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

MINUTES OF MEETING

Immunization Practices Advisory Committee
February 27-28, 1990
Decatur, Georgia

The Immunization Practices Advisory Committee (ACIP) met in the Decatur Conference Plaza of the Holiday Inn, Decatur, Georgia, on February 27-28, 1990. Those in attendance are listed below:

COMMITTEE MEMBERS PRESENT

Dr. Samuel L. Katz, Chairman
Dr. Stanley E. Broadnax
Dr. James D. Cherry
Dr. David W. Fraser
Dr. W. Paul Glezen
Dr. Caroline B. Hall
Dr. H. Denman Scott
Dr. Mary E. Wilson

Ex Officio Members

Dr. Carolyn Hardegree (FDA)
Dr. Paul Albrecht (FDA)
Dr. John R. LaMontagne (NIH)

Liaison Representatives

Dr. David Fedson (ACP)
Dr. Edward A. Mortimer, Jr. (AMA)
Dr. Michael Peterson (DoD)
Dr. Stanley A. Plotkin (AAP)
Dr. William Schaffner, II (AHA)
Dr. Susan E. Tamblyn (NACI)
Dr. Ronald C. Van Buren (AAFP)

Executive Secretary

Dr. Mary E. Guinan

HHS STAFF PRESENT

CENTERS FOR DISEASE CONTROL

Office of the General Counsel

Mr. Kevin M. Malone

Epidemiology Program Office

Dr. Melinda Wharton

Center for Infections Diseases

Dr. Miriam Alter
Dr. Paul Blake

CENTERS FOR DISEASE CONTROL

Center for Infectious Diseases (continued)

Dr. Claire Broome
Dr. Nancy Cox
Dr. Louisa Chapman
Dr. Michael Davidson
Ms. Susan Good
Dr. Daniel Fishbein
Dr. James Hughes
Dr. Harold Margolis
Dr. Steven Ostroff
Dr. Helen Regnery
Dr. Lawrence Schonberger
Dr. Margaret Tipple
Dr. Ted Tsai
Dr. Diana Wells
Dr. Jay Wenger
Dr. Bradley Woodruff

Center for Prevention Services

Mr. Kenneth Anderson
Dr. Roger Bernier
Ms. Rosamond Dewart
Dr. Steve Cochi
Dr. Karen Farizo
Dr. Laura Fehrs
Mr. Conrad Ferrara
Dr. Jacqueline Gindler
Dr. Alan Hinman
Dr. Sonja Hutchins
Dr. Mary Lou Lindegren
Dr. Laurie Markowitz
Mr. John Mullen
Dr. Walter Orenstein
Dr. Peter Patriarca
Mr. Bob Snyder
Dr. Mary Ann Sprauer
Dr. Raymond Strikas
Dr. Roland Sutter
Mr. Ron Teske
Dr. Walter Williams

NATIONAL VACCINE PROGRAM OFFICE

Dr. Yuth Nimit

Others Present

Dianna Ball
Fred Capilupo
Dr. Pinya Cohen
Tony Deahl
Dr. Corry Dekker
Dr. Bruce Dull
Dr. Teryl Frey
Dr. Jill Hackell
Mike Hensley
Dr. Gregory R. Istre
David M. Konys
Dr. Raymond Kuehne
Dr. Saul Krugman
R. Steven Lang
Suzanne Laussucf
D. K. McClintock
Ellen McGuire
Mr. George Moonsammy
Wayne Morges
Dr. David Nalin
Peter Paradiso
Dr. Roselyn J. Rice
Marie Rosenthal
Bob Scott
Karlyn Shedlowski
Gregory Slusaw
L. Stocco
Col. Ernest T. Takafugi
Dr. Aubrey Tingle
Bill Wainwright
Dr. Jo White
Dr. Rafal J. Wyszkowski
Dr. John Zahradnik

IMMUNIZATION PRACTICES ADVISORY COMMITTEE
Meeting at
Holiday Inn - Decatur Conference Plaza
Mary Gay C Conference Room
Decatur, Georgia

AGENDA

Tuesday, February 27

8:30 a.m.	Welcome and Opening Remarks	Dr. Sam Katz Dr. Mary Guinan
8:45 a.m.	Adult Immunization	Dr. Ray Strikas
9:45 a.m.	BREAK	
10:15 a.m.	Pneumococcal	Dr. Michael Davidson Alaska
10:45 a.m.	New Typhoid Vaccine	Dr. Brad Woodruff
11:15 a.m.	National Childhood Encephalopathy Study (IOM)	Dr. Roger Bernier
11:45 a.m.	HCFA Influenza Demonstration Project	Mr. Ron Teske
12:00 p.m.	LUNCH	
1:00 p.m.	Varicella Vaccine Update	Dr. Jo White, Merck
1:30 p.m.	Influenza	Dr. Nancy Cox, et al.
2:45 p.m.	Measles, Etc.	Dr. Walter Orenstein
3:00 p.m.	BREAK	
3:30 p.m.	Rabies	Dr. Daniel Fishbein
4:30 p.m.	H. influenzae b	Dr. Claire Broome Dr. Jay Wenger
5:00 p.m.	ADJOURN	

Wednesday, February 28

8:30 a.m.	Chronic Illness and Rubella	Dr. Aubrey Tingle, Dr. Laura Fehrs, Dr. Teryl Frey
9:15 a.m	Rubella ACIP Statement	Dr. Laura Fehrs
10:15 a.m.	BREAK	
10:45 a.m.	JE Vaccine Update	Dr. Ted Tsai
11:15 a.m.	Hepatitis B	Dr. Harold Margolis
12:15 p.m.	ADJOURN	

2/26/90

The meeting was opened at 8:30 a.m. on February 27 by Dr. Samuel L. Katz, Chairperson, with a welcome by Dr. Mary Guinan. After the attendees introduced themselves and gave their affiliation, Dr. Katz reviewed materials that were published since the last meeting and mentioned that the yellow fever statement was ready to go to press.

Adult Immunization

Dr. Raymond Strikas, Division of Immunization (IM), Center for Prevention Services (CPS), reviewed the proposed changes in the adult immunization recommendations, particularly those pertaining to health care workers, immunocompromised persons, inmates, and travelers, and those involving influenza, tetanus, measles, rubella, mumps, varicella, typhoid, pertussis, and rabies. Sections have been added on vaccine adverse events, *Haemophilus influenzae* type b vaccine and *Vaccinia* immune globulin. Epidemiologic data have been updated for most vaccine recommendations. These changes were briefly reviewed.

Dr. Strikas reviewed data from outbreaks of mumps among vaccinated populations, which led to a discussion of reasons for mumps vaccine failure. The major issue discussed was whether adequate mumps immunity could be effected by receipt of one versus two doses. While primary vaccine failure clearly occurs, secondary or waning immunity has not been documented. Although in one outbreak there appeared to be an increasing risk of mumps with increasing time since vaccination, this may have resulted from the fact that persons who were vaccinated more recently were more likely to have received two doses than persons vaccinated in the more distant past. Dr. Orenstein commented that the efficacy of two doses of mumps vaccine is unknown. Dr. Orenstein also mentioned that the issue of one versus two doses for immunity is relevant to rubella vaccine since two doses will now be routinely administered as part of MMR.

Dr. Strikas said that the Division of Immunization is working on the language for a resolution concerning a second dose for mumps vaccine that they could propose in June of this year. Dr. Katz suggested that individual members of the Committee might be assigned to work on parts of the resolution.

In response to a question about the effectiveness of vaccines in immunocompromised individuals, Dr. Strikas commented on studies being conducted among prison populations in this country and African studies also underway for which data are not yet available.

One committee member recommended being cautious about eliminating the recommendation for pertussis vaccine because the medical community has become more aware of pertussis in adults and its role as a vector of the disease to children. Dr. Orenstein commented that the issue is one of not recommending widespread use of the vaccine in the adult population. Because single antigen pertussis vaccine is not generally available and few persons would really consider such a practice in the United States even if monovalent whole cell pertussis vaccines were readily available, it seems to be a non-issue. When acellular vaccines are licensed, the issue of vaccinating adults will need to be reconsidered.

Epidemiology and Control of Invasive Pneumococcal Disease in Alaska

Dr. Michael Davidson, Arctic Investigations Laboratory, Center for Infectious Diseases (CID), presented data showing high rates of invasive pneumococcal disease Statewide in Alaska during 1986 through 1988 among Alaska Natives compared with rates of non-Natives and other U.S. populations and the specific local guidelines that have evolved for adult immunization of Alaska Natives using the currently available 23 valent pneumococcal vaccine. Recent revision of ACIP guidelines for pneumococcal disease have indicated wider immunization may be warranted for populations with high rates.

Yearly age-adjusted incidence rates for Alaska Natives are 75/100,000 population compared to rates in all other racial groups in Alaska of 13/100,000 and rates in Charleston, South Carolina, of 19/100,000. Age-specific rates for Alaska Natives <2 years of age, 20-39 years, 40-54 years, 55-64 years, and 65 and over were 561, 44, 81, 122, and 226 per 100,000, respectively; for non-Native Alaskans, the rates were 96, 4, 6, 23, and 93 per 100,000 for the same age groups. Rate ratios of Alaskan Natives compared with those of non-Natives ranged as high as 13-fold for adults, 40-54 years of age. Rates for almost all age strata of Alaskan Natives were 3 to 10 times higher than Charleston residents.

Age-adjusted meningitis rates are over 12 times higher in Native Alaskans than non-Native Alaskans and 17 times higher in Alaska Native infants than U.S. infants. Chronic underlying diseases were found in only half of those Native Alaskans, 55-64 years of age, and over one third of those, 20-54 years of age. Native and non-Native Alaskans had invasive infections due to vaccine serotypes 92% and 93% of the time, respectively.

Estimations of vaccination levels include 7.1% of the total population including 56% of those over 65 years of age. Almost half of all vaccine recipients have received their vaccine over 6 years ago. Vaccination guidelines have been extended to include revaccination of all vaccine recipients at 6 years of age, all patients with a history of identified invasive infections, and those with meningeal breach. Additional interpretation of surveillance data and recommendations for extending vaccination guidelines were sought from the Committee.

Questions and discussion that followed the presentation centered on the age distribution of the children under age 2 (peaks at 12 months) and implications of vaccinating women of childbearing age, efficacy studies of the vaccine, detection bias among cases diagnosed in hospitals, and the proportion of Native Alaskans that meet the guidelines for vaccination.

New Typhoid Vaccine

Dr. Brad Woodruff, Division of Bacterial Diseases (DBD), CID, presented information on typhoid vaccine and typhoid, the incidence of which has declined steadily in the United States; between 1975 and 1984, there were an average of 464 cases annually with a death rate of 1.3%. More than 50% of cases were in patients 20 years of age or older.

Groups at risk for typhoid are travelers to areas where there is a recognized risk of exposure to *Salmonella typhi*, particularly in Mexico, Peru, India, Pakistan, and Chile. This risk is greatest

to travelers who have prolonged exposure to potentially contaminated food and water. A second group at risk is laboratory workers who work frequently with *S. typhi*. (One case has been identified through active surveillance.) Sewer workers do not appear to be at risk; there have been no cases among sewer workers in a 10-year study.

Two vaccines are currently available for use in the civilian population in the United States: a newly licensed live-attenuated Ty21a oral vaccine and a parenteral heat-phenol-inactivated vaccine, which has been in use for many years. In controlled field trials in Chile, three doses of the oral live vaccine has been shown to provide approximately 67% protection for at least four years against clinical infection. In a subsequent trial, the incidence of typhoid was significantly lower in the persons receiving four doses of vaccine compared to two or three doses. Because no placebo group was included, vaccine efficacy could not be calculated. A primary series of two doses of a heat-phenol-inactivated typhoid vaccine has been shown to have a efficacy of 51%-73% in several field trials. An acetone-inactivated parenteral vaccine, available only to the armed forces, is somewhat more protective.

Parenteral killed vaccine and live-attenuated Ty21a oral vaccine have never been directly compared in a field trial, but the live-attenuated Ty21a oral vaccine has similar efficacy and fewer adverse reactions than the parenteral killed vaccine. Adverse reactions of the parenteral vaccine include pain at the site of administration, fever, myalgia and headache, but no neurological complications.

During one field trial with live-attenuated Ty21a oral vaccine in enteric-coated tablets, nausea and vomiting were twice as common, but still rare occurrences.

Questions and discussion of the Committee members covered such topics as efficacy rates of typhoid vaccine as compared with other vaccines; possible interactions with other vaccines, particularly polio; use in HIV-positive individuals; and difficulty with compliance given the schedule of administration. At the end of the discussion, Dr. Katz asked members to return their comments on this statement within two weeks.

National Childhood Encephalopathy Study (NCES)

Dr. Roger Bernier (IM, CPS) reported on the IOM workshop conducted in November 1989 that reviewed methods and results of the NCES and made recommendations for future study of encephalopathy and brain damage related to the pertussis vaccine in conjunction with a CDC-sponsored childhood neurological study in Seattle.

Key topics in the workshop were (1) biases related to the selection of cases and controls, (2) biases related to the reported date of onset, (3) inclusion of cases with other etiologies, and (4) the case definition of outcome. It was the general consensus of workshop participants (although not official IOM conclusions) that information from the NCES is not sufficient to know if pertussis vaccine can cause brain damage, but that if it occurs, it is very rare; that perhaps it is not "knowable" if pertussis vaccine causes brain damage; and that it may be a misallocation of funds to pursue the issue.

Dr. Bernier reported on an article in *The Lancet* (February 17, 1990) that reviewed a court decision in the United Kingdom concerning brain damage following immunization with the pertussis vaccine. Since this decision, the Canadian National Advisory Commission has changed their statement to say that NCES data failed to confirm an increased risk of permanent brain damage after pertussis vaccination and various groups in the United States have begun or will begin review of their statements soon.

Varicella Vaccine Update

Dr. Jo White from Merck and Co., Inc. reported on clinical trials with Varivax and stated that the company has applied for license with the Center for Biologics Evaluation and Research (FDA).

Over 5000 healthy children and adolescents have been vaccinated with research type process vaccine since clinical trials began in 1981. A double-blind, placebo-controlled efficacy trial was done in 1982-1984 in 956 children, ages 1-14 years of age. The efficacy of the vaccine was 100% over the first varicella season and 96% over the second season. More recent trials with vaccine made in the production facilities were done to demonstrate consistency of the process. Efficacy in these studies was calculated to be 85% for complete protection from any varicella syndrome in the vaccinated children following household exposure to natural varicella. Of the vaccinated children who developed varicella syndrome following these household exposures, the disease was mild with a mean number of lesions of 48 (compared to 250-350 lesions in unvaccinated children), and most were afebrile. After one year of followup of almost all children who received production lots of vaccine, 1.9% developed a varicella syndrome that was generally mild, consisting of a mean of 48 lesions. The rate of varicella syndrome over the past six years in children who have received research type process vaccine has been approximately 1% - 2% per year with 95% of children remaining varicella-free after six years of follow-up. Those who did develop varicella up to six years after vaccination continued to have mild disease.

The seroconversion rate determined by gpELISA measured six weeks following vaccination with production lots of vaccine was 96%. Seroconversion rates ranged from 95% (children 5-12 years of age) to 98% (children 12-15 months of age). Antibody has been shown to persist in >95% of vaccinees for up to six years after vaccination.

The vaccine has been generally well tolerated (17% reporting mild injection site reaction, 3% reporting an injection site rash, 4% reporting a mild varicella-like rash). Clinical transmission of vaccine-type virus to siblings or day-care playmates has not occurred in clinical studies. Clinically mild zoster has occurred in healthy children who have received the vaccine, but the rate of occurrence does not appear greater than that seen after natural varicella.

HCFA Influenza Demonstration Project

Mr. Ron Teske, IM, CPS, described the two-year project done in collaboration with Health Care Financing Administration (HCFA) to determine if it was cost-effective for Medicare to provide flu vaccine to Medicare Part B beneficiaries as a covered benefit rather than pay for

subsequent treatment of illness. The report to Congress due in September 1990 will state the findings of the first two years of the demonstration are inconclusive to establish cost-effectiveness and will recommend continuing the demonstration for another two years.

The project was designed to supply vaccine, reimburse health care providers for vaccine administration, promote immunization through the media, enroll providers to increase participation in the project, do surveillance, and monitor adverse events. Participation in the first year was relatively low because awards were not made until October; however, because of increased enrollment of providers and mass media campaigns during the second year, participation in the project increased.

Telephone surveys to assess influenza vaccination rates among intervention participants and controls show slightly greater participation among intervention groups. Overall immunization rates were considerably higher than prior studies (42% versus 23%). However, selection of reporting sites and the percentage responding may have biased the survey. Reasons cited for not choosing to receive the vaccine have been good health, perceived side effects, and lack of recommendation by the physician.

In the discussion of the project by Committee members, several expressed concern that the study may fail to show the value of the program because of the small numbers involved and that they hoped data from next year would be more representative.

Influenza

Characterization of 1989-1990 Influenza Isolates and Vaccine Recommendations for the 1990 Season

Dr. Nancy Cox, Influenza Branch, Division of Viral and Rickettsial Diseases (DVRD), CID, presented information on the 1989-1990 influenza season which began unusually early (October and November) with outbreaks of influenza A(H3N2) occurring in North America, Europe and Asia. Subsequently, the number of outbreaks in Western Europe, the United States, and Northern China increased sharply during December and early January. The United States and the United Kingdom along with a few other countries reported excess mortality in the elderly related to influenza, and high rates of morbidity have been reported in all age groups. In the United Kingdom, the epidemic was the most severe since 1976.

Influenza A(H3N2) strains predominated this season, with isolates being made in North America and in 18 European and five Asian countries. Influenza B viruses have been isolated in a number of countries. However, there have been few isolates of influenza A(H1N1).

The antigens selected by the WHO are A/Singapore/6/86-like, B/Yamagata/16/88-like, and A/Guizhou/54/89-like antigens. The actual virus strains likely to be used in the U.S. vaccine are A/Taiwan/1/86(H1N1), B/Yamagata/16/88, and A/Shanghai/16/89(H3N2).

Influenza Surveillance in the United States, 1989-1990 Influenza Season

Susan Good, DVRD, CID, reported on the CDC influenza surveillance system, which is comprised of five reporting sources: 55 state and territorial health departments, 150 sentinel

physicians, 63 WHO collaborating laboratories in the United States that report on viruses circulating, 121 city vital records units reporting deaths, and other sources that report outbreaks and problems.

The influenza season begins October 1 and goes through April. Peak activity this season occurred the week of January 27 with both widespread and regional activity occurring in a majority of States. Since that week, influenza activity has declined. Reports from sentinel physicians showed that influenza-like illness accounted for 2.5% of all visits at the beginning of the season and rose to represent 8.9% of all visits the week of December 30. Culture-confirmed reports of influenza occurred about three weeks earlier than usual this season. Influenza A(H3N2) was reported in all 50 States; only four isolates of influenza B were reported this season.

Twenty-two States reported outbreaks in nursing homes, schools, day care institutions, and other institutions and there was a sharp rise in mortality the week of January 13. Although there is no indication that this season was particularly severe, there was higher incidence than expected, especially when the vaccine was a good match.

Influenza Vaccine Efficacy in Nursing Home Residents, 1990

Dr. Diana Wells, DVRD, CID, reported on an investigation of an outbreak in a Connecticut nursing home (310 residents; mean age, 85 years). The investigation showed a vaccination rate of residents of 92%. The attack rate was 11% (35 meeting case definition); the complication rate for pneumonia was 37% and for death, 5%. The nursing home was made up of nine wings, three of which were unaffected, probably because the residents of these wings were not exposed. The attack rate for vaccinated persons in all nine wings was 10% and for unvaccinated persons was 28%, resulting in an efficacy rate of 64%. In the six affected wings, the attack rate for vaccinated persons was 16% and for unvaccinated persons, the rate was 28%, resulting in an efficacy rate of 43%.

In other studies of outbreaks in nursing homes, vaccination rates ranged from 64% to 91%; attack rates ranged from 24% to 47%, with resulting efficacy rates ranging from 31% to 76%. Attack rates for unvaccinated persons were much higher than those for vaccinated persons and for those vaccinated persons who did contract influenza, the illness was generally mild with fewer complications and no deaths.

Amantadine Use and Side Effects in Nursing Home Residents

Dr. Louisa Chapman, DVRD, CID, reported on studies of the use of amantadine among elderly populations that show increased side effects (disorientation, falls, confusion). The rate for probable side effects was 2.8% and 6.6% for probable plus possible side effects. However the data showed that side effects are significantly less likely when creatinine is known and the dose adjusted. In the same population, the rate for probable side effects and the rate for probable and possible side effects for those with creatinine unknown were 5.9% and 14.7% respectively; for those with creatinine known and dose adjusted--1.4% and 2.8%, respectively.

Influenza and Pregnancy

Dr. Steven Ostroff, DVRD, CID, reported on a study done to determine if pregnant women are at high risk for influenza-related mortality, how often do pregnant women die of influenza-related causes, and how many conditions already place these women at high risk. Investigation of data from NCHS and from the National Pregnancy Mortality Survey (Division of Reproductive Health, CCDPHP) showed that making accurate estimations of influenza-related deaths among pregnant women would be extremely difficult because of poor coding and nonspecificity on death certificates. From the data in the study, very little mortality was detected during pregnancy, but continuing studies are needed to determine if this group is at risk.

Recommendations for the Prevention and Control of Influenza

Dr. Margaret Tipple, DVRD, CID, reviewed the proposed changes in this year's recommendations, the major addition being new sections on antiviral agents for influenza A, recommendations for the use of amantadine, and other considerations for the selection of amantadine for prophylaxis or treatment.

Measles

Dr. Walter Orenstein, IM, CPS, discussed morbidity associated with measles, and prices and appropriations for vaccines. In 1989, there were 16,000 cases of measles and 45 deaths associated with measles (two thirds of whom were preschool children). To date in 1990, there have been 1152 reported cases (467 reported at this time last year) and outbreaks in 16 States. The major failure, particularly among preschool children, is the failure to vaccinate.

The cost of the MMR vaccine has been reduced after years of marked increases in price. The manufacturer will cut their price by 12.5%. When the excise tax is added, the effective price reduction will be 9.1%. State and local agencies can now use the Federal contract with their own funds and pay the federal price. This may help with outbreak control and with implementation of the two-dose schedule. Money has been appropriated for outbreak control ($9.9 million), but the administration did not ask for money for the two-dose schedule; approximately $48 million is needed in the public sector to implement the two-dose schedule. Money has also been allocated to measles laboratories to develop better diagnostic tests, to determine correlates of immunity to measles, and eventually to develop more effective vaccines.

Discussion by Committee members included questions about seroconversion rates among infants, attack rates for those who have received vaccine under the two-dose schedule, and effective ways to get preschoolers into the health care system.

Rabies

Dr. Daniel Fishbein, DVRD, CID, reviewed revisions of the ACIP draft document on rabies prevention including:

- A return to the use of the term "RIG" (rabies immune globulin) to refer to all rabies immune globulin products. ARS is used to denote equine antirabies serum and HRIG is used to denote human rabies immune globulin.
- Rewording of the section on serologic testing.
- Instructions on skin testing before administration of equine RIG.
- Specification of a quarantine period for rare or valuable animals.
- Specification of a time period within which rabies postexposure prophylaxis should begin.
- Rewording of the statement on vaccination schedules used outside the United States; addition of a statement that these regimens have not been approved or recommended by the FDA.
- Deletion of specific recommendations regarding treatments begun outside the United States with biologics of nerve tissue origin.
- Reworded statement on postexposure therapy of previously immunized persons.
- Reworded statement on concurrent chloroquine administration to include structurally similar compounds.
- New statement regarding preexposure prophylaxis for immunosuppressed individuals.
- Addition of a statement on the transmission of HIV, hepatitis B, and other viruses by HRIG.
- Reference to lower serum sickness rates following administration of Sclavo equine ARS than has been previously reported.
- Clarification of the definition of hypersensitivity to human diploid cell vaccine and the management of adverse reactions in those people.

At the end of the discussion, Dr. Fishbein asked for comments on the revised statement by April 15.

***Hemophilus influenzae* b**

Dr. Jay Wenger, Division of Bacterial Diseases (DBD), CID, introduced representatives of three pharmaceutical companies, Dr. Vincent Ahonkai (Merck), Dr. Peter Paradiso (Praxis), and Dr. Michael Hensley (Connaught) who reviewed their companies' studies on the immunogenicity of vaccines for *H. influenzae* b for children 15 to 17 months of age.

Discussion of the issue included whether ACIP would endorse routine use of vaccine licensed for use at 15 months, and covered issues including the necessity of two doses, significant increases in response after 18 months of age compared to 15 months of age, what the American Academy of Pediatrics felt on the subject, what percentage of invasive disease is present in this age group, and simultaneous administration with the DTP vaccines.

A motion was made to endorse routine use of vaccine licensed for use at 15 months. The committee voted unanimously in favor of the motion.

The representative from FDA pointed out that at present only the Merck and Praxis vaccines have been approved for use for this age group, although Connaught's vaccine is under review.

Chronic Illness and Rubella

Dr. Aubrey Tingle, Research Center, Vancouver, British Columbia, discussed the manifestations of acute and chronic arthritis and arthralgia associated with clinical rubella or with rubella vaccination. Clinical manifestations of the disease include three patterns: (1) acute arthritis followed by recurrent periods of arthralgia, (2) persistent disease with continuing, discrete tender affected areas, and (3) progressive destructive arthritis (rare).

Evidence linking rubella virus to the onset of arthritis includes a close temporal relationship of the development of chronic or acute arthropathy, particularly in those who no previous symptoms, and isolation of rubella virus in individuals with arthropathy. Although there are inadequate data, particularly data on chronic arthropathy and on vaccine-associated arthropathy, it does appear there is a syndrome of rubella-associated chronic arthropathy that is more severe with the wild virus, but the true incidences of that associated with the wild virus and with the vaccine are not known. Studies are needed to determine true incidence.

Mr. John Mullen, IM, CPS, presented information on reports of arthritis and arthralgia following rubella vaccination from CDC's Monitoring System for Adverse Events Following Immunization (MSAEFI). Two complementary surveillance systems exist in the United States: FDA receives reports from manufacturers, pharmacists, and health care providers and MSAEFI. The objectives of this surveillance are to identify infrequent illnesses caused by vaccines, develop estimates of occurrence rates, raise awareness of risk by health care providers, and identify areas that require more investigation. MSAEFI has inherent weaknesses that must be kept in mind when interpreting data from this system. These include (1) problems inherent in a passive system; (2) possible temporal reporting bias; (3) vaccine antigens reported are simultaneously administered with other vaccines; (4) lack of background rates on conditions reported; and (5) no precise denominator data (use estimates of total doses administered).

Arthritis and arthralgia are conditions which are followed up one year after the date of immunization by State coordinators who ask about symptoms at one year and report them to CDC. During 1985-1988, 197 persons with arthritis/arthralgia were among recipients of 9.4 million doses of rubella vaccine (21.0 cases per million doses). The reported rate in adults $\geq$20 years of age was 117 per million doses. For acute arthritis alone, the reported rate in persons $\geq$20 years of age was 69 per million doses. On one-year follow-up, the reported rate for chronic arthritis/arthralgia for adults was 8.3 per million doses; for chronic arthritis alone, it was much lower--2.8 per million doses.

Dr. Teryl Frey from Georgia State University reported on a collaborative study to attempt to isolate rubella virus from peripheral blood mononuclear cells taken from 14 vaccinees (six of whom developed joint symptoms) at weekly intervals for up to one year after vaccination and from five individuals who had received the vaccine one year earlier. To increase the sensitivity of the virus detection assay, a polymerase chain reaction assay was developed. The assay was successful in detection of RNA from two wild-type strains as well as the RA 27/3 vaccine strain. Detection could be accomplished using RNA from as little as one infected culture cell. When used to detect rubella virus RNA in peripheral blood mononuclear cells taken from two vaccinees, the assay was positive in one vaccinee from day 4 through 15 postvaccination and in the second vaccinee, from day 9 through 21 postvaccination. The assay was used to detect

rubella virus RNA in mononuclear cells in blood and synovial fluid taken from a group of 10 subjects with the following diagnoses: three with juvenile rheumatoid arthritis, two with rheumatoid arthritis, one with probable Reiter's syndrome, one with paraneoplastic arthritis, one with gout, and two with uncertain diagnoses. The only positive result was from synovial fluid taken from a young woman diagnosed as having probable Reiter's syndrome. Follow-up studies on this patient are in progress.

A presentation on rubella and congenital rubella syndrome (CRS) surveillance data included data on the number of annual cases of postnatal rubella (less than 1000 cases after 1983 and less than 500 after 1987). For 1989, a provisional total of 383 cases has been reported (70% increase over 225 cases in 1988), but this increase may reflect better reporting because of the high incidence of measles. Incidence rates for all reported cases of rubella, for rubella in postadolescents, and for CRS decreased when vaccination efforts targeted these groups and States required vaccination for school entry. Only a few cases of indigenous CRS are born annually and reported. Incidence rates for rubella are greatest in infants <1 year of age. Incidence among 15- to 19-year-olds increased relatively sharply from 1988 to 1989 compared with most other age groups, but rates were still lower than that of the early 1980s. In 1989, males, ages 15-29, comprised 25% of all cases of rubella while women of the same age group represented only 11% of cases. In summary, the incidence of rubella has decreased dramatically and the PHS objective of reducing CRS to <10 cases annually has been achieved, but concern continues about the continuing occurrence of rubella in persons of childbearing age.

A presentation of the persistence of rubella antibody after immunization included a discussion of the results of a number of studies:

- A 16-year followup study in Hawaii (1,179 subjects who had seroconverted following a single dose of vaccine 16 years earlier) found 92% of subjects had rubella antibody at a level of 10 IU/mL or greater. [Chu et al.]
- A study in UK student nurses (12 in study group) found a seropositivity rate of 91.7%. [O'Shea et al.]
- Plotkin et al. followed 29 children for 12-14 years who had seroconverted plus 5 children found to be naturally immune. All children were found to be immune although there was parallel decay in both vaccinnee' titers and those of the children with natural immunity.
- Hillary et al. followed 11 children who received a single dose, 8 children who were revaccinated, and 12 naturally immune children. Seropositivity rate for singly vaccinated children was 91% while both other groups exhibited 100% seropositivity.
- Horstmann et al. studied a small number of vaccinees (less than 35) and reported a 95% rate of seroconversion 11 to 12 years later.

These data suggest that vaccine-related antibodies to rubella persist long-term.

A presentation was given on the seroprevalence of antibodies to rubella in U.S. populations (6% to 20% seronegativity rate, the accuracy of which is contingent on test sensitivity). Although rates have declined somewhat during the 1980s, concern persists because of outbreaks in adults and the shift of peak incidence to older age groups. Data available are not from population-based surveys, rather they represent geographic studies (e.g., Texas survey) or special

groups not necessarily representative of U.S. population (premarital women, Armed Forces recruits).

A presentation on the Vaccine in Pregnancy (VIP) Registry described the system and resulting data. From 1971 to 1989, CDC collected passive reports of women from 49 reporting areas who received rubella vaccine within three months before or after conception. Women were followed to determine the outcome of pregnancy, including spontaneous abortions, live births, and terminations of pregnancy. Data were presented on outcome of pregnancy for women receiving each of three vaccine types during pregnancy which showed an observed risk for CRS following vaccination in pregnancy as zero. The overall theoretical risk for known susceptible women vaccinated during pregnancy is 1.2%, which is much lower than the 20% to 80% risk of CRS associated with wild virus maternal infection in the first trimester and similar to the 2% to 3% of major birth defects in the general population.

Rubella Statement

Dr. Laura Fehrs, IM, CPS, reviewed proposed revisions of the ACIP statement on rubella prevention, emphasizing two issues: dosage schedule for rubella vaccine and adverse events. In this revised version of the statement, one dose is defined as adequate immunization, although many will receive two doses of rubella vaccine as a result of the 2-dose schedule for MMR to improve control of measles. The section on adverse reactions has been revised to provide more information regarding serious, chronic, or recurrent adverse events following vaccination.

At the end of the discussion, Dr. Katz asked Committee members to provide their comments on this draft of the rubella recommendations by April 15.

Japanese Encephalitis Vaccine Update

Dr. Ted Tsai, Division of Vector-Borne Infectious Diseases (DVBID), CID, updated the Committee on the vaccine for Japanese encephalitis, which currently is not licensed for use in the United States, although application for licensing was filed several weeks ago with FDA. Dr. Tsai described the extent of worldwide involvement of Japanese encephalitis (JE) and gave a description of the types of viruses involved and the transmission cycle, noting that JE is endemic in most parts of Southeast Asia. The JE-associated case/fatality rate is 25% and survivors have significant sequelae.

Dr. Tsai described the development and use of an inactivated mouse strain vaccine in 1982 and discussed studies that show an efficacy rate of 91%. Licensing efforts in the United States began when an American student in Beijing died of JE and the family began lobbying for the availability of a vaccine. The Japanese manufacturer discontinued efforts to get the vaccine licensed in the United States because of fear of litigation, but Connaught took over the trials for the vaccine.

Trials with 181 participants show immunogenicity after two doses is not adequate, but after three doses, immunogenicity is 99%. Therefore, recommendations for use include a three-dose schedule with doses given 1-2 weeks apart. The need for booster doses should be monitored serologically at 1-year intervals. The need for immunization had been focused on the risk of

exposure--e.g., living in endemic areas, travelers to those areas, during transmission periods, etc. If the vaccine is licensed, the recommendations could be broader.

Dr. Tsai reviewed other JE vaccines in use in China, Taiwan, and Japan, all of which have reported neurologic side effects, although there have been no controlled studies to provide data to support reports.

Hepatitis B

Dr. Harold Margolis, DVRD, CID, presented information to the Committee concerning funds for the provision of hepatitis B vaccine and HBIG for infants with carrier mothers and information about the States most affected by hepatitis B infection. Discussion by the Committee members covered duration of efficacy of the vaccine in infants; immunization of high-risk populations and the difficulty of reaching them, particularly Asian children; and simultaneous administration with other childhood vaccines.

Other ACIP Business

Members of the Committee strongly urged CDC to conduct the next meeting at the Clifton Road facility even if Committee members had to be transported from a distant hotel.

The dates for the next ACIP meeting will be June 5 and 6 and October 16 and 17.

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., Chairman

Date: 12 May 1990