurs at any early age in discussion with care providers. Providers have also been skeptical of the impact of infant immunization on the prevention of hepatitis B when these infants become adolescents and adults, when the risk for infection is greatest--in other words, how long does immunity from infant immunization last? The project addressed these concerns by assuring that the state would provide vaccines for boosters if the need is indicated. Providers also often questioned why teenagers were not being targeted for immunization.

Another key issue that affects actual implementation of this policy involves lack of communication of maternal screening results and the infant immunization status between hospital services and obstetric and pediatric services in the community. Accordingly, the hepatitis project encouraged parents to become advocates by providing immunization record booklets to all the hospitals to record the first dose. These are given to the parents.

Obtaining consent for the vaccine was another major concern. Communities have taken different approaches to this issue; some obtain consent on admission; some include it in a pre-admission packet that has other forms as well. In others, obstetricians are enlisted to obtain consent prenatally.

The hepatitis project has developed an informational brochure for parents, which is distributed through prenatal classes as well as by pediatricians. The brochure is now being translated into various languages.

She said the main concern of community-based providers seems to be the number of simultaneous injections needed to administer all the required vaccine. Results of a Harvard Community Health Plan survey of 28 parents were that 71% indicated that they would prefer not to schedule an additional visit, even though it meant administering three injections at the same time.

Forty-nine of the 56 maternity hospitals in the state have now instituted routine hepatitis B immunization of infants, and several others give it on preference of the pediatrician. One reason for the state's success is that it provides the vaccine free of charge to all the hospitals and community-based providers. The project is now working with the Office for Children, the state agency responsible for licensing of day cares, to include this vaccine among the ones required for day-care entry. In the future, it will

also be a kindergarten-entrance requirement.

Ms. Lazorik emphasized several lessons her project learned: 1) to solicit provider input in policy development and address their concerns, if feasible, by using a multi-component approach that would include immunization of adolescents; 2) to present infant immunization in the context of an overall strategy to prevent hepatitis B transmission; 3) to encourage communities to develop their own strategies for addressing the issues of hepatitis B screening and immunization results and of obtaining consent; and 4) that free distribution of vaccine gave the message of how important the state considered this immunization to be. (Ten or eleven states now do this.)

The ACIP was very impressed with the Massachusetts project, and asked what plans existed for adolescent vaccination. Ms. Lazorik said they are seeing if any funding is available on the state level for pilot projects.

Occupational Use of Hepatitis B Vaccine

Before breaking for lunch at 1:05 p.m, Dr. Broome mentioned that the OSHA regulations for control of occupational exposure to blood-borne pathogens, issued in December 1991, recommend hepatitis B vaccine for those with occupational exposure to potentially infectious materials. The ACIP issued a recommendation at about the same time that is in strong support of that OSHA recommendation. There has been some confusion about another ACIP recommendation for public safety workers with infrequent exposure to blood; for these, "timely postexposure prophylaxis" should be considered rather than routine pre-exposure vaccination. Some have interpreted this statement as being in conflict with the OSHA rule; Dr. Broome wanted to emphasize that the ACIP clearly supports the OSHA rule.

Reconvening at 2:00 p.m., Dr. Margolis summarized the general and specific objections that universal hepatitis B infant immunization is likely to raise, as Ms. Lazorik's presentation demonstrated. In reference to alternative strategies for adolescents, he said that Minnesota, Wisconsin, Oregon and California are trying to put together adolescent demonstration projects. British Colombia is also launching an adolescent program this fall.

Hepatitis B: Adult Immunization Response Rates

Next, Dr. Eugene Hurwitz, Deputy Chief of the Epidemiology Section, Hepatitis Branch, NCID, presented data on reports of lower-than-expected response rates among adults to hepatitis B vaccination. He said published data on the immunogenicity of the vaccine show that 74%-97% of vaccinees have an adequate response. Factors that have been reported to affect the immune response are age (over 40), sex, obesity, smoking, and immunocompromised conditions. For

example, a recent study of responses to Recombivax among firemen in Connecticut found that 73% of smokers responded adequately, versus 93% for nonsmokers. Obesity (over 200 lbs.) was also a factor, with only 77% of obese employees having an adequate response.

Finally, Dr. Hurwitz described the types of studies CDC is conducting regarding adult hepatitis B vaccination:

1. Immunogenicity of HB vaccine in populations currently being vaccinated, including firemen, public safety workers, and hospital employees.
2. Differences in the immunogenicity between Engerix and Recombivax. A "head-to-head" trial of these vaccines is planned.
3. Can the seroprotection rates can be improved by revaccination with one to three additional doses?
4. Potential usefulness of pre-S vaccines (vaccines that contain antigen not only to S but S1 or S2 or both) in older, obese, and smoking individuals.

A Committee member suggested that the issue of mixing different brands be considered in the list of questions for further studies.

Update on Measles Epidemiology: Maternal Antibody Influence on Infant Immunization

Next, Dr. Lauri Markowitz, IM, NCPS, introduced several speakers to present a variety of data on the issue of whether the recommended age for measles immunization should be lowered in the United States. Currently, the ACIP recommends vaccination at 12 months of age in inner-city areas or counties with recent measles outbreaks; the recommended age for the rest of the country is 15 months.

Update on Measles Epidemiology. Dr. Bill Atkinson, IM, NCPS, summarized recent measles epidemiology, which illustrates the changing age distribution of measles cases. Until 1988, most U.S. cases were in school-age children (5- to 19 years), but by 1990 the proportion of cases in pre-school-age children (under 5) exceeded those in school-age children. In 1991, pre-school cases accounted for 50% of all reported cases. The new low for median age of all reported cases is now 60 months; the highest increase is in those less than 16 months of age.

Among measles cases last year, only 20% were appropriately vaccinated. There were 37 deaths, nine of whom were HIV positive. There are nine current outbreaks in seven states--four of these are preschool outbreaks.

Risk Factors for Measles in Children Less than 16 Months of Age. Next, Dr. Mark Papania, IM, NCPS, summarized a retrospective cohort study of a measles outbreak in New Jersey in 1991 to determine risk factors for children less than 16 months of age. Researchers

postulated that one risk factor would be having a mother who was likely to have vaccine-induced immunity by virtue of her year of birth. The analysis showed that children of mothers born in or after 1968 had an attack rate of 62% (a relative risk of 3.5 [95% C.I.]), compared to 18% for children of mothers born before 1968. The major implication of this study is that the risk for measles in exposed children in the United States less than 16 months of age will continue to increase as the proportion of mothers born since 1968 increases.

Serologic Data on Changing Maternal Antibody Titers. Next, four presentations were made documenting decreasing maternal measles antibody titers, three from the United States and one from Canada. First to speak was Dr. Henry Pabst of the University of Alberta, who reviewed a study of 328 mother-infant pairs that showed a significant difference between babies of mothers who were or were not vaccinated.

Dr. Markowitz summarized a CDC study, conducted in a Los Angeles health maintenance organization (HMO). The data demonstrate decreasing measles antibody titers in U.S.-born women; decreasing seropositivity rates in their children; and higher seroconversion rates to measles vaccine in children born to younger women.

CDC's Dr. William Bellini, VR, NCID, reported CDC antibody assay results demonstrating that children of younger (assumed to be vaccinated) mothers have significantly less measles antibody at 2, 4, and 7 months than children born of the older mothers (who presumably had natural disease). These data demonstrate that an approximate 8-month "window of susceptibility" may be present. Dr. Bellini cautioned, however, that we have to make sure that maternal antibody is the only inhibiting factor to immunization in this younger age-group of children.

Next, Dr. Gail King summarized a review of U.S. birth certificate data of births from 1971-1988 to mothers between the age of 15-44 years of age. These data demonstrate that by the end of this decade or sooner, the vast majority of mothers in the birthing cohort will have been born during the measles vaccine era and will be delivering infants with lower levels of maternal measles antibodies. These data also suggest that the increasing susceptibility at younger ages, due to falling maternal antibody, may be the reason for the rising proportion of measles cases in children less than 16 months of age during the most recent measles epidemic.

Following these presentations, Dr. Markowitz said that CDC has initiated a three-arm, randomized study at an HMO in Minnesota to evaluate this question more directly. She said the ACIP could take three possible actions, based on these data: 1) to leave the recommendations the same as they are now; 2) to change the recommended age for MMR to 12 months; and 3) to alter the

recommendation to allow a permissive vaccination.

There was some discussion among Committee members about making the recommendations more permissive (i.e., using words such as "12-15 months.") However, when Dr. Katz called for a formal vote of members, option #1--not to change the recommendation until further data are available--was decided upon.

Impact of Hib Conjugate

Following a brief break of the Committee, Dr. Jay Wenger described two surveillance systems for cases of Hib disease used to evaluate the impact of the new vaccine against this disease. About 12,000-14,000 cases of this disease are estimated to occur each year in the United States in children under 5 years old. The National Bacterial Meningitis Reporting System is a passive system in which states voluntarily report cases of this disease. The CDC analysis of these data was restricted to 20 states with a total population of 106 million where there was continuous reporting from 1980-1991. There is also an active surveillance system operating since 1989 in four states with a population of 10.4 million people. CDC contacts every hospital laboratory in this surveillance system regularly and conducts periodic laboratory audits.

Analysis of data from these surveillance systems shows that substantial decreases in Hib disease have occurred, that these have occurred in vaccine-eligible age-groups, and that these decreases were clearly associated with national vaccine distribution and administration to the public sector. Decreases were seen in infants before licensure of the vaccine for this age-group and that may be due to an effect on carriage.

Dr. Katz noted that this news was "exciting and wonderful." He said that Duke University has had only one case admitted this year, and that a Finnish physician recently told him that his country hadn't had a single recognized case in 3 years. In short, Dr. Katz said, that future pediatric residents may be as unfamiliar with Hib disease as they are now with polio.

Varicella Vaccine

Dr. Donna Jones said that there was renewed anticipation that the chickenpox vaccine, developed by Merck, Sharpe and Dohme, might be licensed soon. She introduced Dr. Jo White, Director of Research at Merck, Sharpe and Dohme to speak.

Dr. White said their varicella vaccine had a good safety profile in its use with over 9,000 children. There are minor local complaints, a low rash rate, no notable increase in zoster to date, and no clinical evidence of transmission from healthy vaccinees. The vaccine is highly immunogenic (at least 96%) and has excellent persistence (through 6 years). It's efficacious and the

breakthroughs that follow vaccination are very mild disease.

In response to Committee members' questions, she said that 1) eventually the manufacturer would probably consider a two-dose schedule and 2) the manufacturer is planning a large double-blind efficacy study next year to look at using this vaccine to prevent zoster in the elderly.

Re-evaluation of Pneumococcal Vaccine Efficacy and Duration of Protection

Next, Dr. Robert Breiman, BD, NCID, explained that 3 and one-half years ago when data from CDC's Pneumococcal Surveillance System were last presented to the ACIP, the issue of re-vaccination for persons who had received the vaccine 5 or more years before was under consideration. The decision was made to consider re-vaccination for those at highest risk of fatal pneumococcal disease; the Committee "stopped short" of making a recommendation for universal re-vaccination. At that time, the vaccine was considered to be about 60% efficacious in preventing invasive pneumococcal disease. There were insufficient numbers to evaluate the vaccine's efficacy for specific underlying diseases and what the duration of protection was. More data are now available, which would be summarized by Dr. Jay Butler.

Dr. Butler said that, using surveillance and laboratory data, CDC has confirmed that the pneumococcal polysaccharide vaccine is efficacious for preventing serious pneumococcal infection in most immunocompetent persons. CDC found that the vaccine is efficacious in certain immunocompromised patients and that protection following a dose of this vaccine appears to last for 6 or more years. These findings support the current ACIP recommendation that routine re-vaccination is not indicated. However, until more data are available on duration of protection for patients with specific risk factors, re-vaccination should be considered for persons at highest risk of complications from pneumococcal infection, as is currently recommended.

Following Dr. Butler's presentation, the meeting adjourned at 5:55 p.m. It was called to order again on June 10 at 8:30 a.m.

Exiting Members

Dr. Katz introduced Dr. Walt Dowdle, Deputy Director, CDC, who thanked all the ACIP members for contributing to making the Committee such a success and specifically Dr. Mary Wilson, who was leaving after 4 years on the Committee. Dr. Wilson was given a Certificate of Appreciation from Dr. Roper and a copy of *Sentinel for Health*, the newly released history of the CDC written by Elizabeth Etheridge. Dr. Katz noted that Dr. David Fraser was also leaving effective this meeting and recorded thanks to him for his contributions.

Immunization in Bone Marrow Recipients

CDC's Dr. Mark Grabowsky was the first of the day's speakers. He briefly reviewed the draft of the ACIP statement on immunization of bone marrow transplant (BMT) recipients.

Dr. Grabowsky said that immune response in the BMT recipient is a function of three things: the graft composition, the timing of recipient immunization, and immune suppression. Routine vaccine-preventable diseases have not been reported to be significant pathogens in recipients, and long-term survivors may be at high risk of pneumococcal infection. In terms of safety, there have been no severe reactions reported with diphtheria or tetanus toxoid with early immunization, and immunization during the peri-transplant period does not appreciably affect the incidence or severity of graft vs. host disease. With late immunization, that is, 1 or 2 years after graft, no severe effects have been reported, though there have been reports of some strong local reactions. MMR is not typically given in the United States; but in a center in Sweden, where it is given, no early or late side effects have been observed. In terms of effectiveness of immunization in these patients, the response to tetanus toxoid is good, response to three types of polio vaccine to three doses of IPV is moderate, and the response to MMR is lower among BMT recipients than among controls. Dr. Grabowsky went over the suggested immunization schedule for BMT donors and recipients on page 5 of the draft. Two typos were pointed out in the second-to-last line.

Dr. Albert Donnenberg, an expert of this subject from Pittsburgh's Montefiore Hospital, then answered technical questions about the statement. In response to Committee questions, he said that, in the absence of chronic graft vs. host disease and immunosuppressive therapy, live vaccines can be given 1 year after transplant. He also said that hepatitis B immunization is not on the schedule.

There was some discussion about the current titers of antibodies to the common viral and bacterial pathogens in IVIG. Dr. Markowitz said she understood there is a hepatitis and measles standard that the users of IG have to meet prior to release of their IG lots. She said that Dr. Siber, of Massachusetts Public Health Laboratories, prepares his own IG lots and is in the process of going through them to see if there's been a drop in titers since 1950. Dr. Halsey said that manufacturers routinely have such information available on each lot.

It was pointed out that other immunogens might be considered and added to the immunization schedule, once the data regarding their effectiveness are available. Dr. Katz asked that information on cytomegalovirus studies be made available for the next meeting. Other suggestions for the statements were that:

--on page 3, drop the phrase "opportunistic agents" and

substitute "cause of severe illness."
--add the word "seasonal" after "influenza" on the immunization schedule.

Dr. Katz said that any other comments about the statement should be mailed to Dr. Grabowsky by June 19. It was clarified that this statement is not an appendix to another immunization statement, but a separate document. Dr. Donnenberg said he would get together a list of the major BMT centers so that the statement could be mailed to them.

Safety of Jet Injectors

Dr. Steve Hadler, IM, NCPS, said that CDC wanted to revisit this issue after a hiatus of 4-5 years because of numerous requests for recommendations about the use of jet injectors. These have been widely used since 1963. The U.S. military gives about 1.25 million injections a year via this method.

These injectors have basically been considered safe and effective, when used as directed, although there is a slightly increased risk of local reactions. Antibody responses have been found to be comparable, and no serious risks have been identified. However, in 1985, an outbreak of hepatitis B occurred in a weight-reduction clinic associated with one type of jet injector, prompting several groups to reconsider their use. CDC (not the ACIP) informally recommended in 1986 that care, cleaning, and decontamination were necessary to ensure safe use of these instruments. WHO subsequently recommended the use of these injectors only in areas where use of needles and syringes was not feasible (e.g., when vaccination of 9,100 persons in a single session was anticipated). In 1988, the Armed Forces Epidemiology Board recommended that the military should continue to use them.

Early this year, CDC received a request from both the Pan American Health Organization and the Government of Brazil for advice on use of jet injectors for an upcoming campaign in Brazil that involves giving 40 million doses of measles vaccine. In a letter to Dr. Ciro de Quadros, CDC noted that there were no official recommendations but that use should be safe if staff were properly trained and--and this is a departure--if the injector tip were swabbed with acetone or alcohol after each use.

Soon after, CDC received a request from the Illinois State Health Department about use of these instruments for a meningococcal vaccine campaign at the University of Illinois. CDC responded similarly. Then CDC became aware of some new data from Brazil suggesting that Ped-O-Jet injectors--the most commonly used ones for vaccination campaigns--could transfer blood if they became contaminated.

Dr. Hadler then reviewed the 1985 outbreak in detail, presented

data from simulated contamination of jet injectors with blood, and Dr. Glacus de Souza Brito, from the Division of Immunization of the Sao Paulo, Brazil, Health Department, reviewed work being done in Brazil. Also reviewed was mathematical modeling of the possible risk of bloodborne disease being transmitted by jet injectors based on data that CDC now has. Additional information on current use in the military was also reviewed.

Dr. Hadler then reviewed the 1985 outbreak in detail. It occurred in a weight reduction clinic in California. Each client received an average of 28 injections during a 6- to 12-month period in the clinic. The type injector was Med-E-Jet, which has not been widely used for immunization campaigns. It has a different design than other such instruments; it has a detachable tip with a two-part assembly. If blood gets on the tip, it will enter, by capillary action, into the assembly and will remain there unless it is disassembled and decontaminated. The outbreak identified 27 cases of clinical hepatitis B in this population; when several hundred clients in the clinic were tested, 21% were found to have evidence of acute hepatitis B infection.

Dr. Hadler then summarized CDC Hepatitis Branch studies of jet injectors, undertaken in 1985, to simulate contamination of these Med-E-Jet or Ped-O-Jet injectors. The conclusion of these studies was that, if artificially contaminated, both types of jet injectors could transfer serum on subsequent injections. The Med-E-Jet injector became contaminated on the exterior and also on the interior, requiring disassembly to disinfect. Second, the volume of serum transferred could contain infectious virus particles. The risk of serum transfer in the volume transferred was reduced by swabbing the injectors prior to the next injection.

Next, Dr. Glacus de Souza Brito from the Division of Immunization at the Sao Paulo, Brazil, State Department of Health, reported on three field studies in Brazil using human volunteers, undertaken after reports of Med-E-Jet hepatitis outbreak. Injectors are widely used in the military for most antigens, and are used in the Amazon to administer yellow fever, measles and sometimes meningococcal vaccine. They are also planned for use in the National Measles Elimination Initiative. The studies were designed to assess the risk of bloodborne transmission with the use of these instruments. The studies were performed under ideal situations, in the military, and in the Amazon, where such vaccinations are difficult.

Among almost 3,000 injections, results were: 1) The prevalence of visible blood at the injection site immediately after use of the injector varied from 2.2% to 23.3%, being much higher in Amazon studies; 2) Blood showed up in subsequent doses (determined by injecting it into a vial and testing with a dipstick for occult blood) 1% of the time, but as high as 6.6% in the Amazon. 3) In these studies, there was little to no correlation between visible

bleeding and detection of occult blood in the successive vaccine doses; 4) Swabbing between doses using dry cotton seemed to reduced detectability of occult blood. Swabbing may also reduce residual blood content. However, these preliminary results need further confirmation.

Based on these results, the Technical Committee on Immunization of Brazil has tried to quantify the risk of HIV transmission for the National Measles Campaign. The risk of such transmission by HCWs by needlestick is estimated to be 0.3%. By contrast, the risk via jet injectors is estimated to be "in the range of 1 per 238 million to 1 per 476 million injections. Theoretical risk of hepatitis B transmission was determined to be in the range of 1 per 388 to 1 per 3,367 injections.

Based on these risk estimates, jet injectors are currently used in Brazil in the special vaccination campaigns, with the exception of areas with high hepatitis B prevalence, like the Amazon.

Dr. Grabowsky said that CDC has also attempted a model of the risk of HIV and hepatitis B transmission using jet injectors. The conclusion is that the risk of transmission of hepatitis B or HIV is likely to be less than 1 per 100,000 jet injections. In the worst case scenario, there would be approximately 5.1 transmissions of hepatitis B and bout 2-3 transmissions of HIV per 100,000 injections. The risk is lower in populations with lower disease prevalence and when the jet injector is swabbed.

CDC's suggested recommendations are that, although jet injectors can be used safely in low HBV/HIV prevalence areas, to minimize the risk of transmission of bloodborne pathogens, the jet injector tip should be swabbed after each injection. If the jet injector is visibly contaminated with blood, it should not be used until decontaminated.

Dr. Hadler then asked liaison member Dr. Mike Peterson to summarize the military experience with jet injectors. He said that the military has used them since they were invented. Air Force uses them for 160,000 injections a year; the Army for 440,000 year; and Navy 560,000 year. Now all use Ped-O-Jet exclusively. The Army screens for HIV but not for Hepatitis B.

Dr. Grabowsky then asked if the ACIP should make an official recommendation about jet injectors, and if so, in what context (as a separate recommendation or part of general recommendations?) and what recommendations?

Dr. Katz asked if the Committee was in consensus that a recommendation on this subject was within the purview of the ACIP and should be drafted and added to the general immunization statement. The Committee agreed with this. Dr. Hadler agreed to have suggested wording ready for the next ACIP meeting if the

Committee would give a sense of what should be in the recommendations about proper cleaning and disinfection of these instruments. (There had been some discussion, after the presentations, about the fact that acetone is preferred because alcohol is slower drying and leaves an oily film, causing chance of slippage.) A vote was taken to see if the recommendation should say something about swabbing. Only Dr. Carolyn Hardegree voted against it, saying that disposal of swabs would need to be spelled out and that she wanted to discuss the matter with FDA's device people. Dr. Hadler agreed to put together the overheads from the presentation and fax them up to FDA.

The group had a break from 10:05 to 10:15 a.m.

Issues to Consider in Revising General Recommendations on Immunization

Next, CDC's Jay Watson, NCPS, presented a list of items being considered for revision of the ACIP General Recommendations on Immunization. (See handout.) He highlighted the following areas that he particularly wanted input from the Committee on and asked that written comments on these and other issues be submitted by July 1. (Gloria Kovach will send out worksheets on this; then the matter will be re-visited at the fall ACIP meeting.)

--Re. immunobiologics: the schedules and tables need to be updated regarding DTaP, *Hemophilus* vaccine, the 2-dose measles vaccine, hepatitis B, and oral typhoid; two suggestions are to add a table listing the available immune globulins and a section on cold storage.
--Re. route, site and technique of immunization: CDC wants feedback on whether there are any protocols for persons with coagulation defects, when vaccination is recommended; preferred sites for multiple vaccination; definition of "separate site" when the same limb is being used; use of jet injectors; re-dosing of children who vomit OPV; and advice regarding OSHA requirements (is hepatitis B vaccine needed to administer vaccine, and are gloves required?)
--When a person has no documentation about previous vaccinations, do we have data on safety of repeated antigen administration?
--Discuss combining different vaccines, in view of data from Connaught on the reconstitution of Connaught, HIB PRP-T with Connaught DTP.
--Re. altered immunocompetence, should reader just be referred to the new statement the ACIP is publishing on this subject? Should a table be included here?
--Re. misconceptions concerning contraindications to vaccination, should we discuss safety of breastfeeding after killed and live vaccination and should the recent study that showed some interference in response to the measles infection when a person had a current upper respiratory infection be

included?

Dr. Katz asked each member to review this handout and submit written responses by July 1. However, the following comments were made orally:

--Dr. Tamblyn said that Canada has a section on coagulation defects in its immunization guide.
--Re. OSHA requirements, Dr. William Schaffner, liaison representative for the American Hospital Association, said if persons are dealing with individuals and sharps, they would fall under the requirement that they be provided hepatitis B vaccine. It was suggested that this be added parenthetically to the statement. Further, gloves are mandated for *drawing* blood, not administering vaccines.

National Vaccine Injury Compensation Program (VICP) Update

Mr. Thomas Balbier, Director of the VICP, updated the Committee on the NVIC. He said in the past 1-1/2 years a number of changes in the way the program operates have occurred. Dr. Mason organized a task force to look at the VICP and charged it with coming up with a set of comprehensive legislative proposals for fixing it. The Task Force was chaired by Dr. Harman, the administrator of the Health Resources and Services Administration. Mr. Balbier served as Executive Secretary on the task force. It broke into two subcommittees. One subcommittee came up with some legislative proposals that were enacted last year that improved the overall operation of the program.

The other, under Dr. Ken Bart's leadership, looked at the vaccine injury table in the statute, with the expectation that the IOM report due out on the adverse affects associated with pertussis and rubella vaccines would provide the impetus for proposing changes to that table. The subcommittee's recommendations were presented to Dr. Mason, who decided to have an independent group, under the auspices of the NVAC, chaired by Dr. Ed Marcuse, look at the recommendations to make sure they were on solid scientific group. That subcommittee modified them somewhat and sent them on to the full committee's November meeting, where a final set of recommendations was voted on. This was then sent to the Advisory Commission on Childhood Vaccines, the advisory commission for the VICP. That group has come to closure on this whole issue of changing the table. It is expected to be published in the Federal Register very soon.

There has also been a change in the participation by the parents. Dr. Mason has met on two separate occasions with Ann Millan of Dissatisfied Parents Together to talk about some of the operating problems with the program and to discuss the changes to the table. This parents' group also identified an expert to serve on the subcommittee of the NVAC.

Mr. Balbier said that when he took over the program it had over 4,000 pre-1988 claims filed. The program was faced with expected costs of about $2.6 million for paying all those claims, if these cases proceeded as earlier cases had. Now, he thinks those same 4,000 cases will cost half of that--$1.3 million. Reasons for this reduction are: reduction in the award rate to approximately 56% overall from last year; enactment of the 1991 legislative amendments--one of which repealed the requirement to make payments in four equal annual installments; cases are being processed more quickly because of settlements; and improved management of the program, particularly in the way DHHS and the Department of Justice are working together on this program. He introduced the Committee to Dr. Robert Wybel, a member of the VICP staff who also chairs the first interdepartmental quality improvement team, composed of attorneys from the Department of Justice and VICP medical staff, who meet on a regular basis to work on process improvements.

Mr. Balbier called attention to a recently developed publication, distributed to members, entitled *Commonly Asked Questions about the Vaccine Injury Compensation Program*. It will be part of a kit that CDC will be distributing that includes the new Standards for Pediatric Immunization Practices. He then reviewed the weekly status report of the VICP (see handout). He said that the Advisory Commission will meet again next week to try to develop new criteria for newly recommended or new vaccines. Among the questions it will consider are: Should it cover mandated or universally recommended vaccines? Should payment be restricted to children? Should vaccines recommended by the Department of Labor for occupational reasons be covered? The Commission hopes to resolve these questions next week. Adding new vaccines will require legislation. Ultimately, VICP will suggest changes to the Department of Treasury, which sets the surcharges.

Standards for Immunization Practice

CDC's Dr. Vance Dietz, IM, NCPS, updated the ACIP on what has happened with the standards since the February meeting. The final document was distributed to all ACIP members today. The comments of both NVAP and the ACIP were incorporated into the document. The standards were approved by NVAC in April and then by the PHS in early May. Shortly afterwards, they were endorsed by the American Academy of Pediatrics and the Council of State and Territorial Epidemiologists.

Presently a task force has been created to take the necessary steps to implement the standards. CDC is now getting endorsements of all major working groups. Dr. Dietz asked the ACIP to endorse the standards at this time.

He then went over the major changes made since February:

--New title: Standards for *Pediatric* Immunization Practices.

--Statement added that comments represent a consensus of NVAC and a group of experts.
--One standard deleted, that on who can give permission to vaccinate a child was deleted.
--Ordering of standards changed.
--Some wording changes, such as eliminating phrase "false contraindications" throughout the document.
--Words added to standards 11 and 17.
--the table, "Guide to Contraindications and Precautions" had the word "precautions" added to the title and pregnancy has been added as a precaution for both OPV and IPV. The use of IG is also listed as a precaution with MMR. The use of multiple live-virus vaccines within 30 days of each other is now referenced as a footnote.
--Several new additions have been made: on page 16, under conditions for new vaccines, the phrase "Anaphylactic reactions to a vaccine constituent contraindicates the use of vaccines containing that substance." There's also now a footnote on measles vaccination and tuberculin testing, reflecting current ACIP recommendations.

The only suggested change was that the document reflect ACIP's name change. The group unanimously voted to endorse the standards.

National Vaccine Program Update

Dr. Ken Bart, Director of the National Vaccine Program, was unable to attend today's meeting. He gave a summary of his presentation to Dr. Broome, who distributed it to the Committee. (See handout.)

Public Comment Period

Next, Ms. Ann Millan, Director of the National Vaccine Information Center operated by Dissatisfied Parents Together, addressed the ACIP. This center is a national, not-for-profit educational organization which serves as a clearinghouse for information on existing vaccines as well as vaccines still in development. A copy of her entire speech is attached for the record.

Following this presentation, at approximately 11:55 a.m., Dr. Katz adjourned the meeting.

Reference

1. Modlin JF, Onorato IM, McBean AM, et al. The humoral immune response to type 1 oral poliovirus vaccine in children previously immunized with enhanced potency inactivated poliovirus vaccine or live oral poliovirus vaccine. Am J Dis Child 1990; 144:480-4.

Summary of Actions Requiring Follow-Up:

Following is a "reminder" listing of agreed-upon actions. For more details, see the related section of the minutes.

- Dr. Katz asked that the Modlin[1] data on increased reversion to neurovirulence with polio vaccine be presented at the next meeting.
- Dr. Stanley Plotkin offered to talk with Dr. Katz about reversion to neurovirulence before the next meeting.
- Dr. Pierce Gardner was asked, with increased staff support to be provided, to have the BCG Subcommittee look again at such issues as different strains of vaccines and efficacy data on populations analagous to HCWs.
- Dr. Katz asked that a report of the NIH June meeting on research issues regarding BCG be presented at the next meeting.
- Dr. Ted Tsai agreed to make requested changes in the ACIP statement about JE vaccine and to submit the report for publication.
- Dr. Katz asked that information on cytomegalovirus studies be made available for the next meeting.
- Dr. Katz asked all members to submit comments about the ACIP draft statement on immunization in bone marrow recipients by June 19.
- Dr. Donnenberg agreed to assemble a list of the major bone marrow transplant centers so that the bone marrow statement can be mailed to them.
- Dr. Hadler agreed to prepare by the next meeting suggested wording for the agreed-upon addition to the general ACIP recommendations regarding jet injectors.
- Dr. Hadler agreed to fax overhead's of his presentation up to FDA.
- All members were asked to submit written comments about proposed revisions to the ACIP General Recommendations on Immunization by July 1. Gloria Kovach will send out worksheets on this.

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

Samuel L. Katz

Samuel L. Katz, MD, Chairperson
Date: 23 September 1992