IMMUNIZATION PRACTICES ADVISORY COMMITTEE

Meeting at
Auditorium A
Centers for Disease Control
Atlanta, Georgia

AGENDA

October 22, 1991

8:30 a.m.	Welcome and Opening Remarks Introduction and Orientation of New Members
9:00 a.m.	Haemophilus influenzae type b Vaccine Impact
9:30 a.m.	Vaccinia Vaccine in Laboratory Workers
10:00 a.m.	BREAK
10:30 a.m.	Utilization of BCG Vaccine in the context of HIV Infection and Multi-Drug Resistant Tuberculosis
12:30 noon	LUNCH
1:30 p.m.	Immunization in the Immunocompromised
2:45 p.m.	BREAK
3:15 p.m.	Acellular Pertussis Vaccine

October 23, 1991

9:00 a.m.	Influenza Vaccine and GBS
9:30 a.m.	Japanese Encephalitis Vaccine
10:15 a.m.	BREAK
10:45 a.m.	National Vaccine Program - Injury Compensation Program
11:15 a.m.	Federal Implementation of ACIP Recommendations
11:30 a.m.	Infant Immunization Initiative
12:30 p.m.	ADJOURN

Executive Summary

The Immunization Practices Advisory Committee (ACIP) met at the Centers for Disease Control (CDC) on October 22-23, 1991. Dr. Samuel Katz presided as Chairperson; Dr. Claire Broome was Executive Secretary.

Dr. Katz announced the publication of the ACIP statement on DTP. He welcomed new members Dr. Kathy Edwards, Dr. Neal Halsey, and Dr. Rudolph Jackson. He introduced new liaison representatives Dr. Pierce Gardner and Dr. Caroline Hall. Dr. Regina Rabinovich sat in for Dr. John La Montagne. Absent were Dr. David Fraser and Dr. Carlos Hernandez.

Dr. Broome also welcomed new members and announced that names of Committee members and liaison representatives will now be listed in the ACIP statements. She read a description of the Committee's work from its charter, and reviewed the CDC organizational structure for the benefit of new members.

Dr. Broome reported on discussions with the Office of the General Counsel and subsequent clarification of what type of association constitutes "conflict of interest," as well as the need to disclose such associations to the Committee. Anyone with questions on this issue should contact Kevin Malone of the General Counsel's office, through Dr. Broome.

Haemophilus influenzae type b Vaccine Impact was the first agenda item. **Dr. Jay Wenger** served as moderator. **Dr. William Adams** reviewed the data from three independent surveillance systems which looked at the impact of this vaccine in two-month olds: The National Bacterial Meningitis Reporting System, the National Electronic Telecommunications System for Surveillance, and the Meningitis and Special Pathogens Active Surveillance Project. All three systems showed substantial decreases in Haemophilus influenzae and Hib disease in children under 5. A decrease in number of reported cases was seen in age groups for which vaccination was recommended; a decrease was also seen in infants less than one year old before vaccines were licensed for use in this age group. This may have been caused by reduced carriage of the organism resulting from widespread immunization.

Dr. Juhani Eskola, of the National Public Health Laboratory, Finland, reviewed the experience in Finland with Hib conjugate vaccines. The vaccination program, begun in 1986, first used PRP-D, then PRP-D and Hboc, and now PRP-T. In children under five, there has been a sharp decline in the disease since 1986, when there were nearly 180 cases; this year, there have been only two cases, both in very young infants. The disease in Finland has almost been eliminated in children under five, with vaccine coverage rates approaching 100%. The incidence of disease in

older children seems quite stable, except in 1991, when the preliminary data also show a decline in the number of cases.

Dr. Stephen Cochi, Division of Immunizations, updated the Committee on the doses of publicly purchased Hib conjugate vaccine over the last four years. In the fourth quarter of 1990, after licensure, there was a surge of 2 million doses. More than 5 million doses have been purchased so far in 1991. No coverage data is available at this time; however, some preliminary data may be available in the spring.

Vaccinia Vaccine in Laboratory Workers was the next item on the agenda. **Dr. William Atkinson** summarized the level of usage of the vaccine (available only from the Drug Service in Atlanta since 1983); reason for its use; and reported adverse events. A review of 2000 vaccination records over the past several years shows that 60% of all vaccines are doing university or government research work, primarily with recombinant viruses or vaccines. 92% had no symptoms at all following vaccination. No severe adverse events have been reported.

The Committee voted to leave its vaccinia vaccine statement as written.

The discussion of the **Utilization of BCG Vaccine in the Context of HIV Infection and Multidrug-Resistant Tuberculosis** began with **Dr. Sam Dooley, CDC medical officer,** presenting a report on outbreaks of multiple-drug-resistant TB in several hospitals. Dr. Dixie Snider served as moderator.

The reported 15% increase in TB over the last two years includes a number of multidrug-resistant strains, which have caused disease that is extremely difficult to control. Dr. Dooley described outbreaks in a large urban hospital in Florida and three New York City hospitals. Epidemiological and laboratory evidence support nosocomial transmission, both patient to patient and patient to health-care worker. Mortality rates among HIV-infected persons are extraordinarily high: 72%-89%, with death occurring a median of 4-16 weeks from the diagnosis of TB. Dr. Dooley also discussed factors contributing to transmission, including difficulty of diagnosis and failure to follow recommended isolation procedures. He said that health-care workers need to be made fully aware of this particular risk, especially if they are HIV-positive.

Dr. George Comstock, Professor of Epidemiology from Johns Hopkins, reported on results of BCG trials. Throughout the literature, BCG trials have shown tremendous variability with protection rates ranging from 80% down to negative levels. Strains of the vaccine vary in every measurable characteristic. Little correlation has been shown between post-vaccinal

tuberculin sensitivity and protective efficacy. Data also conflict on which animal system reflects the situation in humans.

Mr. Gerard ten Dam, a scientist from WHO, described case-control and contact studies of BCG. Results were again variable. He pointed out that, when all studies are considered, the highest efficacy seems to be when infection takes place shortly after vaccination. Long-term studies done by WHO in Hong Kong, comparing the Pasteur and Glaxo strains, did show a lower incidence of disease with the French strain, especially in the case of percutaneous vaccine. However, due to the side effects of this strain, and the low incidence of TB in general, officials in Hong Kong decided to continue to use the Glaxo vaccine.

Dr. Paul Fine from the London School of Tropical Medicine and Hygiene presented data that included information from his BCG studies in Malawi. Data from Malawi, in a population of 150,000, showed that BCG was imparting 50% protection against leprosy, but little, if any protection against TB. He stated that variability of BCG results is not due entirely to differences between product. Rather, the data suggest (as has long been hypothesized) that interaction between different mycobacterial infections influences the body's response to BCG. Better correlates of protective immunity against mycobacterial disease are needed. At this point, trials are the only way to evaluate efficacy in a given population.

Dr. Robin Huebner described adverse effects of BCG. Studies done by the International Union Against Tuberculosis from 1979-1983 in six European countries showed a risk of local reaction at .387 per thousand. In terms of more serious complications, there were 21 cases of disseminated disease in a population of 5.5 million. The conclusion was that BCG is a relatively safe vaccine.

There is little information in the literature on BCG in HIV-infected populations. WHO recommends that all infants in developing countries be vaccinated with BCG regardless of HIV serostatus, unless they have overt symptoms of clinical AIDS.

Dr. Dixie Snider said that CDC has received many calls from health-care providers and institutions asking for direction on the BCG question, particularly in light of the multi-drug-resistant outbreaks of TB.

Dr. Katz appointed a sub-committee to further discuss the BCG question and the Committee's recommendations. The sub-committee, chaired by Dr. Pierce Gardner, includes Drs. Neal Halsey, William Schaffner, and Ted Mortimer. Dr. Snider will serve as liaison.

Immunization in the Immunocompromised was the next item on the agenda. **Dr. Albert Donnenberg** presented studies that focused on

the pace of immune reconstitution after bone marrow transplantation. Bone marrow transplantation always begins with preparative regimens that are immuno-ablative.

Data presented by Dr. Donnenberg was from a series of studies of sibling-matched HLA identical transplantation. The studies looked at recipients' immune response to a common immunogen (tetanus toxoid), as well as to a more exotic, primary immunogen (sheep red blood cells) given varying combinations and schedules of donor and recipient immunizations and boosters.

In the case of tetanus toxoid, the best combination was both the donor and recipient being immunized. The four-fold rise in titer was much like the rise seen in immuno-intact individuals. In the case of sheep red blood cells, the only regimen that worked was to immunize both donor and recipient.

Data on lymphoproliferative responses suggested that in order to transfer donor memory, the recipient must be immunized early after transplantation. Factors affecting the reacquisition of antigen-specific immunity after transplantation include graft composition and the frequency of antigen-specific donor lymphocytes in the graft itself. Also relevant is the recipient history of antigen exposure after transplantation -- the time, duration and frequency.

Follow-up studies done a year or more after immunization showed that even then, those who received early immunization following transplantation get a higher increase in titer as a response to a late immunization. The strategy of immunizing recipients early after transplant has continued influence, even more than a year after transplantation.

Dr. Donnenberg also presented data from a study done in collaboration with Dr. Halsey on the response of HIV-seropositive and HIV-seronegative women in Zaire to tetanus toxoid immunization. Protective levels of antibody were achieved in 79% of the seronegative women, and in 71% of the seropositive women. The caveat was that the HIV-seropositive women were in the very early stages of HIV disease (ie. asymptomatic, as measured clinically.)

The Committee agreed to review and polish its statement on immunization in the immunocompromised, with changes submitted to Dr. Grabowsky by November 10. The Committee also decided a separate statement was needed on bone marrow transplantation. More time will be taken to review specific transplant immunosuppression regimens, including bone marrow transplants. It was also agreed that the next draft of the statement be circulated for comments to several people who are doing such transplants.

Dr. Steven Wassilak from CDC led a discussion aimed at reviewing the ACIP statement on Acellular Pertussis Vaccine in anticipation of FDA licensing of such products. He introduced Dr. David Klein of NIAID who reported on various NIAID-sponsored clinical trials comparing a number of acellular vaccines to each other and to standard whole-cell vaccines in terms of safety and immunogenicity. A total of 13 vaccines were used.

Overall, the incidence of fever (greater than 101 F. within 48 hours) was less than in earlier trials with both acellular and whole-cell products. For example, incidence of this type of fever with Lederle whole-cell vaccine was 17.1%; with Massachussetts whole-cell vaccine, it was 9.2%. Acellular vaccines averaged 4.2%. There were very few serious reactions (6 out of 2,342 infants), evenly divided between whole-cell and acellular recipients. Among these reactions, persistent crying was reported in 5.6% of whole-cell recipients and in 2.3% of acellular recipients. Immunological data showed PT responses ranging from 14.2 to 181 ELISA units.

After the trial, a task force selected the following vaccines as acceptable for use in up-coming efficacy trials: Bivalent vaccines: SmithKline PT, FHA; Merieux PT, FHA. Multivalent vaccines: Connaught; SmithKline 3-component; Connaught 5-component; Porton 3- or 4-component (depending on antigen breakdown.)

Dr. Klein described an efficacy trial scheduled to begin in Sweden for which the Swedes selected the Lederle whole-cell vaccine, two acellulars (Connaught 4-5 component), the SmithKline 2-component and a DT vaccine manufactured by the National Bacteriological Laboratories of Sweden. Three other trials are currently in progress: a second Swedish trial promoted by the Institutes of Child Health at NIH; a trial in Senegal using Merieux vaccine; one begun last summer in Germany using Lederle-Takeda vaccine. Dr. Klein said NIAID has great interest in establishing trials of the other four task-force approved vaccines, as well as other acellular vaccines. This is being discussed with various sites and manufacturers.

Dr. Jill Hackell of Lederle-Praxis then reported on the efficacy, immunogenicity and safety of Lederle's diphtheria-tetanus toxoid and acellular pertussis vaccine in infants, toddlers and preschoolers. She reported on clinical experience in Japan with the Takeda acellular pertussis component in which overall efficacy determination was 98%.

Dr. Hackell then described U.S. studies on the immunogenicity of Lederle's acellular vaccine administered as a fourth or fifth dose following previous doses of whole-cell DTP vaccine. Results showed APDT to be at least as immunogenic as DPT with consistently higher FHA levels. Dr. Hackell summarized safety

studies among various age groups by saying that percentages of both injection site reactions and systemic events were lower in the acellular pertussis recipients.

Dr. Klein introduced **Dr. Carlton Meschievitz from Pasteur-Merieux-Connaught** to discuss the Connaught vaccine, which contains Biken acellular pertussis concentrate. Dr. Meschievitz presented results of a number of studies and concluded that the Biken 2-component vaccine leads to fewer common local and systemic reactions when compared to whole-cell vaccine. It also has significantly higher antibody levels to LPF and FHA compared to whole-cell vaccine.

Dr. Wassilak led a discussion of the proposed ACIP supplementary statement on acellular pertussis vaccine. In the interest of time, the Committee decided to address the three most critical issues. The first was whether to change the statement on page 9 regarding use of acellular pertussis vaccine at 15 months of age. The Committee decided to let the paragraph stand as written. The second issue was non-labeled use, especially in the case of a child who has not been vaccinated by the age of 18 months. After much discussion, Dr. Wassilak agreed to wordsmith the recommendation, then put it before the Committee for reconsideration. In terms of the third issue, whether to consider the acellular vaccine to be optional or preferential, it was agreed that Dr. Wassilak would wordsmith the statement to indicate that when available, acellular vaccine is preferable because of the lower rates of common side effects.

Influenza Vaccine and GBS was the first item on Wednesday's agenda. **Dr. Robert Chen** gave an overview of the methodology and results of an on-going investigation into the possible association of influenza vaccine with GBS. Studies done in 1976-77 showed an attributable risk of slightly less than 1 case per 100,000.

In December 1990, two cases of GBS were reported within 6 weeks of flu vaccination. To determine whether this was coincidence or causal, researchers conducted passive surveillance using VAERS. Active surveillance was done at several sites with a total population of 16 million. Special surveillance was also done in Washington and Louisiana, an additional population of 7 million. GBS diagnosis was validated by an independent panel of neurologists.

The ACIP had previously asked for direct data on coverage from the 18-64 age group. There had been no direct data for this age group because this group does not normally receive the flu vaccine. To obtain this data, a contractor has been conducting phone surveys since this summer. Relative risk factors obtained so far are as follows: In all adults over 18: 1.1. Persons 65

and older: .4. Persons 18-64: 2.4. (The total number of vaccinated cases that constitute association is small: 7 cases.)

Committee discussion focused on statistical methodology, the controversial nature of the data, and whether these cases are at the margin of detectability of epidemiological methods. The lack of a good denominator in younger age groups is a continuing problem.

Dr. Nancy Cox of the Influenza Branch reported on current surveillance. Two H3N2 Beijing-like viruses and 2 Taiwan-like H1N1 viruses have been reported. There have been reports of influenza B, but no isolates have been received.

The Committee decided to propose no changes to its statement on influenza.

Japanese Encephalitis Vaccine issues were reviewed by **Dr. Ted Tsai**, who also presented a draft statement to the Committee. An FDA Advisory Committee meeting on the Biken vaccine is scheduled for November. This vaccine is intended for use by travelers to Asia deemed at high risk and by the military. The definition of those truly at risk was one major topic of discussion. Also up for consideration by the Committee was the primary immunization schedule and the appropriate booster. Dr. Tsai reviewed the results of several studies. An efficacy trial in Thailand demonstrated efficacy of 91% with two doses. Immunogenicity studies with U.S. citizens and British subjects showed better results with three doses. An Army study comparing two three-dose schedules showed that a schedule of 0, 7, 30 produced geometric mean titers seven-fold higher than a 0, 7, 14 schedule.

Reports from Denmark, Canada and Australia show recent increases in adverse reactions to vaccination, particularly generalized urticaria and angioedema. Epidemiological and laboratory studies have been proposed in collaboration with the Danes, Australians and others to define risk factors among vaccines for developing such adverse reactions to identify the allergin or manufacturing process associated with the reaction.

The Committee decided to take more time to review these issues. A sub-committee was also appointed: Dr. Mary Wilson, chairperson; Dr. Michael Peterson, Dr. Susan Tamblyn; Dr. Carolyn Hardegree. Dr. Ted Tsai will serve as liaison.

Dr. Dan Fishbein gave an overview of the current cases of Rabies, and asked the Committee to consider its recommendations on vaccination in cases of possible exposure to bats. Minor word changes were made in the proposed **MMWR** article.

The National Vaccine Program and the **Injury Compensation Program** were reviewed by **Dr. Kenneth Bart**. He reported on a flurry of activity in both the public and private sector since the White Paper was presented to Dr. Mason in January. A strong emphasis on prevention and improved access for children were the common themes of many organizations, including the CDC and Congress.

Dr. Bart said that to date, there have been 4, 241 claims submitted to the National Vaccine Injury Compensation Program. In 1990, fewer than 20 claims were made directly to the manufacturers; it seems this legislation is having the desired impact. Adequate funding for this program is an on-going concern.

In terms of the **Federal Implementation of ACIP Recommendations**, **Dr. Walter Orenstein** provided information to the ACIP on the funding issues.

Dr. Roger Bernier updated the Committee on the **Infant Immunization Initiative** and asked members to review the draft statement on Model Standards for Immunization Practices. Members were asked to submit comments within several weeks.
Mr. Dennis O'Mara and Dr. Vance Dietz briefly described a set of model standards. They asked the ACIP to pay particular attention to the summary of true and false contraindications and invited members' comments. Dr. Dietz also reviewed both favorable comments and criticism regarding these model standards which have been expressed by a wide variety of health-care professionals, and again solicited the input of the ACIP.

Dr. Katz wrapped up the meeting by asking Dr. Broome to help him prepare a letter to be sent out to Committee members shortly, summarizing assignments, meeting dates, and issues needing a timed response. The meeting was adjourned at 12:35 p.m.

Summary of Agreed-upon Actions:

1. The Committee voted to leave its vaccinia vaccine statement stand as written.

2. Dr. Katz appointed a sub-committee to further discuss the BCG question and the Committee's recommendations. The sub-committee, chaired by Dr. Pierce Gardner, included Drs. Neal Halsey, William Schaffner, and Ted Mortimer. Dr. Dixie Snider will serve as liaison.

3. The Committee agreed to review and polish its statement on immunization in the immunocompromised, with changes submitted to Dr. Grabowsky by November 10. The Committee also decided a separate statement was needed on immunization in the case of bone

marrow transplantation. The next draft of the statement will be circulated for comments to several people who are doing such transplants.

4. The Committee voted to let the following paragraph from page 9 of the ACIP supplement stand as written: "Although immunogencity data in children 15-16 months of age are not currently available, the ACIP believes that the DTaP (Lederle/Takeda) vaccine can be used for such children as part of ACIP-recommended schedule of routine simultaneous vaccination with DTP, OPV and MMR at 15 months of age."

5. The Committee decided to propose no changes to its statement on influenza.

6. A sub-committee on Japanese encephalitis vaccine was proposed. Dr. Katz appointed Dr. Michael Peterson, Dr. Mary Wilson, Dr. Susan Tamblyn and Dr. Carolyn Hardegree to that committee. Dr. Wilson was appointed chairperson. Dr. Ted Tsai at Fort Collins will serve as liaison.

7. Wording in the rabies vaccination MMWR article was changed to: "Since the size of bites by bats may be small in comparison to those inflicted by terrestrial animals, it may be prudent to consider postexposure treatment for patients reporting direct physical contact with skin or mucus membranes by bats or when a bite or mucus membrane exposure cannot be excluded."

8. Upcoming meetings will be: February 12, 13; June 10, 11; October 21, 22.

Welcome and Opening Remarks

The autumn meeting of the Immunization Advisory Practices Committee was called to order at 8:30 a.m. on October 22, 1991 by Dr. Samuel Katz. Dr. Katz welcomed all attendees and announced two absences. Dr. David Fraser, who is now working at the Secretariat of the Aga Khan in Paris, in charge of health and educational activities, sent his regards to the Committee. Dr. Carlos Hernandez was also absent.

Dr. Katz announced that since the last meeting, there was been one major publication, the Committee's "magnum opus" on DTP.

Dr. Katz introduced three new Committee members: Dr. Kathy Edwards, Vanderbilt University; Dr. Neal Halsey, Johns Hopkins University; Dr. Rudolph Jackson, Professor of Pediatrics at Morehouse School of Medicine.

New liaison representatives include Dr. Pierce Gardner representing the American College of Physicians (succeeding Dr. David Fedson); Dr. Georges Peter; Dr. Caroline Hall, returning in a different role as the new chair of the Committee on Infectious Diseases of the American Academy of Pediatrics; Dr. Regina Rabinovich of NIH, sitting in for Dr. John La Montagne.

Dr. Katz asked all Committee members, liaison representatives and attendees to introduce themselves and invited everyone to participate in the meeting. He commented on the diversity of the group, which includes staff members of the Centers for Disease Control, individuals from the Armed Forces, the Public Health Service, and various pharmaceutical and other related firms. One of the characteristics of the meeting has been honest and open dialogue; Dr. Katz expressed his hope that this type of communication would continue.

Dr. Claire Broome, ACIP Executive Secretary, made several announcements. She said that names of all Committee members and liaison members will now be listed in the ACIP statements, acknowledging the hard work of all those involved. Dr. Broome extended her welcome to the new Committee members, and read the following statement from the Committee's charter. "The Committee is officially charged with providing advice and guidance to the Secretary of Health and Human Services, the Assistant Secretary of Health and the Director of the Centers for Disease Control regarding the most appropriate application of antigens and related agents for effective disease control in civilian populations. Additionally the Committee shall review and report regularly on immunization practices and recommend improvements in the national immunization efforts." Dr. Broome re-emphasized Dr. Katz's statement about the importance of free and open

discussion, stressing the fact that CDC counts on the ACIP to consider the issues carefully and to provide an independent assessment of the best approach for an effective immunization program.

Dr. Broome stated that the Committee relies primarily on CDC staff to provide background information and the staff support that makes it possible for the Committee to be particularly effective. She also remarked that the Committee reflects a broad spectrum of expertise, ranging from those in the field of public health to those with expertise in epidemiology, in microbiology as well as those with clinical expertise in pediatrics, internal medicine and infectious disease.

Dr. Broome reviewed CDC's organizational structure, stating that immunization activities are mainly in two different centers. The National Center for Prevention Services (NCPS) provides consultation and delivery of program services. Within NCPS, The Division of Immunizations is the primary division charged with childhood vaccination programs, surveillance, etc. The Division of Tuberculosis Control also falls within NCPS.

The National Center for Infectious Diseases is also involved with vaccine issues. A number of divisions in the Center participate and provide staff support to the Committee on particular diseases. Dr. Broome said that CDC is open to comments from the Committee on how staff support can be improved to help the Committee be more effective.

Dr. Broome then updated the Committee on the potential conflict of interest issues addressed at the last meeting. Internal meetings have subsequently been held at CDC with the Committee management group and the Office of General Counsel to consider the appropriate approach for CDC advisory committees. The consensus was that it is important for anyone who has an association with or a financial interest in a company producing a product under discussion by the Committee to disclose that fact. Although those persons are welcome to participate in the discussion, they are asked not to vote on issues related to such products. Dr. Broome said that in this type of open meeting, there is a need for awareness of such potential conflict of interest.

Kevin Malone of the General Counsel's Office reiterated that it is important to avoid the appearance of conflict. For the benefit of everyone, especially the general public in the audience, it is important for people to "put their cards on the table." Anyone with further questions on this issue should contact Kevin Malone through Dr. Broome's office.

When asked to clarify the meaning of the word "association," Dr. Katz recalled earlier discussions about this issue. Some

parents' groups have criticized the fact that clinical trials have been financed by the pharmaceutical companies themselves and that Committee members have been involved in such trials.

Dr. Broome further clarified the word "association," describing it as an on-going association with a particular company, not simply attending a meeting or giving a lecture. Participation in research studies funded by a particular company, on-going clinical trials, an on-going consultancy with a company, financial interest such as stock ownership: all are examples of an association that should be disclosed.

Dr. Katz then encouraged everyone to ask for clarifications of, or additions to the agenda as needed.

Dr. Jay Wenger introduced the presentations on Haemophilus influenzae type b immunization.

Haemophilus influenzae type b Vaccine Impact

Dr. William Adams reviewed data from several surveillance systems which looked at the impact of this vaccine in two-month olds. Dr. Adams began by saying that licensure of the Hib conjugate vaccine for use in infants beginning at two months of age has finally offered the opportunity to immunize the population in this country at greatest risk for Hib disease. It has been one year since the first conjugate vaccine was licensed. Three surveillance systems were used to evaluate the vaccine's impact.

Dr. Adams briefly reviewed the chronology of vaccine licensure. In 1985, polysacharide vaccine was licensed for use in children two years of age and older. Conjugate vaccines followed with PRP-D in 1987, Hboc in 1988, PRPOMP in 1989, with the age at first vaccination gradually lowered to 15 months. In late 1990, Hboc and PRPOMP were approved for use in infants two months of age and older.

After licensure, some delay in distribution and use is to be expected. As a result of this delay, widespread use of conjugate vaccines occurred for 18-month-olds in 1988; for 15-month-olds in 1990; and for two-month-olds by 1991.

Three surveillance systems at CDC provide information on Haemophilus influenzae, or Haemophilus influenzae type b disease. Dr. Adams reviewed each system and presented currently available data.

In the National Bacterial Meningitis Reporting System (NBMRS), state health departments are requested to report all cases of bacterial meningitis to CDC. The system was begun in 1977; 21 states have reported continuously since then. Although the

sensitivity of the system is 30 to 40% that of active surveillance, Dr. Adams explained that this system offered the best available long-term data.

Dr. Adams showed a graph presenting the number of cases of H. influenza meningitis by year obtained from the 21 continuously reporting states as tracked in four age groups: 0 to 11 months; 12 to 23 months; 24 to 59 months; and over 60 months. The number of cases in all children under five declined in this time period, while the number of cases in the oldest age group remained relatively constant.

Since there may be year-to-year variation in reported cases of disease, CDC also evaluated the relative proportion of disease occurring in different age groups. Very little variation was found in percentage of disease attributable to the four age groups until 1986, when meningitis in 24-to-59-month-olds began to represent a relatively smaller proportion of disease. In 1991, a decrease in relative proportion of disease in 12-to-23-month-olds was seen. In contrast, beginning in 1989, the proportion of meningitis in children 60 months and older increased. The decrease in absolute numbers of cases of meningitis and the increase in proportion of disease in children outside the vaccinated age group are consistent with the use of an effective vaccine.

Dr. Adams then presented data from The National Electronic Telecommunications System for Surveillance (NETSS), which supplanted the National Notifiable Disease System in 1987. Data reported to state health departments are transmitted weekly to CDC via modem for inclusion in the **MMWR**. No typing or culture source information is available. Haemophilus influenzae disease is reported as bacterial meningitis, Haemophilus influenzae. Eight states have continuously reported since 1987: Alabama, Connecticut, Florida, Georgia, Louisiana, Maine, South Carolina and Utah.

In the eight continuously reporting NETSS states, numbers of cases of meningitis decreased consistently in the three age groups of children under 5, but increased in older children. Dr. Adams explained that the increased number of reports in this older group is consistent with improved reporting and surveillance over time, while the decreases in the younger group are consistent with vaccine effect.

In these same eight states, decreases in relative proportion of disease were first seen in 1989 in 23-to-59-month-olds; in 1990 in 12-to-23-month-olds; and finally in 0-to-11-month-olds in 1991. Meningitis in children five years or older represented a progressively larger proportion of disease.

The Meningitis and Special Pathogens Active Surveillance Project supports surveillance coordinators in four areas of the United States to collect detailed case reports from all laboratories in the surveillance area. Isolates are sent to CDC or the state health departments for typing.

Using this system, Dr. Adams said that it is possible to look specifically at H. influenzae type b disease. The numbers of cases decreased dramatically in children under 5. (In 0-to-14 month-olds, a rate of 111 cases per 100,000 was reported in 1989; this figure dropped to 34 per 100,000 in 1991.) Of interest, as also noted in the NETSS and Meningitis Reporting Systems, disease in younger children was decreasing before vaccine was licensed in this group. Dr. Adams stated that one possible explanation (first suggested by work done in Finland) is that conjugate vaccines decrease nasopharyngeal carriage of the organism.

Dr. Adams summarized by noting that three independent surveillance systems showed substantial decreases in H. influenza and Hib disease in children under 5. Decreased disease was seen in age groups for which vaccination was recommended; however, decreases were also seen in infants less than one year old before vaccines were licensed for use in this age group. He commented that further surveillance is needed to confirm the impact of vaccination and to identify unvaccinated groups of children.

During the question-and-answer period, Dr. Schaffner remarked that vaccine use by physicians in private practice is uncontrolled and very difficult to measure. He asked whether there is data comparing those states with aggressive public programs to states whose programs have not yet been implemented. Dr. Adams said this has not yet been done.

Following up on Dr. Schaffner's question, Dr. Peter commented that this would be an excellent opportunity to examine different means of implementation of vaccine (public clinics, vs. public and private, etc.) and its effect on incidence of disease, especially given the increasing number of vaccines available. He said that it is necessary to know the most effective means of introduction.

Dr. David Klein from NIH asked whether other clinical events associated with this disease (besides meningitis) were followed. Dr. Adams replied that the active surveillance data shown corresponded to all invasive Hib disease. Non-meningitic disease showed a pattern similar to meningitic disease; however, the relatively small numbers of non-meningitic cases preclude separate analysis at this time. The NETSS and NBMRS systems do not provide interpretable data on non-meningitic disease at this time.

Dr. Juhani Eskola, National Public Healthy Laboratory, Finland, then addressed the group.

Dr. Eskola began by stating that the incidence of Haemophilus disease was slightly lower in Finland than in the U.S. before trials began. The incidence rate among children under five was about 50 per 100,000. The age distribution was also slightly different. Dr. Eskola commented that this was a favorable position from which to begin a prevention program. Since 1986, there have been three trials in Finland -- or more exactly two trials and a non-randomized vaccination program.

The first trial, conducted in 1986-87, demonstrated the efficacy of the first conjugate PRP-D vaccine. It was an open, randomized trial, comparing children born on odd and even days. Vaccination was at 3, 4, and 6 months, with a booster at 14 months. The control group remained unvaccinated through the age of 24 months.

Dr. Eskola explained that, after receiving results from the first trial, a comparative trial was conducted because it was felt that it was no longer possible to continue to have an unvaccinated control group. The comparative trial, conducted in 1988-89, compared PRP-D and Hboc vaccine, with vaccination at 3, 4, and 14 months of age. The follow up is continuing.

In January 1990, an open, non-randomized vaccination program was begun with PRP-T vaccine given at 4, 6, and 14 months of age. There were no unvaccinated children and no control group.

The published results of the first efficacy trial in Finland show that, in a group of 58,000 children who were fully vaccinated, there were four cases; there were 64 cases in the control group. The efficacy of the vaccine was 90%. It was 100% after the booster dose.

The unpublished results of the comparative trial show that both vaccines worked well with very few cases in either group. In accordance with the better immunogenicity of the Hboc conjugate, there were fewer cases in the Hboc group than in the PRP-T group, although the difference was not statistically significant.

Dr. Eskola further explained that the protective efficacy of these two vaccines was calculated and compared to the data on the expected number of cases. The expected number of cases was calculated on the basis of incidence rate before any vaccination trials were begun. In the PRP-D group, there were 5 cases after the primary immunization series. The expected number based on historical data was 39; the vaccine efficacy in this trial was therefore slightly less than 90%.

The efficacy similarly calculated for Hboc was even better -- 94% after two doses and 100% (as for all vaccines) after the booster dose. Dr. Eskola reported that there have been no cases of vaccine failure after the booster dose.

In Finland, since January of 1990, all children have been vaccinated with PRP-T vaccine. As of the end August of this year, there have been no cases after two doses. Only two cases have been seen after one dose of PRP-T.

In 1987, the carriage rate of Hib, Hi and Pnc were surveyed to show that the bacteria still exists in Finland. According to Dr. Eskola, the results were surprising. In a survey of 725 three-year-old children who either received PRP-D in infancy, at two years of age, or who had not received the vaccine, the carriage rate among the non-vaccinated children was 3.5%, quite close to the figures reported earlier. No cases carrying Haemophilus influenzae type b were reported among those vaccinated.

Dr. Eskola commented that these data might suggest that the conjugate vaccine affects the carriage rate and therefore might also provide a herd immunity effect. For this reason, Dr. Eskola said that he is no longer certain that historical data can be used to calculate efficacy estimates for these conjugate vaccines.

Dr. Eskola concluded his presentation by showing summary data on the number of cases from 1976 on. The vaccination program, begun in 1986, first used PRP-D, then PRP-D and Hboc, and now PRP-T. In children under five, there has been a sharp decline in the disease since 1986, when there were nearly 180 cases. In 1990, there were only 6 cases in this age group; this year there have been only 2 cases, both in very young infants. Dr. Eskola stated that the disease has almost been eliminated in children less than five years old, with vaccine coverage rates approaching 100%. The level of incidence of disease in older children seems quite stable, except in 1991, when the preliminary data also show a decline in the number of cases.

Dr. Katz asked Dr. Eskola when the nasopharyngeal cultures were done. Dr. Eskola explained that the cultures were taken when the children were three years old, and were collected at seven locations throughout the country. The children were required to be healthy, with no antimicrobials for at least two weeks prior to culture.

Dr. Halsey asked Dr. Eskola to comment on the severity of the cases that occurred after a single dose. Dr. Eskola said that so far, the disease in these cases is quite similar to what had been before vaccination.

Dr. Edwards commented on the differing immunization schedule in the U.S. and Finland and asked Dr. Eskola whether this produces a different immune response in Finnish children. He replied that the important difference seems to be the fact that in Finland, children receive DTP at three months of age and the H. influenzae type b vaccines are given starting at four months of age. This carrier priming might explain at least part of the different immunogenicity results.

Dr. Eskola was also asked to describe the vaccine delivery system in Finland. He explained that nearly 100% of all children are vaccinated in public child health centers. The key people there are public health nurses. They follow the children before and after delivery. Children also make several visits to these centers during the first year of life. The public health nurses each work with a limited number of families, so they know the families and the families know them. He added that motivation for vaccinations has traditionally been very high in Finland, which explains the high coverage rates.

Dr. Eskola was also asked whether BCG is still routinely given to infants in Finland. He replied that Finnish children do receive BCG during the first two weeks of life. These are voluntary vaccinations and approximately 98% of the children receive BCG. He went on to say that he could not state how this affects immunogenicity or serology responses because this has not been studied.

Dr. Stephen Cochi from the Division of Immunizations briefly updated the Committee, reviewing several handouts. He commented that data on annual net dosages distributed is submitted by the manufacturers to the Division of Immunizations of CDC. These numbers are up, with nearly 10 million doses distributed so far this year.

Dr. Cochi said that current federal contracts for both of the conjugate vaccines licensed for infants include the Lederle-Praxis contract for routine use in infants, and the Merck contract for special use in Native American infants. Both of these contracts are in effect until next March.

He also gave figures on the doses of publicly purchased Hib conjugate vaccine by quarter, covering the last four years. In the fourth quarter of 1990, just after licensure, there was a surge of 2 million doses. This sizeable increase in total doses by year continued into 1991. More than 5 million doses have been purchased so far this year. The birth cohort in the U.S. is 4 million; therefore there is a potential need of up to 16 million doses for a four-dose schedule, or 12 million for a 3-dose schedule.

Dr. Cochi said there is no coverage data at this time. However a national sample survey of immunization coverage in pre-school-age children is underway through the National Health Interview Survey. This study began in September so preliminary data on coverage may be available next spring.

Dr. Edwards asked if there are any data on vaccine failures, especially after 2 or 3 doses. Dr. Cochi replied that there have been some anecdotal reports of vaccine failures, some coming directly to the Meningitis and Special Pathogens Branch and some through the Division of Immunizations. Consensus seems to be that these are all after one dose.

Dace Madore from Lederle-Praxis shared an overhead showing the cases reported to Lederle-Praxis.

She discussed the results of the Kaiser-Permanente study in Northern California, where the efficacy trial of Hib Titer was conducted. From February 1988-90, there were 24 cases of disease in the unvaccinated population and none in children who received 2 or 3 doses. The Kaiser-Permanente group has continued surveillance in this population. Over the past year, there has been follow-up with an additional 31,000 individuals. In that population, all cases of disease have been in unvaccinated children. In all, some 92,000 people have been surveyed. In this study, there was only one case with a child who had disease after one dose. That child was vaccinated at 6 months and came down with the disease at 18 months.

Dr. Madore also reviewed a summary of all Hib cases reported to Lederle-Praxis. Twenty-eight cases have been reported since licensure. Of those, 22 have been reported in children under 15 months: 15 after the first dose, five after 2 doses, 2 after 3 doses. She commented that these figures should be considered in the perspective of number of doses that have been given, some 17 million to date.

Dr. Madore stated that it may be inappropriate to consider cases occurring before two weeks after vaccination as vaccine failures. After 2 doses, there were 2 cases of disease that occurred after four weeks, and 3 after two weeks. Of those occurring after one dose, about half of those occurred four weeks after immunization.

Dr. Edwards raised the question that if the incidence of disease is similar after two and after three doses, perhaps only two doses are needed. Dr. Katz responded that numbers and timing of doses is an on-going area of concern, especially for the FDA, and that differing recommendations have caused confusion and concern. He also wondered about vaccine schedules, and whether children are actually getting the vaccines at the exact, specified ages. He asked Dr. Eskola whether vaccines (DTP, Hib, etc) are separate in Finnish clinics. Dr. Eskola replied that these vaccines are

separate, but that immunogenicity has been studied, especially for PRPT mixed with DTP or with enhanced inactivated polio vaccine. On the basis of these studies, immunization personnel in Finland have been given permission to mix PRPT with either.

Dr. Edwards asked about the suppression of pertussis antibody responses when these vaccines are mixed. Dr. Eskola responded that a slight decrease in pertussis response has been seen, but that it is not statistically significant.

Vaccinia Vaccine in Laboratory Workers

Dr. Kenneth Hermann prefaced Dr. William Atkinson's remarks by summarizing the current status of the ACIP's position on vaccinia vaccine usage. At the June meeting, Committee members reviewed the draft statement, focusing on the rationale for giving this vaccine to health-care workers in various circumstances. At that time, the ACIP concluded that the risk was so small that requiring this vaccine for health-care workers was not justified and recommended that the statement be revised to reflect that change. This change was made and the revised statement was subsequently mailed out. There was little discussion at that time on the rationale/justification for this vaccine in laboratory workers, which had been the practice for many years at CDC and was the recommendation of the CDC/NIH biosafety guidelines for laboratory workers.

However, since that revised statement was sent out, a parallel document was released this past year by the Advisory Committee on Dangerous Pathogens and the Advisory Committee on Genetic Modification in the United Kingdom. These groups serve advisory roles similar to that of the ACIP. They recommend removing the requirement for vaccination of laboratory workers working with vaccinia virus except in selected circumstances.

Dr. Hermann read the first paragraph on page one of this document, as follows: "It is the view of the ACDP and the ACGM that the risk of complications, serious side-effects and spread of vaccine virus to contacts, although small, is such that, on balance, smallpox vaccination can no longer be a general requirement for work with vaccinia and related poxviruses."

Dr. Hermann said that in addition to this document, there have been a number of comments from researchers and laboratory workers in the U.S. working with vaccinia virus questioning the rationale/justification in the current recommendations for vaccinia vaccination for those working with orthopox viruses. It was felt that the Committee ought to have another opportunity to revisit the June statement.

He then introduced **Dr. William Atkinson** to present data on vaccine usage patterns in the U.S. over the years and the reported adverse side effects from vaccinia vaccination in the U.S.

Dr. Atkinson began by explaining that, in 1983, Wyeth removed vaccinia vaccine from the public market; since then, the vaccine has been available only from the Drug Service in Atlanta. Since that time, laboratories have been required to report back the results of vaccinations, including severe reactions and a variety of local and constitutional symptoms.

From 1983 to 1991, some 4000 people have been vaccinated with vaccine distributed by the Drug Service. Approximately 900 vaccines are expected in 1991.

There has been a slow, steady increase in the number of facilities receiving the vaccine. Since 1983, this vaccine has been distributed to 215 laboratories, with 30 to 40 new labs per year receiving the vaccine.

Review of 2000 vaccination records over the past two and a half years shows that 40% of this vaccine is going to university-affiliated researchers. When the government (including CDC, NIH, NIAID and the U.S. Department of Agriculture) is added to those figures, these groups account for 60% of all vaccines, and about 65% of all facilities.

In the 1991 requests, the most common project stated by the researchers was some kind of recombinant viruses or vaccine research. Out of the 105 facilities for which information was available, 92 cited this type of research, of which HIV and other retroviruses were the most common. About 14 facilities said that they were doing purely viral protein gene-product expression work. A very few were actually doing pure poxvirus research.

The vast majority of these individuals were being revaccinated, after being vaccinated in childhood. Recommended, routine vaccination was discontinued in 1971, but a considerable amount of vaccine was used until 1983, decreasing over time. About 10% of these were primary vaccines (those most likely to have a severe side effect.)

Dr. Atkinson then summarized the reported adverse events. In the past three and half years, in 2100 recipients, 92% had no symptoms at all. There were some local and constitutional symptoms reported, although quite infrequently. Lymphadenopathy occurred in 4% of the cases. Lymphadenopathy, fever and chills are recognized effects of vaccinia vaccine either in revaccination or primary vaccination. Dr. Atkinson commented that calling them side effects may be stretching the definition. If these symptoms are omitted from the list, there were no

serious symptoms or signs in about 97% of all recipients. No severe adverse events have been reported to date.

Dr. Atkinson raised the question of the current ACIP statement, saying that to leave it as is, would be, in essence, to recommend that individuals who work directly with vaccinia or recombinants or animals infected with these agents be vaccinated; they should be revaccinated every ten years. The statement also says that health-care workers involved with clinical trials may be at higher risk than the general population and may be considered for vaccination.

After a brief discussion, the Committee voted to leave the vaccinia vaccine statement as is.

Utilization of BCG Vaccine in the Context of HIV Infection in Multi-Drug Resistant Tuberculosis

Dr. Dixie Snider served as moderator for the next portion of the program. He began by stating that cases of TB are no longer on the decline in the U.S. Indeed, in the last two years, there has been a 15% increase. Normally, a 6% annual decrease would have been expected. The same measures have been used for a number of years to control outbreaks of TB, namely detection and treatment of cases and the use of preventive therapy, primarily with isoniazid. Outbreaks of multiple-drug-resistant TB present a real challenge to control. Dr. Snider stated that a number of people have called to ask whether they should be using BCG vaccine as one of the control measures.

He then introduced Dr. Sam Dooley, CDC medical officer, to talk about the multiple-drug-resistant TB and then Dr. George Comstock from Johns Hopkins will tell us about control trials. Mr. Gerard ten Dam from WHO will talk about case control and contact studies of BCG. Dr. Paul Fine from the London School of Tropical Medicine and Hygiene will talk about new data on data from BCG studies in Malawi that he's involved with and Dr. Robin Huebner on our staff will tell you what we know about adverse effects of BCG, especially in HIV-infected populations.

Dr. Dooley began by saying that in 1988, the ACIP and the Advisory Committee for the Elimination of Tuberculosis issued a joint statement on the use of BCG vaccine for the control of TB. The statement said that BCG vaccination is no longer recommended for health-care workers. Ironically, at this same time, reports began to come in on outbreaks of TB in HIV-infected patients. Concern about this prompted the current discussion.

Recent outbreaks have included outbreaks of multidrug-resistant TB, which have been especially difficult to control. Investigations of these outbreaks have involved the collaboration of hospitals, state and local health departments as well as many

divisions of CDC, including the Division of Tuberculosis Elimination, the Hospital Infections Program, the Division of HIV-AIDS, the Division of Bacterial Diseases, NIOSH and others.

Several questions have been raised: Is there reason to reconsider the policy for BCG vaccination of health-care workers, including those with and without HIV-infection? Is there reason to consider BCG vaccination for some patients with HIV-infection?

Dr. Dooley then presented a summary of four multidrug-resistant outbreaks that CDC has helped to investigate. He included information on patient-to-patient transmission, and on health-care worker involvement.

Dr. Dooley stated that in the past, multidrug-resistant TB was usually associated with acquired drug resistance. However, these outbreaks involved primary drug resistance. These patients developed TB for the first time -- and their first isolate was resistant to multiple drugs. They have been infected by multidrug-resistant organisms.

In all four outbreaks, epidemiological and laboratory evidence both supported nosocomial transmission. Dr. Dooley explained that epidemiological evidence has two components. First: Identifying all multidrug-resistant patients at the hospital, plotting in detail the timeliness of their hospitalizations, clinic visits, and on-set of TB, then looking at those timeliness to identify points of possible transmission from one patient to another. Second: Doing case control studies. In every instance, case-control studies have identified prior hospitalization at the same time as an infectious, multidrug-resistant TB patient as a risk-factor for subsequently developing multidrug-resistant TB.

The laboratory evidence cited by Dr. Dooley included not only the characteristic drug-resistance patterns, but also a relatively new form of DNA finger-printing, which provided supportive evidence in identifying strains of TB involved in these outbreaks.

Dr. Dooley went on to describe the outbreak in Hospital A, a large, urban hospital in Florida. The drug-resistance pattern in this outbreak included strains resistant to at least izoniazid and rifampin. Most were also resistant to ethambutol and ethionamide.

In Hospital A, evidence supported transmission from patient-to-patient both on an inpatient HIV care unit and in an HIV outpatient clinic.

The initial investigation identified 29 patients, from January 1988 to January 1990. After the initial investigation, 36 more cases were been reported, for a total of 65 in this outbreak.

In the initial investigation, 27 of 29 patients were HIV-positive. Most of the subsequent cases were also HIV-positive. Dr. Dooley said that mortality was extraordinarily high: 72% among the initial 29, with death occurring in a median of 7 weeks from diagnosis of multi-drug-resistant TB.

Health-care workers were involved in this outbreak. In the HIV ward and the HIV clinic, the study identified 39 who were susceptible, ie. who had baseline negative skin tests. In a comparison ward (ie. wards where TB patients are not admitted, such as an orthopedics ward or a surgery ward, where risk of occupational exposure should be very low) 15 were susceptible. Among the health-care workers in the HIV ward and the clinic, there were 13 converters. That translates to a conversion rate of 23 conversions per 100 person-years, which is very high. There were no converters on the comparison ward.

One case of active, multidrug-resistant TB occurred among health-care workers at this hospital. Although the information is incomplete at this time, it is known that this isolate, in an HIV-positive individual, is resistant to isoniazid and rifampin. This person did have a previously negative skin test, did have a conversion and was exposed to the multi-drug resistant cases. The patient has responded partially to therapy but is still culture-positive after more than one year of therapy.

The three other outbreaks discussed occurred in New York City.

In Hospital B, the drug resistance pattern was to at least isoniazid and streptomycin. Most of these isolates were also resistant to rifampin and ethambutol. Again, evidence supported nosocomial transmission, in this case on in-patient medical ward. From January 1989 to January 1990, 18 cases were initially identified. Subsequently, 17 more cases were identified, for a total of 35. Of the 18 in the initial group, all were HIV-positive because that was part of the case definition. Again, mortality was very high: 89%, with a median of 16 weeks between diagnosis and death.

Dr. Katz asked if death occurred due to TB, or to other aspects of their disease. Dr. Dooley said it is always difficult to determine this, but in many, if not the majority of these cases, TB was at least a major contributing factor, if not the cause of death.

Health-care workers on the medical units where the drug-resistant TB patients were hospitalized were compared to health-care workers on other hospital units. Although the proportion of

health-care workers on the exposed units who converted was higher (21%) than those on the non-exposed units (14%), this was not a significant difference.

There was one health-care worker case at this hospital. The partial information that is currently available shows that this is a culture-confirmed case in an HIV-negative individual. The isolate is resistant to at least isoniazid, rifampin and streptomycin. This person is currently stable on therapy.

In Hospital C, the drug resistance pattern showed resistance to at least isoniazid, rifampin and streptomycin. Most were also resistant to ethambutol, kanamycin and ethionamide.

Evidence here also supported nosocomial transmission on several inpatient units. From September 1989 to March 1991, the study initially identified 17 cases. Since March, 21 more cases have been identified, for a total of 38. Sixteen of the initial 17 patients were known to be HIV-positive. Mortality rate was 82%, with a median interval of 6 weeks from diagnosis of drug-resistant TB until death.

During the peak of the outbreak (late 1990-early 1991), there were many skin-test conversions among employees at this hospital. Between January 1 and April 30 of this year, out of 116 employees tested in routine testing, there were 24 conversions, for a proportion of 21%. Direct comparison to 1990 data is not possible because the selection processes for testing were somewhat different. However, Dr. Dooley felt that these data do give an overall idea of the difference between the two years, given that the conversion rate was 2% in 1990, compared to 21% in the first quarter of 1991.

Several health-care workers at this hospital have developed active TB. Two are clearly related to the outbreak. One is HIV-positive, the other is HIV-negative. Both are resistant to the same drugs as the outbreak strain. Both have the same RFLP pattern as the outbreak strain.

The HIV-negative individual has improved and is doing well. The HIV-positive health-care worker died, following a fulminant course of tuberculous meningitis.

There are two additional culture-confirmed multidrug-resistant cases among health-care workers at this hospital, but with a different drug-resistance pattern. The RFLP pattern is also different. Both are HIV-positive. Although these cases were not part of the outbreak under investigation, it is not possible to say whether their TB was acquired occupationally, but that is a possibility. Both also had fulminant and fatal courses of TB.

In Hospital D, the drug resistance pattern showed resistance to at least isoniazid and rifampin; many were also resistant to ethambutol and/or ethionamide. Evidence supported transmission on an inpatient HV ward. The initial investigation identified 23 patients from January 1990 to March of 1991. Subsequently, 9 more cases were identified, for a total of 32.

Of the 23 patients in the initial investigation, 21 were HIV-positive, the other two were HIV status unknown. Mortality rate was 83%, median four weeks from diagnosis of TB to death.

At this hospital, health-care workers on medical wards where drug-resistant patients were hospitalized were compared to workers on other wards. Of those on the exposed wards, 8 out of 24 (or 33%) converted their skin-tests, compared to none on the comparison wards.

There is one culture-confirmed case among health-care workers at this hospital in an HIV-positive individual. The drug resistance pattern is resistant to at least isoniazid, rifampin, strep and ethambutol. It is unclear whether this is an occupational case or not. This person had a prior positive TB test in 1971, but has no history of prior active TB, and no history of having had any TB medication. Laboratory data on this case is pending.

Another investigation, which does not involve CDC, is being conducted by the New York State Department of Health in upstate New York at another hospital. At that hospital, 35 skin test conversions among health-care workers were identified in August of this year. There are no known active cases at this point. The likely source case is a patient who was resistant to isoniazid, rifampin, streptomycin, ethambutol, and kanamycin. Preliminary information suggests that there are several other multidrug-resistant patients in this hospital. Also suggested is the possibility of nosocomial transmission.

Dr. Dooley then put the BCG question in some perspective by pointing out that in each of these outbreaks, a number of factors contributed to transmission: difficulty recognizing patients with TB, particularly those who are HIV-infected; the prolonged time required to obtain drug-susceptibility results; delays in initiating isolation; inadequate ventilation for AFB isolation; lapses in AFB isolation procedures (doors not being closed, masks not being used properly or consistently, patients visiting outside their rooms).

Due to delay in receiving drug susceptibility reports, there have been delays in getting patients on an effective anti-tuberculosis regimen; this results in prolonged infectiousness. Dr. Dooley stated that, as a result, the common approach of using an arbitrary number of days of isolation does not work.

Dr. Dooley went on to say that there are many ways in which the risk of transmission of TB can be reduced -- some are procedural and can be instituted fairly quickly. Others, such as correcting ventilation, are costly and will take time. However, although the risk of transmission can be reduced, he said he doesn't believe it can be totally eliminated. Hence, there is interest in other modalities to protect health-care workers in these situations.

Dr. Katz asked whether the families of the patients or the health-care workers were also studied. Dr. Dooley indicated that a few family members have developed active disease. Dr. Katz then asked whether studies were done on tuberculin conversion in the families. Dr. Dooley replied that the contact studies on a lot of these have been difficult to do because the patients have died very quickly.

Dr. Halsey asked about the duration of TB prior to diagnosis. Dr. Dooley said that there is much variation in the clinical presentation; some patients have a more classic, prolonged period of up to months of symptoms before diagnosis. Other patients have a rapid, fulminant course, diagnosed within just a few weeks of onset of symptoms. He stated that this was the case for inpatients as well as outpatients.

Dr. Snider then added his comments to this discussion. He indicated that as far as contact investigations are concerned, for the past two years some $300,000 have been spent in the Florida case, to get that outbreak under control. Part of the control effort included community investigations. He commented that contact investigations don't have a lot of meaning for many of these patients. They're discharged to the streets, or a shelter for the homeless, or to a facility such as a hospice. This makes contact investigation very expensive.

In New York City, just over a million dollars have been awarded for a similar effort, as well as to study other hospitals with the same problem. These costs will also be high.

In reference to Dr. Halsey's question, Dr. Snider said that what is time-consuming is the diagnosis of multi-drug-resistance, not just the diagnosis of tuberculosis. A standard treatment regimen is ineffective; the person remains infectious and continues to transmit.

Dr. Gardner said that he was struck by the conversion rate of health-care workers and the indication that most who developed active disease were HIV-positive. He suggested that people who know they are HIV-positive, or are at risk of HIV positivity for whatever reason, should not be working in a setting where there's likely to be TB, particularly drug-resistant TB.

Dr. Dooley said that the recommendation is that health-care workers be knowledgeable -- educated by health-care facilities -- about this particular risk. Workers must understand the particular risk if they are HIV-positive so they can make an informed decision about assuming that risk.

Dr. Gardner then asked what type of prophylaxis could be offered to these health-care workers. Dr. Dooley replied that this is an extraordinarily difficult question, for which there is no real, satisfactory answer, other than to say that the risk for an HIV-negative person who converts is relatively low. It's not always clear whether infection has occurred due to a drug-resistant case or a susceptible case because most of these people are exposed to multiple cases. Therefore, in those circumstances, it's probably reasonable to proceed with isoniazid preventive therapy.

The problem arises with HIV-positive health-care workers believed to be infected with multidrug-resistant strains. In that case, one should at least consider a multi-drug preventive regimen, which is the same as treatment of active disease. What that regimen would be depends on the drug susceptibility pattern of the probable source.

Dr. Katz commented that in his experience, many HIV-positive individuals volunteer to work in the clinics, provide transportation for families to and from the clinics, and provide respite care.

Dr. Clements asked Dr. Dooley whether particular procedures, such as inducing sputum or performing bronchoscopy, put health-care workers at greater risk.

Dr. Dooley indicated that it has been difficult to look at specific risk factors in these outbreaks. He commented that in Hospital A, there was an association between people who were exposed to an infectious person receiving aerosol pentamidine. This cough-inducing procedure seems to be a factor in that situation. Dr. Dooley went on to say that it is difficult to get base-line skin test data, especially for physicians, so it is difficult to get data on people who are actually performing bronchoscopies. Most of the health-care workers in the above situations were nurses responsible for direct patient care.

Dr. Snider commented that the question of BCG is part of a larger strategy to try to control TB. CDC is also working with NIOSH to bring in a group to talk about ultra-violet lights, and with the American National Standards Institute to talk about particulate respirators. CDC does have a preventive therapy recommendation and is collecting standardized information. Guidelines have been issued on controlling TB in health-care institutions. CDC

considered recommending that HIV-positive individuals not work with TB patients, then decided that was too strong. Dr. Snider concluded by saying that BCG should be considered in the context of what has been happening.

Dr. George Comstock, Professor of Epidemiology at Johns Hopkins, reported on results of BCG trials.

Dr. Comstock began his remarks by saying that BCG is different from almost any other vaccine, because vaccination itself interferes with the tools available to investigate and control other factors. With BCG, one creates tuberculin sensitivity, which researchers rely on for monitoring and for prophylaxis.

Dr. Comstock then summarized a number of BCG trials. The variability, according to Dr. Comstock, was tremendous, ranging from a protection rate of 80% down to some trials that showed negative protection. Dr. Comstock stated that these trials give no idea of which vaccine is the effective one.

Very few of the vaccines were prepared recently. Up until the late 1960's, BCG cultures were routinely made every month, making mutations very likely. Strains of these vaccines differ in every measurable way -- colony characteristics, biochemical characteristics, animal protection, drug resistance, pigmentation. Dr. Comstock commented that it is then logical to assume that these vaccines also vary in efficacy.

Dr. Comstock remarked that one should think of BCG not as a single vaccine, but as multiple vaccines.

Information presented by Dr. Comstock also showed little correlation of the post-vaccinal tuberculin sensitivity, which many people consider an indicator of cell-mediated immunity, with the protective efficacy shown in the trial.

Dr. Comstock also showed summary data to support his contention that at this time, it is not known which animal system reflects the situation in humans.

These have been the two traditional measures of the efficacy of BCG vaccine. At the moment, they are not helpful.

Furthermore, Dr. Comstock stated that when talking about BCG's in the U.S., one only needs to consider the two that are licensed. Of the five trials of the Tice strain, two by Dr. Rosenthal in the 1930's and 1940's indicated that it was very effective. Two others by the Public Health Service in Georgia indicated no or negative effectiveness. Another one in Illinois was also negative.

These trials occurred so long ago that no conclusions can be drawn as far as current efficacy. However, past history is not a cause for optimism.

The other available strain is the Connaught strain. Dr. Comstock said that, to his knowledge, that strain had never been put through a controlled trial. It has been studied in one case-control study in Manitoba. The problem with case-control studies is that one not only measures the efficacy of the vaccine; one also measures the effectiveness of the TB control program. If one gives vaccine to the rich and placebos to the poor, distilled water would probably work reasonably well. If one gives vaccine to the poor and placebos to the rich, a good vaccine can look bad. In this study, they found that the effectiveness of the program in the northern rural areas was about 30%. In the south, in the cities, it was about 60%. Dr. Comstock learned that in the north, the system is haphazard. Those who are vaccinated are the people who happen to be in the village when the nurse gets there. The nurse doesn't get there very often because the weather is bad, there aren't many nurses and the villages are isolated. So in this area, it's almost a natural controlled trial.

In the south, those vaccinated were the babies born in the hospital. Those who didn't get vaccinated were born at home. The socially advantaged received the vaccine and the socially disadvantaged did not. Dr. Comstock said that in the south, the 60% actually measured both the vaccine efficacy and the socio-economic differences between the two groups.

Dr. Comstock remarked that there was therefore some indication that the Connaught strain was moderately efficacious.

In summary, Dr. Comstock touched on other aspects of the BCG question. He reiterated that this is not just an immunization problem. When one immunizes with BCG, one causes some degree of tuberculin sensitivity -- which is what researchers rely on to monitor the effectiveness of other control procedures -- environmental control (adequate ventilation), ultra-violet lights, masks. Dr. Comstock stated that the magnitude of the problem of drug-resistance in health-care workers is not yet known -- the numerator has been seen, but not the denominator. To make a balanced judgement, it is necessary to know how frequently this occurs and in what circumstances.

Dr. Comstock also restated the problems of giving prophylaxis. People are being exposed to cases that are both isoniazid-resistant and those that are susceptible to isoniazid. If people are protected against 90% of these infections, then the tuberculin test is useful.

Dr. Comstock said that, although BCG is essentially a harmless vaccine, with some local complications, there is concern about the problems of vaccinating someone with a poor immune system. Three other studies in the literature suggest that the incidence of lymphomas are greatly increased in people who have been vaccinated. That's part of the equation that needs to be taken into account, especially in a low-risk group.

In the ensuing discussion, the point was made that none of the other control measures (ventilation, ultra-violet light, masking) have been adequately or precisely evaluated to date, and that this needs to be done.

Mr. Gerard ten Dam, a scientist with WHO, presented summary data on WHO-assisted case-control studies on the efficacy of BCG vaccination against childhood TB.

One series of studies on meningitis showed no clear cut result. Mr. ten Dam reiterated Dr. Comstock's point that there are many different BCG's. Although WHO tried to find out which strains were more effective, different countries use different strains, and more than one strain may be used within a particular country. Although studies in Brazil used only one strain, no other country used that strain, so there was no basis for comparison.

Other case-control studies in the literature on meningitis, for which Mr. ten Dam presented summaries, showed a higher efficacy rate, again with different strains and brands of the vaccine being used.

He also commented that many of the control studies are done by doctoral candidates. They may have done preliminary studies, then proceeded when they found some degree of protection, so there may be some degree of bias.

Mr. ten Dam then presented results of contact studies. When they found a case of TB that was smear-positive, they actively followed the child. The risk of finding TB is about 30% upon first exam. The disadvantage of this type of contact study is that serious forms of TB are not found. As the study is done, for ethical reasons, when TB is suspected, the child is treated. Most diagnosis is done by X-ray.

Although the results showed some efficacy (60-70%), Mr. ten Dam stated that the results were far from perfect.

Mr. ten Dam remarked that if one goes through all studies done on BCG, one finds a wide variety of efficacy. The highest seems to be when infection takes place shortly after vaccination. A guideline may be that BCG seems more effective in the short term, and that the long-term effect is unknown.

He also remarked that in Scandinavian countries, BCG was introduced precisely because of observations that were done in student nurses. This was really the basis for the BCG international campaigns.

WHO also did a long-term study in Hong Kong, summarized by Mr. ten Dam. In this four-year study, comparing the Pasteur and the Glaxo vaccines, all children were vaccinated. There was no control group.

Vaccines were administered intradermally in the government hospitals. This type of vaccine was given to 81,000 children. Percutaneous vaccine was used in all other hospitals, given to a total of 70,000 children.

Because the French strain is more virulent, the dosage was smaller.

There was a lower incidence of disease with the French strain, especially in the case of the percutaneous vaccine. However, there were also more complaints about reactions to this strain. Other data suggested that the French strain might be slightly more effective; however, due to the side effects of the French strain, and the very low incidence of TB in general, officials in Hong Kong decided to continue to use the Glaxo vaccine.

Dr. Paul Fine, from the London School of Tropical Medicine and Hygiene discussed his experiences with BCG in Malawi.

He recalled the fact that, a number of years ago, researchers in the United Kingdom came up with high efficacy results for BCG, while U.S. studies showed low efficacy. In the United Kingdom, the opinion was that researchers had chosen a good vaccine. Researchers in the U.S. said that their results reflected complicated interactions between infections with different mycobacteria. Now things have changed. As an American working in England, Dr. Fine said he was amused to note that here in the U.S., differences are now explained in terms of vaccines. Meanwhile, in the United Kingdom, differences are being explained in terms of interactions between mycobacteria.

Dr. Fine shared data showing a wide range of efficacy of BCG against TB, and also against leprosy.

In one study, two different strains of virus produced exactly the same level of efficacy. In another, the same strain (freeze-dried Glaxo) produced widely differing results.

Dr. Fine then presented data from the work going on in Malawi over the last 12 years, in a study called the Leprosy Evaluation Project in the Karonga district, with a population of 150,000.

BCG was introduced in 1974 in mass campaigns among school children, then continued through the infant immunization services. Freeze-dried Glaxo vaccine was used throughout.

House-to-house surveys in the late 1970's recorded scar status. (There had been no written vaccination records.) There was a great deal of skin-testing using RT23 tuberculin (the Copenhagen product), with follow-up done on both TB and leprosy.

This population is now the site of a large vaccine trial against leprosy and TB. One of the important hypotheses is whether two BCG's are better than one. Many countries have repeated BCG as part of their routine policy, but this has never been evaluated anywhere. This was the first trial of repeated BCG's.

A high proportion of people up to 30 years old had a clear BCG scar, reflecting the introduction of the vaccine in the 1970's, with about 50% coverage.

Other data showed that 2-3% per year converted to skin-test positive.

Data from this population suggested that BCG was imparting 50% protection against leprosy in both sexes, but little if any protection against TB, regardless of age at the time of vaccination.

Dr. Fine commented that these data are similar to the results from Chingleput, and also recent studies in Kenya. He wondered if this might suggest interaction between BCG and different mycobacteria, rather than strain or product differences. Or perhaps BCG needs different antigens to protect against TB rather than leprosy. The answers are not known.

An additional study looked at TB and leprosy risks by RT23 tuberculin status collected some years prior to onset of disease. There was no evidence that any BCG-induced tuberlin sensitivity might be related to protection. Skin-test conversion associated with BCG vaccination is not a measure of protection.

Dr. Fine summarized his remarks by saying that the trials and comparisons from Malawi suggest that the variations in BCG efficacy are not due entirely to differences between product. The data are consistent with the long-standing hypothesis of interaction between different mycobacterial infections, and the way this may influence the body's response to BCG. He also stated that better correlates of protective immunity against mycobacterial disease are needed. Trials are the only way to evaluate efficacy in a given population. There are no reliable immunological correlates to tell us whether a response indicates that an individual has been protected.

Dr. Fine was asked what percent of persons receiving BCG develop a scar, and how the intensity of cellular reaction affects that development. Dr. Fine replied that more than 90% of those who receive a full dose of BCG develop a scar. That percentage is lower in the first year of life, in part because infants are often given a lower dose, and also because the immune response is less.

In response to another question, Dr. Fine discussed HIV seropositivity in the population described earlier. In this rural area, 6-7% of the population is seropositive. There is an eight-fold increase in the risk of TB with HIV-seropositivity, but no association with leprosy at all. Again, according to Dr. Fine, this is a negative finding that perhaps is telling us something.

Dr. Robin Huebner addressed the issue of the safety of the BCG vaccine.

She began by describing a normal reaction to BCG: after one week, there is a red, indurated area 5-15 millimeters in diameter. At 3-4 weeks, the center softens, a crust forms, then falls off, leaving a 10-millimeter ulcer. Between 6 and 10 weeks, there is a 3-7 millimeter flat scar. Generally, at this point, there is immunity. In some individuals, ulcers may be larger and slower to heal, taking 4-5 months.

The presence of BCG in healthy children several months after vaccination has been demonstrated by puncture biopsy of the liver. BCG dissemination is therefore considered a normal process; it is not known how long BCG persists after vaccination.

Complications of BCG depend on the strain used, the dose (viable units per dose), mode of application and the age of the vaccinee.

Currently only one BCG is licensed for immunization in the U.S.: the Tice vaccine, a substrain of the Pasteur Institute strain. It is a percutaneous multiple-puncture vaccination.

Dr. Huebner went on to discuss studies by the International Union Against Tuberculosis on complications following BCG. The first was a retrospective study begun in 1974, involving a search of all world literature from 1921-1982. This group also surveyed 71 countries from 1975-77. An estimated 1.5 billion people have been vaccinated with BCG between 1948 and 1974. In the original retrospective study, it was found that risk varied by country, by complications and by age of vaccinee.

It was felt that estimates were low and that the diagnostic criteria were not well documented. So in 1979, a prospective study was begun in six European countries: Denmark, East Germany, Hungary, Romania, four cities in West Germany, and

Croatia in Yugoslavia. Some 5.5 million people, mostly children, were vaccinated. They were followed until 1983. Participating countries followed their own national guidelines and gave their own BCG's. In some countries all infants were vaccinated; in others, only high-risk infants received the vaccine.

In terms of local reactions, the risk calculated per thousand was .387. There were 848 reactions, mostly regional lymphadenitis. 76% of the reactions were seen within the first 6 months, 30% within 3 months after vaccination. Risk varied significantly between countries, depending on the vaccine and the viable units per dose.

For the more serious complications, risk was calculated per million. Out of 5.5 million people, there were 21 cases of disseminated disease in four of the six countries. No serious complications were reported in Denmark or West Germany. 73% were diagnosed within the first 6 months. A serious immune defect was suspected in 6 cases occurring in very young children. Overall, in older children, the risk of serious disease was 4.29 per million. Dr. Huebner pointed out that there was one figure putting the risk of disseminated BCG for immunocompromised infants at 1%.

There were no fatal cases among older children and none were found to have immune defects.

The conclusion from this was that BCG is a relatively safe vaccine.

Dr. Huebner went on to say that there is little information in the literature on BCG in HIV-infected persons. WHO recommends that all children be vaccinated with BCG, regardless of HIV serostatus, unless they have overt symptoms of clinical AIDS. She briefly summarized data that has appeared in several papers on children: 10 children (5 in France, 5 in Zaire) who developed lymphadenitis at 4-15 months post-vaccination, after the development of clinical AIDS symptoms. All were treated with antibiotics and the lymphadenitis resolved. Seven out of 67 seropositive children in France developed axillary adenopathy. Five out of 185 seropositive children Zaire developed regional lymphadenitis; these numbers are not significantly different from HIV-uninfected children. 24% of seropositive children in the Congo developed lymphadenitis; again this was not significantly different from HIV-uninfected children.

A very limited number of cases of HIV-infected adults with BCG complications have been reported in the literature.

Dr. Katz asked what studies have looked at skin-test reactivity to tuberculin protein in HIV-infected children. Dr. Huebner replied that in the Congo, researchers found that children who were HIV-infected were less likely to be tuberculin positive following BCG.

Dr. Katz commented that the use of BCG in the immunocompromised is an area of increasing concern, and that the purpose of the preceding presentations was to "sow the seeds of deliberation."

During the ensuing discussion, Dr. Snider asked whether the Committee wanted to modify its BCG statement. CDC has been asked by the New York City Department of Health, the Greater New York Hospital Association, by infection control people, and by physicians around the country in hospitals facing multiple-drug resistant outbreaks whether BCG should be considered as a part of the control measures. BCG vaccination was not previously recommended in the guidelines issued in December, 1990, as part of infection control in health-care settings. All other modalities were recommended, but not BCG. Prior to that time, there was little information about multi-drug resistance, high mortality rates and the magnitude of transmission.

Dr. Snider went on to say that, subjectively, people are having trouble finding enough isolation rooms, or the money to retro-fit rooms, in order to implement existing guidelines. Due to this, there is interest in other ways to protect health-care workers and patients; BCG is one possibility.

Dr. Snider said that CDC felt this question should be taken to the appropriate advisory groups. Moreover, there is concern about what clinical studies should be encouraged. Every option must be explored to control TB.

Comments by Mr. ten Dam and others reiterated the lack of data on BCG in HIV-infected individuals and the difficulty of HIV testing overall. One Committee member remarked that he was "underwhelmed" by the data on BCG, but impressed with the ominous nature of the problem of TB transmission in hospitals. Dr. Katz stated that increased surveillance in hospitals and clinics was one measure that is clearly indicated. Dr. Gardner commented that he felt it would be appropriate to recommend that immunocompromised or HIV-infected individuals not work in TB wards, and that seemed a more effective control measure than BCG.

Dr. Schaffner reiterated the fact that none of the current control measures appear to be efficacious, and that it would be foolish to rule out any possible approach. He went on to say that institutions have a responsibility not only to their workers, but first of all to their patients. Therefore, there may be a role for serologic screening in the TB control effort, even though this is a delicate political question. Dr. Snider

replied to this by saying that skin-test conversions are occurring in other places inside the hospital; transmission is occurring outside the hospital -- emergency room, emergency medical people, etc. It is also known that none of the four hospitals discussed earlier followed the CDC guidelines for preventing transmission. As a counterargument, workers could say they were not in an appropriate environment. Dr. Snider also commented on a public aspect alluded to earlier by Dr. Katz. What happens to the availability of health-care providers for HIV-positive people? He said that he and others have been struck by the anecdotes of how many care-givers to HIV-positive people are HIV-positive themselves. He stressed that there is a need to consider the whole picture.

Dr. Clements seconded Dr. Comstock's remark that there is a need to know the denominator in order to define the risk. She also said that "health-care worker" is a very broad term that needs to be defined better.

Captain William Berg from the Navy Environmental Health Center echoed the concerns expressed by others when he wondered whether health-care workers would want to draw attention to themselves by announcing their HIV status under these circumstances.

Dr. Katz concluded this discussion and the morning's session by indicating that a sub-committee would be formed to further discuss the BCG question and the Committee's recommendation. The meeting was adjourned for lunch at 1:00 p.m.

When the meeting reconvened at 1:50 p.m., Dr. Broome recognized the contributions of Cheryl Counts to the workings of the ACIP and presented her with a token of appreciation.

By way of further closure to the BCG discussion, Dr. Katz commented that many Committee members felt that something more needed to be done, but were not sure what, either in terms of revision to the recommendation, or in terms of encouraging additional studies. **Dr. Katz asked a sub-committee to look more carefully at these issues. The sub-committee, chaired by Dr. Pierce Gardner, included Dr. Neal Halsey, Dr. Bill Schaffner and Dr. Ted Mortimer. Dr. Dixie Snider will be the liaison for the BCG working group.**

Dr. Katz also introduced Dr. Ed Thompson, State Epidemiologist from Mississippi, the new representative of the State and Territorial Epidemiologists.

Immunization in the Immunocompromised

Dr. Mark Grabowsky introduced **Dr. Albert Donnenberg, from the University of Pittsburgh.** Dr. Donnenberg presented studies that focused on the pace of immune reconstitution after bone marrow

transplantation. Both common and exotic immunogens were used as probes of the developing immune system. He expressed the hope that this data would be of some relevance in formulating an objective policy on the immunization of immunocompromised individuals.

By way of background, Dr. Donnenberg said that bone marrow transplantation has had successful application for primary marrow failure, such as aplastic anemia; for the treatment of malignant neoplasms; and also for treatment of genetic diseases such as severe, combined immune-deficiency syndrome.

Regardless of the disease for which it is being given, bone marrow transplantation begins with marrow ablative preparative regimens. This therapy is also immuno-ablative -- the ablation is complete.

All of the data presented by Dr. Donnenberg was from sibling-matched HLA identical transplantation. The donor graft itself contains about 2-to-4 x 10 to the 10th nucleated cells, and is really bone marrow suspended in peripheral blood. About 25% of the nucleated cells in the graft are actually peripheral blood cells, and 4 to 5 billion of these cells are mature, peripheral blood lymphocytes. The small minority of these cells are strictly required for transplantation. These several billion lymphocytes have many biological functions in the new host, including the mediation of adoptive transfer of donor immunity. Immune memory of the donor, can, under appropriate conditions, be conferred upon the recipient.

When looking at immune responses to tetanus toxoid after bone marrow transplantation, Dr. Donnenberg said that data showed that antibody titers declined (over 16 weeks) to about four-fold lower than the initial titers. Lymphoproliferative responses were never detectable against tetanus toxoid, or any other exogenous protein antigen. This is the fate of recipient immune memory in the bone marrow transplant recipient: A loss of antibody titer and the absence of antigen-specific lymphoproliferative responses (at least for exogenous agents. This is not always true for endogenous agents such as viruses.)

To investigate the role of donor immunity and adoptive transfer, a four-arm study was designed. The primary immunogen was tetanus toxoid. As far as the immunization protocol, donor-recipient pairs were randomized to one of four arms, independently for each of several antigens (tetanus, KLH, sheep red blood cells.) Donors were immunized on day-minus-7; recipients were immunized on the day of transplant, immediately after marrow infusion. On day 60, all arms received a boost of tetanus and KLH.

Thus there were four possible combinations: donor and recipient immunized; donor only; recipient only; no one immunized.

In the assay, with seven healthy volunteer subjects immunized with the same vaccine preparation, a four-fold rise in titer was common; levels then dropped off and stabilized a little higher than the initial value (followed up to 180 days.)

With the bone marrow transplant recipients, all of the people had protective titers when they started. The best combination was both the donor and the recipient being immunized. In these cases, the four-fold rise in titer was very much like what was seen in immuno-intact individuals, although the titers fell off slightly more quickly.

In the next best combination, the recipient was boosted at the time of transplant. There was some slight effect with the donor immunized only. When neither was immunized, the results were consistent with the four-fold decline in titer described earlier.

The study showed that donor immunity can be transferred, and that the optimal strategy is to boost the donor who is already antibody-positive a week before transplant, and to immunize the recipient as soon as the graft is obtained.

Dr. Donnenberg then showed data on lymphoproliferative responses from the same study. They also suggested that in order to transfer donor memory, the recipient has to be immunized early after transplantation -- it is a "use it or lose it" type of phenomenon. The day-60 booster in all arms had no effect.

Looking at sheep red blood cells as a model for primary immunogen (something neither donor nor recipient has seen before) there was a very different story. Only one regimen worked in this case -- immunizing both the donor and the recipient. Looking at IGG and IGM responses, it seems this isn't a true, primary response; rather, it's the primary response of the donor. If the donor made it to IGG in the seven days before the marrow was harvested, the recipient had IGG. If the donor was just making IGM, the only response in the recipient was IGM. This is, therefore, the carry-over of primary response that was already initiated in the donor. The recipient is not competent at this point to mount a primary response. However, primary responses initiated in the donor can carry over.

Dr. Donnenberg went on to discuss the investigation of whether these responses could be boosted. He commented that, with multiple-immunizations and boost protocols, the number of cases are limited. Some 50+ patients were enrolled in these studies. Hence, assumptions had to be made.

In a study with tetanus and diphtheria toxoids, it was decided that the donors would always be immunized with both immunogens. The study looked at the effects of immunization on day zero (the day of transplant), day 35 and day 60, as well as possible combinations. The assumptions: immunization to tetanus and diphtheria would have similar requirements; the responses were independent of each other. Based on preliminary evidence, the assumptions seem justified.

There were three arms in the study; recipients were immunized with combinations of tetanus and diphtheria, giving 6 of the 8 possible combinations.

In terms of antibody responses to tetanus and diphtheria, responses to most of these regimens were similar, with the exception of donor-boost only, and late boosts at weeks 5 and 9.

In terms of cell-mediated immunity, as measured by lymphoproliferative responses, the only clear winners were recipient boosts at 0 and 5, and recipient boosts at 0 and 9.

Dr. Donnenberg summarized the data for humoral immunity, saying that the most effective regimens all included early immunization at week 0; in the least effective ones, only the donor was immunized, or the recipient got the immunization late. The data was similar for cell-mediated immunity.

Dr. Donnenberg stated that these results seem to reinforce the idea that the earlier you show these antigens to the recipient, the more likely you are to transfer responses.

The responses when the individual is immunized on day zero are of the same magnitude as those in immuno-competent individuals.

Factors affecting the reacquisition of antigen-specific immunity after transplantation include graft composition (the time and agents with which the donor is sensitized through immunization or natural exposure), and the frequency of antigen-specific donor lymphocytes in the graft itself. Also relevant is the recipient history of antigen exposure after transplantation -- the time, duration and frequency.

Dr. Donnenberg commented that this issue is further complicated by the superimposed effects of immunosuppression -- both because of agents that are used because of graft vs. host disease (GVH) prophylaxis; GVH disease therapy, and the effects of chronic graft vs. host disease which is itself immunosuppressive; and the immunosuppressive effect of viral infection.

Conclusions per Dr. Donnenberg were: Donor immunity has a profound influence on the recipient's immune function. Half-life of donor immunity is short in the absence of antigen exposure in

the host. The durable reconstitution of humoral and cell-mediated responses can be affected by appropriate immunization of the donor and the recipient.

Dr. Donnenberg also stated that retention or increase in specific antibody is a marker for in vitro antigen exposure. For viral infections, just maintaining a titer is evidence that the patient has actually seen the antigen, either by exogenous immunization, or by natural infection, or by reactivation of viral infection.

Lymphocyte purging and graft vs. host disease treatment can alter the magnitude of antigen-specific response. Another aspect which interests Dr. Donnenberg is that bone marrow allografts can be engineered for specific immunologic properties, through donor immunization and selective lymphocyte purging. If you want to get rid of specific lymphocytes, for instance those that cause GVH disease, you can do this, and still have the benefits of adoptive transfer of donor immunity. This is because when you immunize a donor, you change the separation properties of those antigen-specific cells. Dr. Donnenberg said that it is possible to remove 99% of the lymphocytes, and spare lymphocytes that are in the process of an on-going immune response in the donor. It is possible to selectively transfer antigen-specific donor immunity.

Follow-up studies were done on the above patients from one year to several years after transplantation; studies were also done on patients who were immunized more than a year after transplantation.

Patients who were on this protocol and received early immunization, were compared to those who did not receive early immunization, looking at the effect of late immunization. The current recommendation is that one year after transplantation, patients receive tetanus, diphtheria and killed polio vaccines; response to tetanus and diphtheria was monitored in Dr. Donnenberg's laboratory.

A year or more after immunization, titers were very low, perhaps even sub-protective, in patients who had not received early immunization. In both groups (those who did or did not receive early immunization), there was a significant response to immunization with tetanus and diphtheria -- much higher than the response in a normal individual. Even a year or more later, those who received early immunization get a higher increase in titer as a response to a late immunization. Dr. Donnenberg stated that this is evidence that the strategy of immunizing recipients early after transplant has continued influence, even more than a year after transplantation.

Dr. Donnenberg stated that in the case of titers late after transplantation, there was a 2.7-fold increase for having immunized the donor; there was a 2.8-fold increase for having immunized the recipient; there was a 26-fold increase for the late immunization itself; presumably, one can multiply these if all three immunizations have been given.

Additionally, the purpose of this research was to determine how long-lasting were the effects of the late immunization, starting at 50 weeks after transplant and going to 100. The data compared individuals who received late booster immunization with those who had not received late boosters. In individuals who did not receive late boosters, titers continued to fall to sub-protective levels. In individuals who did receive late boosters, titers were long-lived and high enough to be protective.

Dr. Donnenberg also presented data from a study done in collaboration with Dr. Halsey. This was a study of the response of HIV-seropositive and HIV-seronegative pregnant women in Zaire to tetanus toxoid immunization, comparing pre- and post-immunization status.

Protective levels of antibody were achieved after immunization in 79% of the seronegative women and in 71% of the seropositive women. There was no apparent difference in the efficacy of immunization. The caveat here was that these women were in the very early stages of HIV disease (ie. asymptomatic as measured clinically).

During the ensuing discussion, Dr. Clements commented on the fact that in the study in Zaire, the HIV-positive women appeared to have lower pre-titers. She said that when looking at the response of HIV-positive individuals to influenza, she has noted that in HIV-positive people, progressively in terms of status of their disease, the starting titer is much lower; they may not be able to sustain a memory response.

Dr. Donnenberg was asked whether live virus vaccines are used in bone marrow transplant patients. He replied that they are not; for polio, a killed vaccine is recommended; MMR is given, but not until two years after transplantation, and only in patients who are not receiving immunosuppressive medication for chronic GVH disease. He stressed that these are empirical recommendations. His recommendation is that recipients receive tetanus, diphtheria and killed polio one year after transplantation; two years after transplantation, they receive measles, mumps and rubella.

Dr. Grabowsky then addressed the statement on immunization in the immunocompromised.

He reiterated the original intent of these statements: to be a user-friendly compilation of existing ACIP statements. He raised the point that for some of the recommendations in the tables, even though they are labeled a compilation, there's no specific statement in the recommendation pertaining to that antigen on immunocompromised. The tables don't take into account the degrees of immunosuppression associated with different clinical entities.

Suggestions from the Committee and others have been noted: include an introductory statement; summarize the general principles of immunosuppression; improve the organization of the footnotes. Several members previously raised the issue of citing relevant literature, and asked for the inclusion of various immune globulins and vaccines. Several members had also noted that the statement should define the doses of steroids, including topical and short-term, which are immunosuppressive.

Dr. Grabowsky then requested guidance from the Committee on several issues: categories of immunosuppression and which antigens or immune globulins to be included; inclusion of issues other than whether to use or not use the antigen, including unusual side effects, suboptimal immune response, extra boosters or altered dosages and special precautions. Finally, he asked whether there is a need for a separate statement on bone marrow transplantation, and whether publication should be delayed until there is a recommendation on bone marrow transplantation issues. One suggestion was that there be two statements: a compilation of existing statements, and a second statement on bone marrow transplantation.

Dr. Peter felt that a separate statement on bone marrow transplantation would be useful. He said national standards in this area would be very helpful and perhaps should not be part of a broader statement. This was the general consensus of the Committee.

The Committee agreed to review and polish the statement in its present form, giving Dr. Grabowsky any additional comments by November 10. The Committee decided to take more time to review specific transplant immunosuppression regimens, including bone marrow transplants.

It was also agreed that the next draft of the statement be circulated for comments to several people who are doing transplantations.

Acellular Pertussis Vaccine

Dr. Steven Wassilak from the Centers for Disease Control introduced the presentations on acellular pertussis vaccine.

He stated that one year ago, Lederle and Connaught indicated to the Committee that they were interested in licensure of an acellular pertussis vaccine product for booster use -- 4th and 5th doses. Since then, Lederle's application has been reviewed by the FDA Advisory Committee. In anticipation of licensure, the ACIP is reviewing its statement.

He then introduced Dr. David Klein of NIAID to discuss NIAID-sponsored clinical trials of acellular pertussis vaccine.

Dr. Klein gave an overview of NIAID efforts over the past year and a half, evaluating new acellular vaccines in the clinic and initiating new clinical trials as a follow-up to the trial performed in Sweden several years ago.

In light of the many vaccines becoming available, it was decided to evaluate these vaccines in a standardized format. A large phase-two study was initiated in six vaccine evaluation treatment units which are under contract with NIAID. The purpose was to directly compare the various acellular vaccines, to each other, and to standard whole-cell vaccines in terms of safety and immunogenicity.

Thirteen acellular vaccines were examined; all 13 were combined with diphtheria and tetanus and compared to two, conventional whole-cell vaccines from Lederle and the Massachusetts State Health Labs.

The infants in the study were enrolled in the six centers and randomly assigned to receive the vaccines at 2,4, and 6 months of age. The vaccines were administered in a double-blind fashion. Approximately 120 infants were enrolled in each center. All of these vaccines had previously been studied in adults and in 18-month old children and were considered safe. The infants were bled prior to receiving vaccine, and one month after the third immunization, at 7 months.

Certain characteristics were common to all the acellular products. They all contained an inactivated pertussis toxin; the components were all very highly purified; they were shown to be protective in animals; there was a natural infectivity induced by the antibody to the individual components.

There were monovalent, bivalent, trivalent and quadravalent vaccines among the 13 that were used. The Sclavo and Massachussetts Public Health vaccines were among the monovalent

vaccines; they were not identical. They were inactivated differently; also, the Sclavo vaccine is a recombinant and the Massachussetts vaccine is not.

There were four bivalent vaccines: Merieux, SmithKline, Connaught, Biken. There were five trivalent vaccines: the first three, Sclavo, Lederle and SmithKline, contained the pertussis toxin, FHA and the 69KD outer-membrane protein, referred to as pertactin. The latter two from Connaught and Porton contain pertussis toxin, FHA and two types of fimbriae -- agglutinogen 2 and agglutinogen 3. Quadravalent vaccines included Lederle-Takeda and Connaught with pertussis toxin, FHA, pertactin, fimbriae -- agglutinogen 2 in the former; 2 and 3 in the latter.

A total of 2,342 infants were enrolled in 6 centers. The idea was to immunize at least 120 infants per vaccine in each center. All centers received each of the acellular vaccines. These studies are on-going in the form of a booster study. Recipients are receiving the corresponding acellular vaccine at 18 months.

To summarize adverse reaction data: There were no fevers over 105 F. There were 3 fevers greater than 104 F. (2 with a whole-cell product and 1 with an acellular product.) Overall, very few fevers over 103 F. were observed. Across the board, the incidence of fever for both the acellular and the whole-cell vaccines was less than what had been seen in earlier trials.

For example, with the Lederle whole-cell vaccine, the number of children with fever greater than 101 F. within 48 hours was 17.1%. With the whole-cell Massachusetts vaccine, the number of children with fever greater than 101 F. within 48 hours was 9.2%. With the acellular vaccines, the average was 4.2%

For other non-serious reactions (redness, swelling, pain at the site, fussiness, anorexia, etc.), there was no particular pattern observed between any of the acellular vaccines. With the whole-cell vaccines, there was a slightly higher incidence of these types of events.

In terms of serious adverse reactions (fever over 105 F., hyporesponsiveness, convulsions, high-pitched screaming, excessive crying), there were very few -- 3 among whole-cell recipients and 3 among acellular recipients. The only difference that was distinguishable among these reactions was persistent crying, reported in 5.6% of the whole-cell recipients and in 2.3% of the acellular recipients.

In terms of immunological data, the study looked at the antibody response, using a 16-fold above minimal detectable level and 4-fold above background level. (Data for the Sclavo recombinant was entered late and not included in this summary.)

PT responses ranged considerably from a low of 14.2 ELISA units to a high of 181 ELISA units (referring to GMT's).

By way of reference, for the whole-cell Lederle vaccine, the baseline response was 67 ELISA units.

Response to other antigens varied considerably. 100% of the children responded to the tetanus portion of the vaccine. About 85-90% responded to the diphtheria portion. The administration of Hib vaccine at the same time (in a different leg) with DTP had no profound effect on any of the titers to the various antigens that were examined.

After the trial, a task force was put together to evaluate all the vaccines and select those vaccines they felt would be acceptable for use in the up-coming vaccine efficacy trials. Criteria included safety, immunogenicity, laboratory characteristics (purity, residual enzyme activity, etc.) and acceptability to the host country.

Vaccines selected by task force included two bivalent vaccines (SmithKline PT, FHA; Merieux PT, FHA) and four multi-valent (Connaught, SmithKline 3-component, Connaught five-component, Porton three- or four-component, depending on breakdown of antigens.)

(Some of the others were rejected for the following reasons: significant levels of residual toxin, unacceptable levels of contaminants, immunogenicity, incomplete safety and immunogenicity data, lack of interest in a monovalent product. No vaccine was excluded for safety reasons or for high levels of endotoxins.)

While the phase-two study was going on, a contract was awarded to four sites (Great Britain, Canada, Italy and Sweden) to do feasibility studies and determine disease rates for pertussis for efficacy trials in those same countries. In May of 1991, a review panel selected Sweden as the best site for such a study. Presented with a choice of the vaccines described above, the Swedes selected the SmithKline two-component vaccine, and the Connaught vaccine with PT, FHA, pertactin and agglutinogens 2 and 3. The Swedes selected a two-component vaccine in order to maintain continuity from the previous study, and to try to demonstrate that two antigens are sufficient to provide protection.

Dr. Klein then described the protocol for Swedish studies, which includes two trials. The aim of trial 1: Estimate protection of acellular and whole-cell vaccines against typical pertussis as compared to a placebo. The secondary aim is to explore relative protection against sub-clinical infection and to explore serological correlates of protection.

In this placebo-controlled double-blind study with four arms, the Swedes are using the Lederle whole-cell vaccine, the two acellulars (Connaught 4-5 component), the Smith-Kline 2-component, and a DT vaccine manufactured by the National Bacteriological Laboratories of Sweden. The trial is scheduled to begin in February, 1992. The DT preparations will be administered at 2,4, and 6 months of age, comparable to the schedule used in this country. Projected enrollment is 10,000 infants and will take up to one year. The children will be followed for an average surveillance period of 30 months. The surveillance will be active; parents will be contacted immediately after the child is sent home, 24 hours later and 14 days later. During the 14-day period, parents will be asked to fill out an event/reaction card; this information will be sent on to investigators. Parents will be contacted the first year on a monthly basis, then bimonthly after that.

There will be a pre-bleed. A cohort of 750 children will be bled one month after the third immunization, at 7 months. All the children in this trial will also be bled at 12 months, then one or two years later.

For the second part of the trial, the emphasis will be to demonstrate relative efficacy and safety. This trial will not begin until the safety issue has been eliminated -- ie. it has been demonstrated that there are no harmful effects for any of these vaccines. About 18 months after the beginning of trial 1, the Swedes will initiate trial 2. It will be multi-centered, double-blind, randomized, 3 arms, a relative efficacy comparing whole-cell with the two acellular vaccines. It will be administered according to a schedule comparable to what is used in Sweden, that is at 3, 5, and 12 months of age. They will recruit a total of 50,000 infants over a period of 18 months. This trial will include 16 centers clustered around Stockholm. The possibility of including more vaccines and more children is also being considered. Due to the size of the study, follow-up will be passive, based on routine lab reports of culture-confirmed cases, and parental reports. Researchers feel confident that Swedish parents are very familiar with what a case of pertussis is.

Follow-up for the two studies will essentially overlap. The trial for phase two will end approximately three months post-third-dose.

Four efficacy trials are currently on-going around the world. The Swedish trial began October 1. Another study is on-going in Sweden in the Gottenborg area, promoted by the National Institutes of Child Health at NIH. There's a study in progress

in Senegal using Merieux vaccine. And there's a study which began this summer in Germany using a Lederle-Takeda vaccine. All these trials will last from 2 to 5 years. It's hopeful that some form of efficacy will be available by 1995.

Of the six vaccines offered to the Swedes, two were selected. The remaining 4 have not been incorporated into an efficacy trial. NIAID still has a great deal of interest in additional trials of at least these four, and perhaps other vaccines. The prospect of other studies is now being discussed with other manufacturers and other sites (Canada and Italy) using slightly different protocols from those used in Sweden, but essentially comparing placebos and whole-cell vaccines to the acellular vaccines.

Limiting factors include logistical factors and funds. Hopefully, details can be worked out within the next three to four months.

Dr. Katz asked what convinced the Swedes to include a whole-cell arm this time. Dr. Klein said the Swedes have been very concerned about pertussis for many years. There had been much discussion about the possibility of whole-cell vaccines, but everyone thought an acellular product would be available very shortly. The public became concerned about the lack of an available vaccine and was anxious to reduce the high incidence of this disease in Sweden. The public also now believes that adverse events associated with the vaccine are not as severe as once thought.

Dr. Katz also asked if in Sweden, the majority of the disease is in the first two years of life. Dr. Klein said this is true; however, there is disease in older children and adults; very few families have never seen a course of this disease.

Dr. Jill Hackell of Lederle-Praxis addressed the Committee, sharing data supporting the use of this product in infants, toddlers and pre-schoolers. She talked about Lederle's diphtheria-tetanus toxoid and acellular pertussis vaccine in terms of three major areas: efficacy of the vaccine, immunogenicity as compared with Lederle's DTP whole-cell vaccine, and data supporting the safety of the vaccine.

The clinical experience with Takeda's acellular pertussis component includes its routine use in Japan since 1981. More than 16 million doses have been distributed. Lederle and Takeda have also performed collaborative clinical trials in Japan. Earlier studies were done in the United States. Wyeth combined the Takeda component with their own diphtheria and tetanus toxoid

and performed studies in infants and toddlers. Lederle also conducted large-scale clinical trials; in the course of these, more than 6500 doses were administered to more than 2600 children.

In December, 1985, an interagency task force with members from the FDA, CDC and NIH visited Japan to study the Japanese experience with these acellular pertussis vaccines. They noted the success of the Japanese at controlling pertussis, following the introduction of acellular pertussis vaccines as a group in 1981. A series of household contact studies was reviewed; efficacy in these ranged from 78-92%. The task force concluded that these vaccines, as a group, were efficacious in Japan.

There were two types of acellular pertussis vaccines used in Japan at this time: T-Type (T for Takeda) contained 4 pertussis antigens, FHA, LPF, 69KD outer membrane protein and pertussis agglutinogen. FHA predominated over LPF in this type of vaccine. At the time of the task force's review, this type represented 80% of the market.

The other vaccine in use was the B-Type (B for Biken). It contained 2 pertussis antigens, FHA and LPF, in equal proportions. This vaccine accounted for about 20% of the Japanese market.

To look at the specific efficacy of the Takeda vaccine, Takeda did a household contact study in Japan, working with Dr. Ted Mortimer, Dr. Jim Cherry and Japanese physicians. Index cases of pertussis were identified; the study looked at incidences of pertussis within 7 to 30 days of household contact, both in vaccinated and unvaccinated children. There were 62 vaccinated contacts and 62 unvaccinated contacts. One in the vaccinated group acquired typical pertussis; in the unvaccinated group, there were 43 cases. Overall efficacy determination was 98%, with 95% confidence intervals. Eight children in the vaccinated group and four children in the unvaccinated group had a mild respiratory illness in this time period which could have been mild, atypical pertussis. Even with these children counted in the efficacy determination, efficacy is still excellent, at 81%. Dr. Hackell concluded that the Takeda vaccine effectively prevents pertussis disease in children, as shown by the Japanese studies.

Dr. Hackell then described studies done in the U.S. comparing the immunogenicity of Lederle's acellular pertussis vaccine, combined with diphtheria and tetanus toxoids, with the Lederle whole-cell vaccine. The acellular vaccine was administered as a 4th or 5th dose to children whose previous doses in the series were whole-cell DTP vaccine.

Serology determinations were taken just before immunization and one month after immunization. There was a series of Lederle multi-center studies with consistent results. These results were also supported by those of the Wyeth and NIAID studies.

Dr. Hackell discussed one representative study in each of the two age groups. The first study was done in 17-24-month-olds. It was randomized and double-blind, conducted at 7 centers. Children were given either APDT or the whole-cell DTP vaccine for their 4th dose in the series. There were 350 children who received one of four lots of APDT; 50 received one lot of DTP. This was the lot-consistency study. There were no differences among the four lots.

Geometric mean titers one month post-immunization showed that there was an equivalent response among APDT and DTP recipients, for LPF, 69KD and agglutinin. For FHA, the reponse in the acellular pertussis recipients was significantly greater than in the whole-cell recipients.

No difference in immunological response to the vaccine was found based on age.

Similar results were seen in 4-to-6 year-olds in another randomized, double-blind study carried out in three centers with children who had received four previous doses of whole-cell DTP vaccine. Children were randomized to receive either APDT or the whole-cell vaccine.

Results for LPF and 69K were similar. The FHA was again significantly higher among recipients of the acellular pertussis vaccine.

In terms of immunogenicity, APTD administered as a 4th or 5th dose is at least as immunogenic as the DTP which has been so effective in the control of pertussis in the U.S. LPF and 69KD were similar and FHA was consistently higher among APDT recipients. Diphtheria and tetanus responses were also similar throughout.

Dr. Hackell went on to discuss the safety studies. More than 6500 doses were administered at 20 study centers throughout the country. There were comparative studies, all of which were randomized and double-blind, as well as some open studies. Again, the results for safety were supported by the results of earlier studies done by Wyeth and NIAID.

Certain local reactions and systemic events were recorded on a parent diary card. Events were collected at 30 minutes, 3 hours, 6 hours, 24 hours, 48 hours, 72 hours after immunization, and then daily for 10 days. The study site called the parents at 24-48-, and 72-hour intervals and at 14 days to ensure follow-up.

At many centers, parents were also called quarterly for one year after immunization to monitor infections and hospitalizations.

In 17-to-24-month-olds, acellular pertussis recipients had consistently lower percentages of reactions (ie. tenderness, erythema, induration, injection site temperature, fever, drowsiness, irritability and antipyretic use.) Prophylactic tylenol was not part of this protocol at the centers; however, the parents did administer it. Although difference in fever was not quite statistically significant, the P value was .06. 21% of the parents administered tylenol in the DTP group; 5% of the parents administered tylenol in the APDT group. This was a statistically significant difference.

Among four-to-six year olds, safety data were also similar. The acellular group had significantly fewer injection site reactions. Difference in fever also achieved statistical significance. Drowsiness and irritability were low in both groups in this age group. Antipyretic use was again significantly less among acellular recipients.

Dr. Hackell then presented an additional study with infants to support the difference in reactogenicity between the acellular and the whole-cell vaccine. In this randomized, double-blind study conducted in 10 centers, children were randomized to receive either the whole-cell vaccine or the acellular vaccine at 2,4, and 6 months of age. Reactogenicity and antipyretic use were consistently less in the acellular group.

When results of all age groups were pooled, percentages of both injection site reactions and systemic events were lower in the acellular pertussis recipients.

Lederle also looked at children who developed events considered contraindications to further doses of pertussis vaccine, based on the earlier ACIP/AAP recommendations. Although results of infant trials and trials of older children were pooled, all of the events occurred in the infant trials. Dr. Hackell also compared these data with studies done at UCLA in the late 1970's.

Again, there was clearly a reduction in adverse events with the acellular pertussis vaccine when compared to the whole-cell vaccine.

Dr. Hackell summarized by saying that local reactions are less frequent and severe with Lederle's acellular pertussis DT vaccine. There was no pattern of late local reactions when events were collected after 14 days.

In terms of systemic events, there was less fever and less antipyretic use among APDT recipients, as well as less drowsiness, less fretfulness and less crying. There was no

difference between acellular and whole-cell vaccine recipients in the incidence of infections or hospitalizations.

Dr. Wassilak said that in addition to data from Lederle, the Advisory Committee for the FDA has heard data from Connaught, but has made no decisions to date regarding their license application. He then introduced Dr. Carlton Meschievitz from Pasteur-Merieux-Connaught to discuss the Connaught application for booster use.

Dr. Meschievitz began by commenting that Connaught will be appearing before the FDA Advisory Committee on November 12 and 13.

He said that diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed Biken-Connaught is bulk filled, labeled, packaged and released by Connaught Laboratories, Inc. The purified acellular pertussis concentrate is produced by the Research Foundation for Microbial Diseases of Osaka University, or Biken.

This vaccine produced by Biken is combined with the licensed diphtheria and tetanus toxoid products manufactured by Connaught Laboratories. The Connaught vaccine contains FHA and PT in a 50-50 ratio. The fermented cultured product is purified by salt precipitation, high-speed ultra-centrification, and ultra-filtration. Detoxification with formaldehyde is performed in a manner whereby reversion to toxicity is not seen. The final vaccine contains 3.75 micrograms of FHA, expressed as protein nitrogen, and 3.75 micrograms of PT per dose. The diphtheria and tetanus toxoid components are added to contain 6.65 Lf and 5 Lf respectively per dose. The combined antigens are precipitated in the presence of aluminum potassium phosphate and preserved with 1:10,000 thimerosal.

The vaccine has been in use in Japan since 1981. Over 13 million doses have been distributed. Currently, three of the six Japanese manufacturers are producing the B-Type vaccine.

Dr. Meschievitz briefly touched on new findings from the Swedish trial by Dr. Olin. It is the only randomized, placebo-controlled trial completed to date. The trial included children aged 5 to 11 months, with a two-dose regimen given two to three months apart, and contained pertussis-only vaccine, JNIH-6, the same as the current Biken vaccine used in the U.S. trials, with the same formulation of PT and FHA. The study also included a monocomponent vaccine, especially made for the trial, which was PT only, at 6 micrograms per dose. A placebo was also included in the trial.

In the first publication, the evaluation point was at 15 months, following one month after the second dose. The original case definition, which was any cough with a positive culture, resulted in 70% efficacy for the Biken vaccine. However, with more typical pertussis with a cough longer than 30 days and a positive culture, the efficacy was at 80%. Following the breaking of the blind, last year at the International Pertussis Symposium, Dr. Olin presented an update of the data, now in its fourth year of follow-up. At this point, under the original case definition, the vaccine is 77% efficacious; with a more typical culture-confirmed pertussis, 92% efficacious.

The monocomponent and the bicomponent vaccines were equally protective in the case of severe disease. It was in the milder cases that the bicomponent vaccine offered better protection.

Dr. Blackwelder of NIH independently re-analyzed the efficacy data and presented his findings at the International Symposium last September. In that analysis, the two-component Biken vaccine was 84% effective against a cough lasting longer than 21 days. When the cough was defined as 8 spasms or more on 1 or more days, the vaccine was 87% efficacious.

Based on the results of the Swedish efficacy trials, upon which Connaught bases its claim of efficacy for the fourth and fifth dose, Connaught concluded that the two-component vaccine protects against typical whooping cough. Two doses protect for at least four years, and the JNIH-6 vaccine provides protection which Connaught believes is comparable to whole-cell vaccine.

In the U.S., Connaught has conducted three large safety and immunogenicity trials in infants as a fourth dose following three doses of whole-cell vaccine, and as a fifth dose following four doses of whole-cell vaccine, at four to six years of age. The trials were all randomized and double-blind, and contained Connaught whole-cell vaccine as the control.

Immunization schedule in the infant study was 2, 4, and 6 months. Dr. Meschievitz presented this data in support of the fourth and fifth dose application. Blood was drawn at 2, 6, and 7 months and there was safety monitoring throughout the period.

The 18-month trial was simpler in design: one dose at 15 to 20 months of age, a blood draw at baseline and four to six weeks later, safety monitoring at both points. The four-to-six year old fifth dose trial was identical in design.

To date, almost 6000 subjects have received some 8000 doses of Biken acellular pertussis vaccine.

For the safety and immunogenicity portion of the trial, there were 240 4-6 year olds receiving the acellular vaccine, 373 15-20 month old infants, and 400 2,4, and 6 month old infants.

The greatest reactivity at the injection site was at 6 hours, with a marked decrease after that. For each indicator (tenderness, erythema, swelling), there were sizeable reductions with the use of acellular pertussis, as compared to whole-cell.

In terms of fever, irritability and drowsiness, there was a two-to-five fold decrease among 15-to-20-month-olds with the acellular vaccine. Large reductions were also seen in anorexia.

Dr. Meschievitz also summarized the antibody data: LPF done by ELISA, antibody to FHA also done by ELISA, CHO-cell toxicity (another indicator of LPF), diphtheria and tetanus.

In each instance, antibody response to LPF was significantly higher than whole-cell. In addition, there is a significant increase with each subsequent dose in all age groups.

Dr. Meschievitz also showed the GMT of serum LPF antibody from the Swedish trial (a selected set of 49 sera, tested post-dose-two by the FDA.) In the 18-month-old infants, and the 4-to-6-year olds, there was a sizably higher titer of antibody to LPF.

Similarly, CHO-cell responses were also quite dramatic, including CHO-cell responses in infants.

FHA response with the acellular vaccine was significantly higher than with whole-cell. Compared to the Swedish trial, FHA levels were again comparable or higher.

There was also good response to tetanus. In 18-month-old infants and 4-to-6-year-olds, antibody response to tetanus was equal to or statistically greater than with whole-cell vaccine. The same was true for diphtheria response in the booster dose.

Dr. Meschievitz also discussed Connaught's large safety trial in 15-20-month-old infants, which looked for local, minor systemic and major systemic reactions, such as seizures, hypotonic-hyporesponsive episodes, and unusual cries. A three-day telephone contact, a 30-day telephone contact, a three-month telephone contact were done for hospitalizations and deaths. A one-year physician chart review was also done.

There were no surprises in terms of common local and systemic adverse effects. The data for 1400 children were similar to those shown with smaller samples in earlier trials.

As of October, there are 2,388 subjects who have been enrolled in the 15-to-18-month trial and have been followed for at least three months. In that group, there have been no hypotonic-hyporesponsive episodes, no severe systemic bacterial infections, no vaccine-related seizures, and nine instances of persistent crying. Projecting from the whole-cell results in the previous trial with similar surveillance methods, 80 of those events would have been expected. There were 18 incidence of unusual or high-pitched crying; based on the previous whole-cell study, there would have been 40 such events expected. There was no severe fever within the first three days after vaccination, no deaths, encephalitis or anaphylaxis.

To additionally confirm safety, Connaught has also been conducting a trial in infants. To date, 2300 infants are enrolled, with one month or greater follow-up after the first dose and a very similar profile of adverse effects.

Dr. Meschievitz concluded by saying that Connaught feels that the Biken two-component vaccine leads to fewer common local and systemic reactions when compared to whole-cell vaccine. The two-component vaccine has significantly higher antibody levels to LPF and to FHA compared to their whole-cell vaccine; LPF and FHA antibody responses are comparable to those in Japanese and Swedish children where efficacy has been demonstrated. Close to 6000 infants and children have been followed for one to 12 months after vaccination.

Dr. Wassilak then led a discussion of the ACIP proposed supplementary statement on acellular pertussis vaccine. He emphasized that the timing of licensure is uncertain, and that the statement was drafted in anticipation of a product or products being available in the near future, and that when such a product is licensed, the statement could be refined.

Points to consider included: Appropriate cautions against unlicensed use of the product; policy issues such as what to do for a child who hasn't previously been vaccinated by age two; what is the recommendation for 15 months of age, since the product currently under review is not going to be licensed for 15 months of age. A major policy issue is what should be said about routine use. Is the acellular vaccine preferred? Is it optional? And are there special circumstances where the acellular product may be preferred or optional for the fourth and fifth doses?

Dr. Wassilak also commented on his quandary on how to abbreviate this product, since there is no standardized abbreviation when referring to any and all products.

He said that minor comments may be sent to him by mail. In the interest of time, the Committee decided to address the three most critical issues.

The Lederle product application is for licensure at 17 months through 6 years of age, specifically stating that it is intended for the 4th and 5th doses. The Connaught application also specifically states that it is intended for the 4th and 5th doses, but with data available from 15 months on.

The product has not been proposed to be licensed for the first three doses. Dr. Wassilak asked whether the Committee would like to consider recommending either of these products in special circumstances when children have not previously been vaccinated and are at least two years old.

Dr. Halsey raised the question of terminology. He said that ACIP has long considered the first four doses to be the primary immunizing series. In one place in the document, the 4th dose is referred to as part of the primary series; in another, it is called a reinforcing dose; elsewhere it is referred to as the 4th dose. He felt this could add to the confusion of practitioners, especially with vaccines being licensed for the 4th and 5th dose.

He also wondered about additional confusion if the two vaccines were licensed for beginning use at different ages (15 or 17 months.)

Dr. Katz raised the question of the legal aspect of giving a product earlier than the age for which it is licensed. Kevin Malone confirmed that this is considered part of the physician's practice.

Another point of discussion was the possible confusion resulting when the recommendation in the package insert differs from the recommendation of the FDA or the ACIP. Dr. Katz felt that the practitioner was more likely to consult the MMWR, the Red Book or statements from the Academy of Pediatrics.

Dr. Bart also commented that conflicting recommendations on use help no one. He noted that there are three use committees and two policy committees, all of which make recommendations, in addition to the package insert. Different people use those references based on who they affiliate with. He urged consonance among all these recommendations to the greatest possible degree.

Dr. Clements asked when data on the use of pertussis vaccine in 15-month-olds would be available. Dr. Hackell replied that the studies are on-going; hopefully within six months some data will be available.

Dr. Hardegree commented that package inserts have been and continue to be modified based on the recommendations of the ACIP and other organizations. The process is not static. Licensure occurs with a given set of data; when new data become available, changes can be made. ACIP, in her opinion, needs to decide what is the best way to make its own recommendation, recognizing that it may not be exactly what the companies have applied for.

Dr. Katz summarized by saying that even theoretically, if there were some loss of immunogenicity, or efficacy (which most doubt), by moving from 17 months to 15 months, that would be greatly overbalanced by the numbers of children who would get a 15-month booster in contrast to a 17 or 18-month booster.

The Committee then voted to let the following paragraph from page 9 of the ACIP supplement stand as written: "Although immunogenicity data in children 15-16 months of age are not currently available, the ACIP believes that the DTaP (Lederle/Takeda) vaccine can be used for such children as part of ACIP-recommended schedule of routine simultaneous vaccination with DTP, OPV and MMR at 15 months of age."

The Committee then discussed the question of non-labeled use, vaccinating a child who hasn't previously been vaccinated by the age of 18 months.

Dr. Peter said he preferred to simplify the situation by leaving the statement as is: recommendation of whole-cell vaccine for the first three doses, at any age; acellular vaccine for 4th and 5th doses. He was concerned that recommending acellular vaccine for primary doses in older infants might open the door to wider use of the acellular vaccine at a younger age. Even though the acellular vaccine would probably work, the data is not yet available to support this use.

Another proposal was to recommend whole-cell vaccine for primary immunization under two years of age. For primary immunization over two years of age, either acellular or whole-cell vaccine would be recommended.

Dr. Bart recalled the Japanese data on acellular pertussis vaccine and its apparent efficacy in children two or older. He commented that there are perhaps many unreached populations of children who, for whatever reason, have not been immunized. If there is an effective vaccine for older infants, why not offer it? He felt many more pediatricians would be comfortable with acellular pertussis, due to concerns about adverse reactions to the whole-cell vaccine.

A question was raised that this might cause many people to delay immunization until age two. Dr. Edwards expressed concern that recommending the acellular vaccine for primary immunization in

older children might open the floodgate for unlabeled use in younger children. There was a question in her mind about the Lederle vaccine's ability to induce adequate primary antibody response to the pertussis toxin. She felt there are good reasons why the acellular vaccine is not approved for use in 2, 4, and 6 year-olds. She preferred to recommend whole-cell vaccine for primary injection regardless of age.

Dr. Hall said that the recommendations could make it clear when the respective vaccines should be used, and that it was impossible to predict or control unlabeled use.

Dr. Wassilak volunteered to wordsmith the recommendation, then put it before the Committee for reconsideration. The vaccine would be not contraindicated; there would be a paragraph addressing special circumstances when a child has not been immunized or has not completed primary immunization by age two.

He again raised the question of whether this should a be preferential- use vaccine or an optional-use vaccine. So far, in terms of the statement, it has been an optional-use vaccine under routine circumstances. Under certain circumstances, with a family or personal history of convulsions, it is a preferred-use vaccine.

In response to this question, the issues of cost and availability were addressed to the manufacturers.

A Lederle representative indicated that a large number of doses would be available, assuming the vaccine passed all tests. Although exact cost figures were not available, this is a highly purified vaccine and some cost increase should be expected.

A Connaught representative concurred with the comment on cost.

After a discussion of cost constraints, Dr. Wassilak agreed to wordsmith the statement further so it would indicate that when available, the acellular vaccine is preferable because of the lower rates of common side effects.

The meeting adjourned at 5:35 p.m. Dr. Katz asked the Committee to reconvene at 8:30 a.m., contrary to the 9:00 a.m. time indicated on the agenda.

Dr. Katz called the meeting to order at 8:30 a.m. on Wednesday, October 23.

Influenza Vaccine and GBS

Dr. Robert Chen was the first presenter of the day, discussing GBS and influenza virus vaccines.

He briefly reviewed the methodology of the on-going investigation for the benefit of the new members on the Committee, stating that this is a major collaborative effort among many groups within CDC.

In 1976-7, the swine flu vaccine was shown to be associated with GBS at an attributable risk of slightly less than 1 case per 100,000 vaccines. Despite controversy, validation studies in Minnesota and Michigan showed that this was a real association, with an elevated risk confined to the first six weeks after vaccination. Unfortunately, researchers were unable to establish the biological mechanism for this association.

In December 1990, two cases of GBS were reported within six weeks of flu vaccination from an HMO in Colorado that had given out about 30,000 doses during their routine campaign targeting high-risk groups. The question was raised whether this was coincidence or causal.

To examine this, researchers looked at several different data sources, including passive surveillance through VAERS. Active surveillance was conducted in three primary sites, with a total population of 16 million adults: 1) 10 sites where HCFA was conducting a flu vaccine cost-effectiveness study; 2) the state of Colorado where the index cases occurred; and 3) two HMO's in California that are the largest in the country.

Two other sites with an additional 7 million population were interested in doing special surveillance, the states of Louisiana and Washington.

Dr. Chen described the methodology in the primary sites (HCFA, Colorado, California HMO's): Early in January 1991, researchers tried to find all cases of GBS with onset since summer 1990, by contacting practicing neurologists, plasmapheresis centers and hospitals in these areas, looking for medical discharges with the code for GBS. In Washington and Louisiana, only practicing neurologists were contacted.

The vaccination status was ascertained separately for each GBS case that was found, in order not to bias the association. The GBS diagnosis for each case was validated by an independent panel of neurologists blinded to vaccination status and antecedent illness status. Only cases considered definite, probable or

possible were included in the analysis. (Approximately 42% of these were deemed definite, 57% probable and 1% possible,)

In July 1991, Drs. Joe Kent and Paul Simon went back to California and Colorado to validate the completeness of the case findings; this was necessary because of the six-week plus delay in onset of GBS.

The ascertainment of the denominator data in terms of vaccine coverage was also important. For persons 65 and older, there were two types of direct data from 1990-91. Each of the HCFA centers had a monthly tracking system. A random survey was also done at the end of the season. In Colorado and California, the figures weren't quite as precise. Numbers were extrapolated from the 1988-89 National Health Interview Survey figures. In the 18-64 age group, there was no direct data available on coverage because this age group does not normally receive the flu vaccine. Dr. Chen stated that researchers were uncomfortable with those numbers; ACIP had previously requested that some direct estimates be made for 1990-91.

A contractor experienced in random digit-dialing phone surveys was hired. Two universes were selected: a separate one for the HCFA sites where a higher coverage was expected; and one for Washington and Louisiana which was expected to be more typical of the general population. In the latter group, a larger sample size had to be obtained because a lower coverage rate was expected. People were asked questions about the receipt and timing of their flu vaccine since July, 1990, and whether or not they had one of the ACIP indications for flu vaccination.

The coverage survey showed prevalence of risk factors, and the corresponding percent of vaccine coverage. 46% of the population had some risk factor for receipt of the vaccine, as defined by the ACIP. Only 14% of these people were vaccinated.

Dr. Chen presented the final relative risk figures: In all adults 18 and over, the relative risk is 1.1. In persons 65 and older, the targeted group for flu vaccine, relative risk is .4. There was a mild elevated risk in persons 18 to 64: 2.4. In all ages, a risk window of 6 weeks was assumed. The confidence interval overlaps 1, and takes into account the fact that, for the denominator data, it was necessary to do a sampling scheme; a degree of uncertainty is built into the confidence interval.

If the data from Washington and Louisiana are included, adding a population of 7 million to the original population of 16 million, the relative risk figure doesn't change very much.

Dr. Chen noted that the total number of vaccinated cases detected is small: 7 cases, or 0.80 cases per million person-weeks.

Dr. Chen was asked about the statistical method used to calculate relative risk. Dr. Phil Rhodes explained that, in this study, the relative risk was controlled for age.

Dr. Chen recalled that in 1976, the conclusion of association was based not only on the elevated relative risk. The argument was that the onset interval was non-random, and in fact peaked in week 3. In the 1991 study, from passive surveillance, the peak was in week 2; this may have been due to recall bias, however. From active surveillance data across all sites, the peak was definitely not obvious. Therefore, the pattern found in active surveillance sites in 1976 was not found in the 1991 study.

Dr. Halsey asked how much analysis of these data has been done at CDC, suggesting that they are very controversial, as were the data in 1976. He asked whether the data will be further reviewed systematically before they are released.

Dr. Chen responded that he wanted to present more data before addressing this.

The 1976 study also looked at the prevalence of antecedent illness in the four weeks prior to GBS onset among vaccinated individuals compared to the unvaccinated. The argument was that flu vaccination substituted as a trigger for other antecedent illness as a cause of GBS. It was considered highly significant that relatively fewer vaccinated people had a history of antecedent illness. The 1991 study showed very similar numbers. (1976: antecedent illness in 33% of vaccinated vs. 62% in unvaccinated. 1991: antecedent illness in 31% of vaccinated vs. 77% in the unvaccinated.) However, a question may be posed about recall bias in the vaccinated, since these people already suspect vaccine as a cause, they may be less likely to recall other antecedent illnesses.

Looking at all passive surveillance data on vaccine adverse events, combining the public and private sectors and the different reporting systems from 1979-89, the range was 1-13 cases of GBS annually following flu vaccine, with mean and medium of 6. This year, 18 cases have been reported, 10 in the younger age group and 8 in the older group. Introduction of the VAERS reporting system coincided with the peak of flu season in 1990, however, which makes interpretation of the data difficult. This high number may be a reporting artifact, based on enhanced delivery of reporting forms. (More than 260,000 physicians received VAERS forms in the mail in October, 1990.)

Approximately 30 million doses were delivered this year; by chance alone, given different estimates of background rates of GBS, one would expect 45-85 cases within 6 weeks of flu vaccination; thus 18 may not be such an alarming number.

Dr. Chen summarized these findings by saying there was definitely no elevated risk in all age groups 18 and over. There was no elevated risk in the major target age group for flu vaccine. There may be a slightly elevated risk in the younger age group. Dr. Chen said he would argue that the antecedent illness and passive surveillance data lean slightly in favor of association, whereas the onset interval data probably do not. He acknowledged that, as Dr. Halsey pointed out, these data will be controversial.

Dr. Chen then contrasted the data with the 1976 swine flu findings, which showed elevated relative risk of 7.6 in all age groups. The highest was also in a younger age group: among 25-44-olds, the relative risk was 12.2. Dr. Chen said that, due to lower exposure and a smaller study, the data he presented could not so narrowly define the age groups. The attributable risk in 1976 was approximately 9 excess cases per million doses.

If the 1991 findings are real, the attributable risk is about 2.5 excess cases per million doses. Extrapolated for the country, this would have resulted in about 47 excess GBS cases. By contrast, using very conservative estimates for the 18-64 age group, flu vaccine would prevent 41-144 deaths and 680-1808 hospitalizations.

Dr. Chen also commented that these findings are based on small numbers, despite the investment of extensive resources. (Seven vaccinated cases in the 18-64 group; only one additional vaccinated case when the study was expanded by 7 million people.) He said that this study was perhaps at the margin of detectability of epidemiological methods.

These numbers are in the range of the original alleged attributable risk of encephalopathy after pertussis vaccine, which was also about 3 per million. An Institute of Medicine committee consulted with CDC on whether a study of encephalopathy following pertussis vaccination should be repeated in the U.S. After reviewing the evidence and a pilot study, the IOM committee concluded, that while perhaps technically feasible, the study would be logistically nearly impossible and would stretch the epidemiologic method to the breaking point. The IOM committee was also concerned that such a study would not be definitive. Dr. Chen said he felt this situation was very similar.

What are the lessons for future years of flu vaccination? Two independent data sources looked at the months when flu vaccine is likely to be given: The MSAEFI data (the adverse-event reporting

system, 1979-1990) and the HCFA Medicare claim data. The two reports are identical. What they show is that the bulk of the vaccine is given in a very short window. By the time the "alarm" came in December of last year, the horses were already out of the barn. Compounding the difficulty of timely alarm is the delay in onset of GBS and its lengthy hospitalization. Finally, efficient, unbiased case-finding is extremely difficult.

The assessment of association is perhaps most feasible in retrospect, and only by accumulation of data from multiple years. With flu vaccine, this will be difficult because the composition changes annually. In terms of vaccine safety monitoring, passive surveillance can only provide a signal; it cannot evaluate causality due to lack of controls.

Dr. Chen described a large, linked database system that is now in effect. In this type of database, computerized vaccination records, for example in an HMO, are linked with a computerized outcome database (inpatient, outpatient, ER, laboratories). With this as a cohort, it is possible to do nested case-control studies. There are built-in unvaccinated controls, person time, complete capture of exposure and outcome. A current contract with three HMO's involves following cases of adverse effects of all vaccinations through 7 years of age. With additional resources, follow-up could continue into adolescence and adulthood. Dr. Chen stated that an ACIP endorsement would be helpful. He also noted that rare outcomes like GBS will always be difficult to assess, even with large, linked databases.

Dr. Clements asked whether someone would present data on GBS in the armed services to be factored into the discussion. Dr. Chen and Dr. William Berg both addressed this, saying that, so far, there is no indication of elevated rate of GBS among people who went to the Middle East. Dr. Chen said that there is some argument that the military is intrinsically different because this population receives many more vaccinations; the GBS susceptible cohort may be exhausted earlier. Even the 1976 study did not find association in this group.

Dr. Halsey reiterated his earlier question about what is happening internally at CDC and what the next step is with these data. He suggested that CDC bring in some outside people, perhaps those involved in the 1976 study, to review the data in every possible way.

Dr. Chen acknowledged the potential volatility of the issue. Researchers worried that just launching the study would put the credibility of the vaccine in doubt. He said the group is putting the data together so it can be reviewed. He also stated that Dr. Schoenberger has been very involved from the beginning, giving the benefit of his experience. Many aspects of the

methodology directly addressed the criticisms of the 1976 study, for example, case review by an independent panel of neurologists. Dr. Chen agreed that another independent look at the entire process would be a good idea.

As a suggestion for future studies, Dr. Istre commented that a major deficit has been the lack of a good denominator in the younger age groups. He felt this was an issue in the study presented by Dr. Chen, given that the denominator for 18-64-year-olds was obtained through a telephone survey. The accuracy of this survey is unknown and the 14% vaccination rate may be an underestimate. Dr. Chen said this was a good point, remarking that this is a generic problem with adult immunizations.

Dr. Chen was also asked about the degree of agreement among the neurologists in case identification. He replied that the accord between the neurologists and the EIS officers in the field was very good -- about 90% of the cases rated by EIS officers as definite, probable and possible were so rated by the independent neurologists. Each case was independently reviewed by two neurologists. If there was a discrepancy -- even between a definite and a probable -- the form went on to two more neurologists who independently reviewed it again; then, all four met to reach a consensus.

There was then some discussion on whether the Committee wished to modify its statement regarding influenza vaccine. Several members commented on the benefit of the vaccine, compared to what seems to be a very marginal risk.

Dr. Nancy Cox of the Influenza Branch of CDC briefly updated the Committee on current surveillance. She commented that a press release, which was meant to encourage people to get their immunization this year, instead was interpreted in the media as a warning of a "killer flu on the way." Hence the Influenza Branch has received a tremendous number of phone calls from the media and the public. She said they had tried to quell the panic and simply encourage people to get routine immunization.

Predictions were based on the fact that it is most likely that H3N2 will circulate this year. One H3N2 Beijing-like virus has been identified in a 6-year-old in New Orleans. Baylor has also reported an H3N2. In addition, 2 Taiwan-like H1N1 viruses have been identified. There are reports of influenza B, but no isolates have been received. Last year's surveillance was summarized in a handout.

Dr. Katz asked for a decision from the Committee on whether the statement on influenza vaccine should be changed; no changes were proposed.

Japanese Encephalitis Vaccine

Dr. Ted Tsai presented information and a draft statement on Japanese encephalitis vaccine. The FDA will meet to discuss Biken's application for licensure in three weeks. The vaccine was previously available in the U.S. on an investigational basis from 1983-87, through travel clinics in collaboration with CDC. Licensure is being sought because of increasing numbers of travelers to Asia as well as to accommodate the military.

Dr. Tsai asked the ACIP to consider three points: The primary immunization schedule and the need for boosters; an apparently new pattern of adverse reactions; vaccine usage.

Japanese encephalitis (JE) is the leading cause of viral encephalitis in Asia. The 50,000 cases reported annually (in the Peoples' Republic of China, Korea, Japan, Southeast Asia, the Indian subcontinent and parts of Oceania)is undoubtedly an underestimate.

The virus is transmitted among certain culex mosquitoes to wading birds and to pigs, which are the principal vertebrate amplifying hosts. These mosquitoes are prolific in the flooded rice fields of Asia's rural areas. With piggeries adjacent to human dwellings, all elements of the viral transmission cycle are present "in the backyard."

Only 1 in about 200 infections leads to clinical neuroinvasive disease; however, illness is usually severe. 25% of the cases are fatal with an equal number of survivors having serious neurologic sequelae.

JE acquired during the first and second trimesters of pregnancy leads to fetal death and abortion. No ill effects have been reported with infection in the third trimester.

Risk for travelers is generally low. Since 1981, 7 cases of JE have been reported among travelers or expatriates. Of those, 4 were military personnel or dependents. In order to put some sort of denominator on this, Dr. Tsai presented Department of Transportation figures on the number of travelers to Asia over the past 5-6 years. Two to three million people fly to Asia each year. Based on these rough figures, one can estimate a risk of less than 1 case per million travelers per year.

An alternative estimation of risk may be obtained by examining incidence rates in a hyperendemic area, assuming a high estimate of 1 case per thousand per year and recognizing that transmission is limited to about 5 months out of the year. The monthly risk then is 1:5000; weekly risk is 1:20,000.

Risk is highly variable. There was one case where a child who traveled for only two weeks in Bali, making infrequent excursions into the countryside, acquired JE.

A single efficacy trial has been reported. This study was done among Thai children. It showed that two doses (given a week apart) of either the commercially available monovalent vaccine (produced from the Nakayama strain of JE virus) or a bivalent vaccine (also containing the Beijing strain) were equally efficacious in protecting against JE. Two cases were seen in the vaccinated groups (one after monovalent vaccine, one after bivalent); 11 were seen in the placebo tetanus toxoid group. Vaccine efficacy was therefore 91%.

An earlier field trial was done in Taiwan in 1965 with a prototype of the current vaccine. Vaccine efficacy was 80% when two doses were given. One dose was not efficacious.

Although these two trials and the vaccination regimen used in Asia consists of two doses in the primary schedule, immunogenicity studies conducted among U.S. citizen and British subjects showed that two doses were associated with seroconversion in fewer than 80% of vaccines. Three doses led to seroconversion in 88% - 100% of vaccines. The geometric mean titer associated with the three-dose schedule was about four-fold higher.

In a CDC study comparing distribution of neutralizing antibody titers in two-dose recipients to recipients of a three-dose series, 77% of two-dose recipients seroconverted (developed neutralizing antibody titers of 1-to-8 or greater). Among recipients of three doses, 99% seroconverted. The respective geometric mean titers were 28 and 141.

A second drawback of the two-dose immunization schedule is that 6-12 months later, only 29% of the vaccines retained a neutralizing antibody titer of 1-to-8 or greater. The geometric mean titer of seropositive individuals was 47. Almost three-quarters of them were seronegative.

Based on these data, and other suggestions that better seroconversion rates were obtained when vaccine doses were given further apart, the Army conducted a comparison of three-dose schedules. A short schedule of day 0, 7 and 14 was compared to compared to a longer schedule of day 0, 7, 30. All vaccines in both schedules seroconverted. However, the geometric mean titer associated with the longer schedule was about seven-fold greater (692 versus 104 on the day-60 bleed.)

Based on these data, the proposed recommendation for primary immunization is for a 3-dose schedule on day 0, 7, and 30.

When it is impossible or inconvenient for travelers to adhere to this schedule, the abbreviated schedule of day 0, 7, and 14 is an acceptable alternative.

Dr. Tsai then reviewed available data on the longevity of neutralizing antibody following primary immunization. In a one-year follow-up of soldiers in the Army trial mentioned previously, 6 to 12 months after primary immunization, there was no significant decline in neutralizing antibody levels. Unfortunately, there is no follow-up data beyond one year.

A booster was given at this point, and five months later the geometric mean titer increased almost fifteen-fold.

Dr. Tsai also presented data from Japan, illustrating the fall of neutralizing antibody after a two-dose schedule. Under this regimen, it was appropriate to give a booster at one year. This is how the vaccine is used in Japan and elsewhere in Asia. It is less clear when a booster should be given after a three-dose primary immunization series.

Dr. Tsai said that in terms of the draft of the recommendation, a comment had been made on the proposed recommendation for boosters. A proposed revision would be to say that insufficient data are available to make a recommendation on when boosters should be given, and that when necessary among travelers, expatriates or soldiers who may be exposed for a prolonged period, serologic monitoring after one year may be in order.

Dr. Tsai then invited discussion of the proposed immunization schedule. He was asked how available serologic monitoring would be. He said this would probably be done at the CDC laboratory at Fort Collins. A screening neutralization test would look for antibody above 1 to 10. He indicated that a new pattern of adverse reaction was causing concern about giving doses unnecessarily.

When the question of efficacy was raised, Dr. Charles Hoke, who did the study in Thai children in 1985-86, addressed the two cases of what might be called vaccine failures. These two cases of encephalitis were clinically indistinguishable. Because of the size of the study, it was not possible to do blood samples of all the vaccine recipients. These two children were not among the cohort of 1500 from whom blood samples were taken. It is possible that these were vaccine failures; however, this was a two-dose regimen and the current recommendation calls for three doses.

Dr. Tsai then discussed adverse reactions to the vaccine. He said that, until recently, JE vaccine had been associated with a low and predictable rate of mild local and systemic adverse reaction. About 20% of vaccines reported some local reaction,

consisting mainly of local tenderness, pain and redness. (A large trial, reported by Sanchez, among U.S. soldiers, reported a higher rate of 23%.) Mild systemic reactions are reported in about 10% of vaccines, consisting primarily of fever, headache, myalgia, chills, and gastrointestinal complaints.

Because the vaccine is prepared from mouse brain as a starting material, there has been concern about the possibility of vaccine-related neurologic complications. Dr. Tsai presented data from Japan, whose adverse reaction reporting system relies on sentinel hospitals and clinics. Over a more than thirty-year observation period, there has been a fairly consistent low rate of neurologic complications temporally associated with immunization; however, there are no control group observations for comparison. The rates are less than 5 per million.

Although the starting material of the vaccine is mouse brain, the manufacturing process exhaustively purifies the brain suspension. The myelin basic protein content of the final product is controlled below 2 ng/ml, which is well below the concentration or quantity of neurologic material needed to produce experimental allergic encephalomyelitis in guinea pigs.

On the basis of these data and the manufacturing process, there has been no suggestion of neurologic complications.

Dr. Broome asked what kinds of neurologic complications have been reported. Dr. Tsai said that these include convulsions, paralysis, weakness, as well as meningitis and encephalitis.

Dr. Tsai went on to present data on an apparently new pattern of adverse reactions, published in Lancet and reported by the State Serum Institute in Denmark. Additional reports also came from Canada and Australia. The reactions consisted primarily of generalized urticaria and/or angioedema. The angioedema varied in severity from a slight swelling of the lips and face, to one case requiring resuscitation with epinephrine.

In addition to generalized urticaria and angioedema, three patients from Denmark had associated problems, arthralgias and arthritis, and one case had both urticaria and erythema multiform. Potentially related adverse reactions also were seen in one patient who had erythema multiform alone and another patient who had erythema nodosum.

Dr. Tsai pointed out that, with the exception of the one patient who needed epinephrine, all of the other cases recovered rapidly with steroids and/or antihistamines.

Taking cases of generalized urticaria or angioedema alone, 22 of the 24 developed these adverse reactions after receiving the second or third dose of the vaccine. It is known that at least 13 of the patients reporting these adverse reactions received JE alone.

The incubation period between vaccination and onset of symptoms ranged from 12 hours to 3 days. In most patients, there was a considerable delay, with a median of 2 days. In view of this interval, the clinical immunology consultants have suggested that this set of adverse reactions are most appropriately called delayed generalized systemic reaction or delayed anaphylaxis.

Dr. Tsai then presented data that suggest this pattern of reactions may be new for JE vaccine. From October, 1983 to October, 1989, no cases of urticaria or angioedema were reported through the established adverse reaction reporting systems to the State Serum Institute in Denmark. Between November, 1989, and June, 1991, 19 such cases were reported, a highly significant difference.

In Australia, all seven such cases of adverse reactions were reported after June, 1990, although the vaccine had been distributed there since 1987.

However, in retrospect, there appear to have been similar adverse reactions reported in the United States in the CDC trial conducted between 1983 and 1987. During this time, when CDC was distributing the vaccine under IND, there were two cases with allergic-like reactions. One patient developed generalized anaphylaxis five minutes after receiving the first dose of vaccine. In the second case, generalized urticaria occurred seven hours after the first dose.

Discussing the data on generalized systemic reactions following JE vaccine, Dr. Tsai pointed out that rates of reaction (by lot) varied quite a bit; however, most of this variation can be explained by the circumstances of surveillance and the circumstances under which the vaccine was given.

The two travel clinics (Fairfield Hospital in Australia and University of Calgary in Canada) reported the highest rates, from 50 to 104 per 10,000. The national surveillance systems in Denmark, Sweden, the United Kingdom and Australia, reported rates ranging from .7 to 12 per 10,000.

Dr. Katz asked why such large numbers of the Danish population had been vaccinated. Dr. Tsai explained that in Denmark there has been a very liberal policy of immunizing travelers. Whereas in the U.S. the JE vaccine was available under IND and was

advised only for travelers going to rural areas during the transmission season and staying for two weeks or longer, no such restrictions were used in Denmark.

Dr. Susan Tamblyn commented that when the University of Calgary data were presented at the International Travel meeting, data were also presented from the largest Canadian travel clinic. The two showed quite discrepant results. The clinic which handles the bulk of the vaccine saw extremely low rates of adverse reactions. (The vaccine, which is not licensed in Canada, is made available through the emergency drug release program.)

Dr. Tsai was asked whether there have been any investigations of those lots of vaccine that had higher rates of adverse events. He answered that Mike Hensley from Connaught is in Japan now, examining the quality control records of the lots presented in the data. One of the problems is what to consider a control lot, ie. lots not associated with adverse reactions. About 80% of the vaccine production goes to Thailand and Sri Lanka; although an effort has made to obtain reports on adverse reactions from those two countries, no information has been received. Those countries have made no reports to Biken.

Dr. Tsai went on to say that there have been 34 lots produced since April, 1988. Eight of them have been implicated in adverse reactions. Of the remainder, 21 were distributed exclusively to Sri Lanka and Thailand. Therefore there is no data on whether these lots have been associated with a similar pattern of reactogenicity. There has been some preliminary investigation into the protein content of vaccine, but again, the problem is the lack of control lots.

Dr. Katz asked whether children are routinely vaccinated for JE in Japan. Dr. Tsai said that only about 10% are vaccinated.

Dr. Tsai said that, at this point, constituents associated with this pattern of reactogenicity have not been defined, and epidemiological and laboratory studies have been proposed in collaboration with the Danes, the Australians and others. The purpose is to define risk factors among vaccines for developing this kind of adverse reaction, and to do laboratory studies to identify the allergin or manufacturing processes associated with the reaction.

Dr. Halsey asked about the risks of a three-dose regimen, and whether those rates are higher than those for a two-dose regimen. Dr. Tsai referred to a table in the draft statement, which actually showed lower rates of reported local and systemic reactions after three doses. He went on to say that the pathogenicity of the reaction is not yet understood.

The Committee briefly discussed the intended use of the vaccine by travelers. Dr. Tamblyn commented on the explanation of risk at the top of page 7 of the draft statement. She felt the risk for travelers needed to be more narrowly defined. There have been problems in the past with availability of vaccine, and figuring out who is truly at risk.

Dr. Tamblyn said that a letter to the editor of Lancet, (October 5, 1991, included in the supplementary materials distributed to the Committee) stated that use of JE vaccine has been suspended in Australia pending investigation of adverse reactions.

Dr. Broome said that she had the opportunity to talk with the Danish investigators at a recent meeting. She said their surveillance system has been quite consistent for a number of years, during which large numbers of doses of vaccine have been used. They have, as Dr. Tsai reported, seen a dramatic increase in these reactions (urticaria, angioedema) in recent years. She commented that this might be more an area for the FDA, but that to try to figure out what has changed with the vaccine is a central issue.

In terms of the usage statement, Dr. Tsai said that because there has been at least one case of JE in a traveler with a very short period of exposure, he found it difficult to arbitrarily define a minimum time period of travel for which immunization was recommended. He said he made the time period deliberately vague, leaving the decision up to the traveler and his physician. The recommendation was phrased as "for travelers at high risk," defining high risk as travel to a developing country, during the transmission season, travel in rural areas, for an extended period. Risk is also associated with extent of outdoor activities, age and pregnancy. Alternatives to immunization include use of repellents, and reduced exposure to mosquitoes.

Dr. Katz said he felt the Committee needed more time to review and discuss the materials under consideration. Questions to be answered include for whom the vaccine will be recommended, and with what sort of caveat. Concerns about reactions also need to be addressed. Dr. Halsey asked that data be broken down by age.

Dr. Tamblyn commented that the Biken package insert contains a "scary laundry list" of additional precautions, for which no data have been presented. She said Biken had been contacted for these data, but nothing had been received to date. A comment was made that this may have been a translation problem; no data have been available to support these precautions.

Dr. Bart felt that the Committee should wait until after the FDA meeting, so that the results of that meeting could be part of ACIP's deliberations. He doubted that licensure would be immediately forthcoming.

A sub-committee was proposed. Dr. Katz appointed Dr. Michael Peterson, Dr. Mary Wilson, Dr. Susan Tamblyn and Dr. Carolyn Hardegree to that committee. Dr. Wilson was appointed chair. Dr. Ted Tsai at Fort Collins will serve as liaison.

Dr. Broome then updated the Committee on statements currently in press. She said that the adult immunization statement should be out by the end of October. The hepatitis b statement should be out before the end of the year. She said this was the current MMWR schedule. She also said that there had been continuing discussion with the editor of the MMWR about what would be the most user-friendly format for the statements. She asked Committee members to think about this for the next meeting, and to consult with their constituents. Some of the format changes have already been made: inclusion of a summary statement and compilation of recommendations in one place. Length has also been an issue, as well as level of supporting documentation. Should these be very inclusive documents, or more abbreviated?

Dr. Katz also asked that as much information as possible be mailed out in advance of the ACIP meeting. He also suggested leaving material at the Emory Inn, where most members stay, the evening before the meeting begins. This would increase the Committee's efficiency.

Rabies Update

Dr. Dan Fishbein gave a brief presentation on rabies, which was added to the published agenda. Dr. Fishbein described three recent rabies cases in humans, which will be reported in the MMWR. He said discussion of exposure in one of these cases needs to be consistent with ACIP recommendations.

By way of background, Dr. Fishbein explained that rabies in the U.S. fell sharply during the 1950's, due to improved control of dog rabies. There was an unrelated rise of cases in other animals. There was very little change in the number of human rabies cases associated with the introduction of human rabies vaccine.

Monoclonal antibodies have been used to identify a number of different strains of this virus. Generally, domestic animals are infected by wild animals.

The majority of the wild animal cases in the U.S. are in skunks and raccoons. Typically, in 1990, out of 4,878 cases of animal rabies, bats made up slightly less than 15%. While there may be local episoadics of infection in other wild animals, bat rabies is everywhere, in all contiguous 48 states, every year, to a low degree.

In terms of the epidemiology of human rabies, there has been a fall in the number of domestically acquired cases, and an increase in the late 1970's and 1980's in imported cases. (Imported cases can either be Americans exposed outside the U.S. or people from other countries who happen to develop rabies while in the U.S.) In addition to these presumably dog-related cases that were imported, there have been some wild animal cases.

In 1991, for the first time since 1984, there were 3 cases. This is the first time since 1979 that cases were acquired in the U.S.

The first of the three, and the most recently reported, was a 27-year-old woman who lived in rural north Georgia. No bite exposure was reported by the patient. Monoclonal antibody analysis revealed that she was infected by the strain found in the silver-haired bat. The only reported "exposure" was that her boyfriend killed a bat with his foot some six weeks before she became ill.

In the next case, most pertinent to the ACIP, a 29-year-old male, who lived in an abandoned house in Arkansas, awakened when a bat landed on his face. He and his girlfriend looked for a bat bite or scratch but found nothing. Three weeks later, he developed classic rabies. The same strain was found through monoclonal antibody analysis as was found in the Georgia case. There was a great deal of uncertainty about exposure in this case; conflicting reports by friends said he had been bitten.

In the third 1991 case, a 55-year-old woman living in south Texas on the U.S.-Mexico border, had no reported exposure to rabies. However, the county in which she lived was experiencing a raging epizootic of dog and coyote rabies. Some of the animals on the farm where she lived had died recently under suspicious circumstances but had not been tested for rabies. There was no report of a bite or exposure; however, monoclonal antibody analysis showed the dog and coyote strain that was circulating.

Dr. Fishbein said that half of the 16 cases reported in the U.S. since 1981 have had no recognized exposure to the disease. If imported cases are excluded, there are seven cases. Five of these are due to exposure to bats; in 4 out of 5 cases, there was no reported bite.

None of these people consulted a physician or a health department.

Generally bat-related human rabies is caused by the silver-haired strain, although rabies in other types of bats has also been reported. However, the silver-haired bat does not make up the majority of animal isolates.

The current ACIP statement says that if no bite or scratch is found, treatment is not needed. Dr. Fishbein asked to extend the recommendations for post-exposure prophylaxis to include patients like the man in Arkansas. Still excluded would be the many people who merely see a bat, but have no bite or non-bite exposure. Suggested wording was: "Since the size of bites by bats may be small in comparison to those inflicted by terrestrial animals, it may be prudent to consider postexposure treatment for patients reporting physical contact with bats even if a bite cannot be positively identified."

Dr. Tamblyn asked whether mucus membrane exposure had been ruled out in the Arkansas case. This would fall within standard guidelines. Dr. Fishbein said that although none was reported, this may have occurred. Dr. Tamblyn felt the wording was very broad, and would include people who pick up a bat to dispose of it, who kick it, etc.

Dr. Halsey felt the wording should indicate direct physical contact either with skin or mucus membrane with live bats.

Several people expressed concern about health departments being inundated with calls on possible exposure in dead bats, or other dead animals. Calls about picking up dead bats were reportedly quite common.

Wording was changed to "patients reporting direct physical contact with skin or mucus membranes by bats or when a bite or mucus membrane exposure cannot be excluded."

Dr. Katz announced the dates for upcoming meetings: February 12 and 13; June 9 and 10; October 21 and 22, 1992.

National Vaccine Program -- Injury Compensation Program

Dr. Ken Bart reviewed what has happened since the National Vaccine Advisory Committee's White Paper, presented to Dr. Mason in January. There have been several meetings, as well as various activities in the legislature and in the private sector.

Dr. Bart described this as a watershed year, with immunization discussed in many forums with unprecedented interest and intensity. The measles epidemic which engendered the White Paper is seen in fact as a symptom of the primary health care system, and the problems of access to children, especially reaching high-risk children at the appropriate age. The public sector delivery system was found to be non-user-friendly. In addition, there were barriers both in policy and management, resulting in substantial reduction in coverage.

For the benefit of new members, Dr. Bart outlined the three use committees: The ACIP, the FDA, and the Committee on Infectious Disease of the Academy (Red Book.) The two policy committees for immunizations are the National Vaccine Advisory Committee, established to advise Dr. Mason and the National Vaccine Program on immunization, and the Advisory Committee on Childhood Vaccines (ACCV), the advisory body of the National Vaccine Injury Compensation Program.

Dr. Mason made the comment, before one use committee, "If we can't deliver immunizations effectively, what can we deliver?" This rhetorical question was a rather serious indictment of the current situation.

The responses to the White Paper in the public sector were many. CDC for some time had been aggressively addressing the issues in the paper, with efforts like its infant immunization initiative. The most specific response was directed by Dr. Mason and involved the formation of an interagency committee on access to immunization. Set up in February, it includes four departments and 13 agencies throughout the Public Health Service, the Department of Health and Human Services, as well as the Department of Agriculture, Housing and Urban Development and the Department of Education. This effort has become known as the strategic response not only to the measles epidemic, but to the delivery system problems as well.

This response was incorporated into both the 1992 and 1993 budget processes.

In the private sector, a number of groups have become involved, including the Academy of Pediatricians, the Children's Action Network, and IEAC, an education and action committee from CDC, coordinating some 40 community-based agencies.

There have been hearings in Congress in both the Senate and the House and for the first time the President's budget reflects an emphasis on prevention. Either a $60 or an $80 million dollar increase over 1991 for immunization specifically has been proposed.

The White House also conducted a ceremony to kick off a series of city visits, again, drawing national attention to the immunization issue.

There are three committees of the National Vaccine Advisory Committee working from the White Paper, looking at problems of access. They have spoken with representatives of labor, manufacturing, insurance, and Medicaid, and will publish a report by the end of the year.

A committee on licensure and regulation is working with the FDA. Another committee is working on the requirement that a national plan for this decade be enunciated.

Four evaluation studies are being done: The follow-on to the Institute of Medicine study on pertussis and adverse events; review of the vaccine information pamphlets; assurance of vaccine supply; package inserts.

Dr. Bart also described the Children's Vaccine Initiative. In September of 1990, there was a world summit for children. Some 70 heads of state met in New York, under the auspices of UNICEF. The purpose was to bring the issues of those who are most vulnerable to the attention of world leaders. A recommendation was made to improve the access to children, to ensure that the world's immunization programs are sustainable. This means simplification of immunization schedules, reduced numbers of doses, earlier immunization, consideration of maternal immunization, new combinations of vaccines, etc. This may seem to be only a vision, but it is based on real concerns.

Injury Compensation Program

Section 312, the report provided by the Institute of Medicine by statute, was in response to a request for a review of the state of knowledge on the adverse events associated with pertussis and rubella. This report has stratified events in the literature into four categories, looking for causes of specific adverse events, in order to provide a taxonomy on which a compensation program can be effectively based.

Dr. Bart reported that Dr. Mason formed a task force to review that report, and that task force has made recommendations to him. He has requested a scientific peer review of these recommendations, scheduled for November 8.

Dr. Bart presented the summary of current adjudications: To date, there have been 4,241 claims submitted to the National Vaccine Injury Compensation Program. This program was intended to be a no-fault, non-adversarial, non-tort compensation system which would facilitate the compensation of children who had been injured as a result of having received mandatory vaccines.

Funding was set up to differentiate between retrospective and prospective claims (relative to when the National Childhood Vaccine Injury Act went into effect.) 4,095 retrospective claims have been filed, some 3000 of those after a major advertising effort by the Injury Compensation Program in FY 1990.

There have been 146 claims filed post-legislation, ie. since 1988. The filing period for prospective claims is three years, and is not yet complete. There have been 644 claims adjudicated,

of which 244 were perceived as compensable. 344 claims were dismissed (most of which were retrospective), and 76 were deemed non-compensable.

CDC has maintained a surveillance system over the last few years of claims that have come to manufacturers. It is believed that an effective immunization program will require an effective compensation program. In the decade prior to this legislation, the numbers of litigations rose rapidly (255 claims against manufacturers in 1985-86); prices of vaccine went up and manufacturers left the marketplace. If the program is to work, one would expect that claims would no longer be filed against manufacturers. In 1990, fewer than 20 claims were made directly to manufacturers. Hence the legislation may be having the desired impact.

Dr. Walter Orenstein reported on surveillance done in cooperation with DTP manufacturers -- Lederle/Praxis, Wyeth, Connaught. In terms of law suits filed against them by year, in 1980, there were four law suits filed. The major adverse publicity on DTP began in 1982. By 1986, when the act was signed, there had been 255 law suits filed. Since then, the number of suits has dropped dramatically, to a total of 19 in 1990 against the three manufacturers.

Dr. Bart then explained that there is a concern about availability of resources to ensure compensation for retrospective claims. Post-1988 compensation is dependent upon an excise-tax-based trust fund. Retrospective claims are "funded" by an appropriation of Congress, which has been $80 million per year over the three-year life of the legislation. To date, the 255 awards have totaled $158 million. With the mean compensation being $1.2 million, a conservative estimate is that it would take $2.6 billion to compensate all 4000 claims. It is clear that the current $80 million per annum for three years is inadequate. Solutions are under discussion in Congress.

Another concern is the appropriateness of the injury table in the aids to interpretation, and whether it is fully based on science as a determinant for causation and therefore the basis of compensation. This is the basis on which the IOM report will be reviewed.

In terms of the budgetary allotment for the National Vaccine Program, the House has voted additional program resources. The Senate is less convinced. The Senate proposed $2.3 million, basically the operating costs of the National Vaccine Advisory Committee and a number of evaluative studies in the office. The House proposed $12.5 million, the additional monies being for program resources to be used as catalytic money to be used by agencies for high-priority, unmet needs.

Dr. Jackson asked about the adjudication process, and whether any of the 19 suits that still stand come from individuals who have decided to go straight to the company. Dr. Orenstein said he was unaware of any who had been through the program. Up until January 31, people with retrospective claims had a choice of a litigation process or they could go into the compensation program. If one goes through the compensation process, and is awarded money, one has the option of accepting or not accepting that settlement. Once the settlement is accepted, one is not allowed to then sue the manufacturer.

Federal Implementation of ACIP Recommendations

In the interest of time, Dr. Walter Orenstein simply reviewed the current status of federal funding.

Dr. Broome and the Committee then recognized Leona McMeans for her assistance to the ACIP before and during the meeting.

Infant Immunization Initiative

Dr. Roger Bernier asked the Committee to review the draft statement on Model Standards for Immunization Practices and submit comments within several weeks.

Dr. Bernier traced the effort to improve vaccine delivery, from the early days of childhood immunization under Secretary Califano and the launching of the measles elimination program, to the period in the mid-80's with low measles morbidity, to the recommendation for two doses by ACIP, to the infant immunization launched by CDC in 1990, followed by the White Paper.

During the period described by Dr. Bart, 1991, there are several guiding documents. One was the original plan for the infant immunization initiative, calling for action in five areas: service delivery, assessment, information/education, operations research, surveillance. The measles White Paper, alluded to by Dr. Bart, contained 13 recommendations, 10 of which pertain not just to measles, but to other vaccine-preventable diseases. The last document was the action plan mentioned by Dr. Bart, the product of the interagency committee convened by Dr. Mason. It includes more than 100 action steps for federal activities.

Since the White Paper was released in January, there have been numerous meetings and unprecedented attention at the highest political levels. There has also been a campaign by Secretary Sullivan to visit six cities and help unveil local plans for the implementation of the goal to reach 90% coverage in two-year-old children by the year 2000.

One of the recommendations in the White Paper was to develop new standards for immunization practices. They've been in

development since the spring and hopefully will be completed by the end of the year and released under the auspices of the National Vaccine Advisory Committee.

Dr. Katz asked why the year 2000 was set as a goal for 90% coverage. Dr. Bernier said that in his opinion, the solution to this problem will require such fundamental changes in the delivery system, that at least that many years will be needed. He stated that converting this to a user-friendly system is no small undertaking.

Dr. Katz said that in his travels he observed a much better job being done in terms of immunizations in southeast Asia, with far fewer resources because there is a commitment and a high priority given to the needs of children.

Dennis O'Mara, chief of the Program Operations section, Program Services Branch, within the Division of Immunization, and Dr. Vance Dietz briefly described a set of model standards for immunization practices. Mr. O'Mara acknowledged the work of the other members of the in-house work group, Drs. John Mullen and Roger Bernier.

Mr. O'Mara said that many authors have proposed models to address the problem of delivering immunization services. One of the most appropriate involves the relationship of consumers (parents and their children), providers and systems. Barriers in each of these components contribute to the low coverage levels in pre-school age children.

Problems at the consumer level relate to the behavior patterns of the parents (knowledge and attitude towards immunization and preventive health-care in general.) Although consumer-oriented issues appear important, failure to vaccinate may also be due in large part to barriers within the immunization delivery system, and to barriers created by providers within the system.

Examples of barriers at the system level include unnecessary prerequisites for the administration of vaccines, such as requiring appointments rather than offering walk-ins. In many clinics, immunization services are not offered daily. Clinics may operate only part of the day. Long waiting periods and pre-immunization physicals can also act as barriers.

Providers create barriers by failure to take advantage of all contacts children have with the system. Missed opportunities can be divided into two categories: Providers fail to screen and vaccinate children who have come in for other reasons; providers don't always give all the vaccines for which a child is eligible

on a particular immunization visit. This is due to a lack of understanding of contraindications, or failure to understand or accept the recommendation for simultaneous administration of different vaccines.

To achieve the goal of 90% coverage by the year 2000, the approach to the delivery of immunization services will have to be changed. Ideally, this objective would be reached within the context of comprehensive child health care. Nevertheless, one can't afford to wait for the current delivery system to extend this type of comprehensive care to the entire eligible population.

To address the immediate issue of under-immunization, NVAC has recommended the development of standards for immunization practices. These are intended to provide guidance on how to eliminate barriers at the system and provider levels. They are directed to all health professionals who are actively involved in the administration of vaccines or the management of immunization clinics.

In many locations, the standards may represent an ideal against which managers can compare their current operations, and thereby quantify the resources they will ultimately need to meet the objective.

Mr. O'Mara asked the ACIP to pay particular attention to the summary of true and false contraindications, included as part of the draft statement. He invited their comments on both the content and the language.

Dr. Dietz then briefly discussed the development of the standards, their evaluation and impact. The development of the standards involved input from 24 health-care agencies. They have given their opinion on who the audience should be, which issues should be addressed, what the actual content and format of the standards should be. They have also critically reviewed the comments received from the first two drafts.

The physician community is represented by four agencies, including the American Academies of Family Physicians and Pediatrics, the American College of Emergency Physicians, and the AMA. Five nursing organizations have also participated.

A number of public health organizations with representatives on the working group have reviewed the document. Representatives from seven health care administration organizations have also reviewed the document (representing such diverse groups as those involved in maternal and child health, primary health care, Medicaid, and migrant health issues.)

Furthermore, the document has been distributed to all 63 state immunization project directors, who have in turn distributed it to both public and private providers.

Dr. Dietz reported that, to date, the reaction has been very positive. The opinion is that the standards are both very relevant and necessary. The guide to contraindications has also been very well received.

There have also been several criticisms. Originally, the standards were distributed without the qualifier "model." Some reviewers did not approve of the use of the word "standards," and preferred the word "guidelines." Several people noted that the lack of available resources would prevent many providers from complying. Several state immunization project directors had concerns that inability to comply with federally mandated standards would make them liable for providing substandard services.

It was therefore decided to add the qualifier, to acknowledge the standards address the ideal for which to strive.

A concern was raised that the development of standards for immunization services somehow implies that immunizations are more important than other child health services. Reviewers pointed out that although the resurgence of measles is a marker for problems within the immunization delivery system, more important, it is a marker for problems within the entire national health-care delivery system. Some have argued that instead of a vertical approach addressing one service, a more horizontal approach is needed to ensure adequate, comprehensive, child health-care throughout the nation.

The work group agrees with the need for this comprehensive care, but believes that the present immunization system requires immediate change.

The other question which came up was whether the standards should be addressed to the public sector, the private sector, or both, and whether there should be one set, or two sets of standards. After reviewing the comments, the work group is considering one set addressed to both sectors.

Two immunization model demonstration projects are being implemented, using the standards as a core. These are in Albuquerque and San Diego. The impact of the standards on immunization coverage will be evaluated.

Dr. Dietz again invited the Committee's comments on the standards.

Dr. Thompson asked the Committee to consider whether it is offering a model, which may or may not be followed, or standards, which are basic, and which then can be used as means of obtaining the resources necessary to meet the standards.

Dr. Dietz said there will be a continuing opportunity to discuss this point.

It was acknowledged that the balance between idealism and realism is a fundamental issue. The intent is not to make the standards so idealistic that there is no hope of achieving them, nor so realistic, that what is described is minimal, or the lowest common denominator.

Dr. Katz said that the goal should be to set ideal standards which then become realistic. There needs to be an incentive to close the gap.

Dr. Thompson said that one public health district in Mississippi, a poor rural district, has already reached the goal of 90% coverage. It can be done.

Dr. Halsey seconded the opinion that goals can be set which at first seem unachievable, citing program for the eradication of polio. Without goals, people won't strive, and even if those goals can't be met immediately, deadlines can be set.

Dr. Katz wrapped up the meeting by asking Dr. Broome to help him prepare a letter to be sent out to the members within the next week, reiterating assignments, dates of the next meeting, working group members, goals, liaisons, and other issues needing a timed response.

The meeting was adjourned at 12:35 P.M.

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, M.D., Chairperson

Date: 11 May 1992