DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL

MINUTES OF MEETING

Immunization Practices Advisory Committee
October 24-25, 1985
Atlanta, Georgia

The Immunization Practices Advisory Committee (ACIP) met in Auditorium A at the Centers for Disease Control, Atlanta, Georgia, on October 24-25, 1985. Those in attendance are listed below:

COMMITTEE MEMBERS PRESENT

Dr. Samuel L. Katz, Chairman
Dr. Ellen S. Alkon
Mrs. Betty F. Bumpers
Dr. Jeffrey P. Davis
Dr. David S. Fedson
Dr. Anne A. Gershon
Dr. Joan K. Leavitt
Dr. Edward A. Mortimer
Dr. William Schaffner II

Ex Officio Members

Dr. William S. Jordan, Jr. (NIH)
Dr. Harry M. Meyer, Jr. (FDA)
(represented by Dr. Elaine Esber)

Liaison Representatives

Dr. Philip A. Brunell (AAP)
Dr. J. M. S. Dixon (NACI)
Dr. Jarrett Clinton (DoD)
(represented by Dr. John Herbold)

Executive Secretary

Dr. Jeffrey P. Koplan

COMMITTEE MEMBERS ABSENT

Dr. Donald A. Henderson

Liaison Members

Dr. Theodore C. Eickhoff (ACP)
Dr. Albert W. Pruitt (AMA)

HHS STAFF PRESENT

FOOD AND DRUG ADMINISTRATION

Center for Drugs and Biologics

Dr. Elaine Esber
Dr. Gerald Quinnan

HEALTH RESOURCES AND SERVICES ADMINISTRATION

Bureau of Health Care Delivery and Assistance

Dr. Allan Noonan

CENTERS FOR DISEASE CONTROL

Office of the Director

Mr. Robert Alden
Ms. Verla Neslund
Dr. Gary Noble
Ms. Gwen Strickland-Cid

Center for Infectious Diseases

Ms. Nancy Arden
Dr. Claire Broome
Dr. Kenneth Herrman
Dr. Alan P. Kendal
Dr. Olen Kew
Dr. Margaret Oxtoby

CENTERS FOR DISEASE CONTROL (continued)

Center for Prevention Services

Dr. Robin Biellik
Dr. Roger Bernier
Dr. Edward W. Brink
Dr. Robert Carr
Dr. Robert T. Chen
Dr. Alan R. Hinman
Dr. J. Michael Lane
Dr. Ida M. Onorato
Dr. Walter Orenstein
Dr. Peter A. Patriarca
Dr. Susan Robertson
Dr. Stephen Preblud
Dr. Steven Wassilak
Dr. W. W. Williams

Epidemiology Program Office

Dr. Zeng Guang
Dr. Gary Hlady
Dr. J. J. Sacks

International Health Program Office

Dr. T. Stephen Jones

OTHERS PRESENT

Mr. Gary Bridi
Dr. Bill Buens
Dr. Francis Cano
Dr. Kenneth Cartwright
Mrs. Leslie Chapman
Mr. Robb S. Chapman
Col. Alfred K. Cheng
Mrs. Karen Cline
Dr. Pinya Cohen
Dr. Adamadia Deforest
Commander Mark Dembert
Dr. Ingram Douglas-Hall
Dr. Arthur Y. Elliott
Dr. Kevin Geraghty
Dr. Robert Gerety
Mrs. Judy Glomb
Dr. Alan Goldschein
CDR Vern W. Harpole
Dr. Jill Hackell
Dr. Harriett Kiltie
Dr. Andre Lamotte
Dr. Bruce Lesser
Dr. Mark Levner
Dr. Steve Mento
Dr. John Modlin
Dr. Benjamin Nkowane
Dr. Patricia J. Patrick
Dr. E. W. Neil Pearson
Dr. Philip J. Provost
Dr. Lorraine Radick
Dr. B. A. Rubin
Dr. Jill Schneider
Lt. Col. Ernest T. Takafuji
Mr. Charles Taylor
Dr. Tito R. Ubertini
Dr. Ronald J. Vallancourt
Dr. John Weber
Ms. Sue Wheat
Dr. Richard F. White
Dr. Roy Widdus
Dr. Paul J. Wilson

The meeting was opened at 8:30 a.m. on October 24 by Dr. Samuel L. Katz. Dr. Elaine Esber represented Dr. Harry M. Meyer, Jr., FDA, and Dr. John Herbold represented Dr. Jarrett Clinton, Department of Defense. Dr. Koplan announced the appointment of Dr. Katz as the new Chairperson of ACIP.

Dr. Alan Hinman, Division of Immunization (DI), Center for Prevention Services (CPS), CDC, gave introductory comments on the background information to be presented on the status and risks of poliomyelitis. The epidemiology of poliomyelitis in the United States has undergone substantial changes during the past decade. The use of oral polio vaccine (OPV) has resulted in the virtual elimination of the disease in this country.

In 1982 and 1983 all cases of paralytic poliomyelitis in the United States were vaccine associated. These facts are a reminder that the balance of risks and benefits of oral poliovaccine use needs to be constantly re-examined. The classification of poliomyelitis cases based on new laboratory techniques as well as epidemiological criteria should help in these re-examinations. The continuing problem of OPV-associated paralysis, the experience of several European countries where poliomyelitis has been controlled by exclusive use of inactivated polio vaccine (IPV), and the development of an improved IPV have stimulated renewed interest in IPV in the United States. However, these factors must be balanced against recent outbreaks of poliomyelitis caused by wild strains of viruses in some countries using IPV.

Poliomyelitis Vaccine Efficacy

Dr. Robin Biellik, DI, CPS, presented data on seroconversion and duration of humoral antibodies after receipt of OPV. He provided estimates of seroconversion and persistence of humoral antibody to poliovirus using current recommended vaccination schedules for OPV in the United States and comparisons with other proposed vaccines and schedules. Seroconversion and seroprevalence rates among infants and young children after one dose of OPV are difficult to interpret due to the confounding effect of maternal antibody. He reviewed the literature concerning both the degree of seroconversion achieved after the second and third doses of OPV and the persistence of immunity after completing primary immunization. To date, approximately 400 million doses of OPV have been distributed throughout the nation, and since 1980 more than 95% of kindergarten and first-grade children have had complete (three or more doses of OPV) primary poliomyelitis vaccination. Proof of protection from paralytic poliomyelitis disease provided by OPV has been derived indirectly from the dramatic decrease in disease incidence observed through national surveillance activities as well as from the absence of cases in vaccinees and direct measures of serologic evidence of immunity.

The best estimates of seroprevalence following two doses of OPV are 80-98% to poliovirus type I, 100% to type II, and 90-100% to type III. After a three-dose schedule, the rates are 96-100% (type I), 100% (type II), and 96-100% (type III). Five years after completion of primary immunization, seroprevalence rates of 92-98%, 98% and 84-87% to poliovirus types I, II, and III, respectively, are reported. These data provide evidence that in the United States the current recommendation of three doses of OPV for primary immunization against poliomyelitis is sufficient for protection against naturally acquired poliomyelitis disease.

Dr. Roger Bernier, DI, CPS, reviewed the limited information on the immunogenicity of IPV following use of the single product currently available in the United States. Based on a study carried out in Finland and on manufacturer-sponsored studies, the currently recommended U.S. schedule of four doses of IPV beginning at 2 months of age can be expected to produce detectable antibody in 87-97% of children in the first year of life (after three doses) and in essentially all completely vaccinated children by 18 months of age (after four doses). The persistence of detectable antibodies elicited by the current product is unknown, but Swedish investigators have documented persistence in essentially all vaccinees tested 2 to 12 years after four doses of their IPV product.

Dr. Bernier then discussed a new, more potent IPV. Based on published and unpublished observations on the immunogenicity of improved, more potent (40-8-32) IPV, the vaccine appears able to induce near 100% seroconversion after two doses, with significant boosts in antibody levels occurring after a third dose at an interval of at least several months. The seroconversion rate induced by one dose at an early age (e.g., 2 months) is difficult to measure with certainty because of the presence of maternal antibody. Where assessment has been possible, seropositivity levels 1 to 2 months after one dose have ranged from 50-90%. Also, seropositivity after the first dose at an early age (e.g., 5 months) appears to decline quickly, particularly for poliovirus type III. A critical question is the number of doses of 40-8-32 IPV required for protection against polio. Based in part on the responsiveness of children receiving a second dose, even when failing to produce detectable antibodies after one dose, Salk has stated that children vaccinated with one dose of vaccine possess immunologic memory and will be protected from paralytic polio by mounting an adequate and rapid secondary-type response upon infection. Available data support the adequacy of two doses in achieving very high levels of seropositivity, approaching nearly 100% even when the interval between doses is as short as 2 months and the age at first vaccination is as early as 2 months. U.S. data suggest that these levels of seropositivity can persist for at least 14 months in the absence of circulating wild poliovirus and in the absence of any evidence of boosting by circulating OPV. It is uncertain whether a third dose of IPV will add measurably to the duration of protection conferred by two doses. If persistence of detectable antibody is taken as the index of protection, data from Israel indicate that 100% seropositivity can be maintained for at least 4 years, although the decline in GMT's is considerable. Only further study over extended periods will be able to determine the persistence of detectable antibody, although the validity of such studies in the presence of circulating wild or vaccine virus is open to question.

Dr. Ida Onorato, DI, CPS, compared data on intestinal immunity induced by IPV and OPV. An advantage of OPV is its ability to induce intestinal immunity and to limit the spread of wild poliovirus through the community. An improved IPV has been developed in Europe, and results from clinical trials at Johns Hopkins University and elsewhere show that it produces serum antibody levels equal to or higher than those produced by OPV. Direct evidence from studies in which IPV recipients were challenged by feeding with OPV suggest that IPV may produce some intestinal and pharyngeal immunity. IPV recipients consistently showed decreased pharyngeal and intestinal poliovirus excretion rates after OPV challenge compared to unvaccinated children, but intestinal excretion was greater in IPV recipients than in OPV recipients.

The duration of intestinal and pharyngeal immunity produced by IPV or OPV is unknown. Since a proportion of both IPV and OPV recipients are infected and excrete poliovirus in feces after challenge with poliovaccine virus, intestinal immunity is incomplete. The ability of improved IPV to produce intestinal and pharyngeal immunity equivalent to that produced by OPV and to equally limit the spread of any imported poliovirus in the community is still uncertain.

Dr. Onorato also reviewed data from studies on the spread of vaccine virus to contacts of OPV recipients and the effect of this on the community and the individual. Another advantage of OPV over IPV is that OPV vaccination results in shedding of vaccine viruses and their spread to unvaccinated persons. The spread of OPV viruses from vaccinees to family and, to a lesser extent, community contacts may contribute to individual and population immunity. Since some countries have also reported the elimination of wild polioviruses and paralytic poliomyelitis by the exclusive use of potent IPV, the relative advantages provided by the ability of OPV viruses to spread in the community should be reassessed.

Vaccine Safety

Dr. Benjamin Nkowane, Division of Epidemiologic Studies, Illinois Department of Public Health (formerly from DI, CPS, CDC), reviewed and discussed six methods for assessment of risk based on data obtained in the United States and from other countries to convey an estimate of the risk associated with the use of OPV. His data included a 1970-1979 WHO-conducted study, with 11 countries participating. Data from only six countries were used in the calculation of risks, since 5 countries did not use OPV routinely for the entire period. The second data source contained information from a 1973-1984 study of vaccine-associated paralytic poliomyelitis in the United States; during this period only trivalent OPV was distributed in the United States.

The various estimates of risk of OPV demonstrate the overall rarity of vaccine-associated paralytic disease. The risk of paralysis associated with OPV is not uniform with each dose of vaccine administered, the risk being greatest in both recipient and contact following first dose of OPV to recipient. The estimate of 1 case per 500,000 first-dose recipients of OPV represents the best available overall estimate of risk among susceptible persons. There was an average of less than 3 recipient vaccine-associated cases per year from 1973 to 1984.

Dr. Olen Kew, Division of Viral Diseases (DVD), Center for Infectious Diseases (CID), reported on molecular aspects of contemporary poliovaccine research. This included genetic variability of poliovirus genomes as a contributing factor to vaccine-related poliomyelitis, prospects for improved poliovaccines and recent contributions from basic research, advances relevant to development of nonviable poliovaccines, and advances relevant to development of improved attenuated vaccines.

Dr. Steven Wassilak, DI, CPS, reviewed information on adverse events following IPV. A perceived major advantage of IPV is that it is generally free of adverse effects. Few studies have been made but most support this assumption. The large-scale 1954 Francis Field Trial found that less than 1%

of vaccinees experienced minor reactions, the same rate as in placebo recipients. Serious medical events after inoculation were reported in less than 1 per 10,000 doses, also equal in frequency to the rate in placebo recipients. Surveillance of vaccine-associated adverse events after licensure, although incomplete, indicates that serious biologically plausible adverse events after IPV are rarely reported to CDC, FDA, or manufacturers of IPV. Attribution to IPV of adverse reactions is often uncertain because of concurrently administered vaccines, particularly DTP. A placebo-controlled study of the frequency of medical events after a more potent IPV product was performed at Johns Hopkins University. Overall, local reactions of any kind were reported in 2.5% of recipients and 1% of placebo recipients at 6 hours, and 1% of both groups at 24 hours. Because of differences in DTP vaccine lots given concurrently with IPV or OPV, systemic reactions were not studied in a parallel manner (there were no differences with febrile reaction reports). The exact frequency of clinically significant reactions, if any, is unknown.

Dr. Walter Orenstein, DI, CPS, presented data and led a discussion evaluating the safety of combined schedules of OPV and IPV in the prevention of vaccine-associated polio. The major consideration is whether the combination will be safer than OPV alone, approaching the safety of IPV alone. The combined schedules using IPV first theoretically would lead to gut immunity, lifelong immunity, and prevention of vaccine-associated polio. Such schedules are more expensive, resulting in as many as twice the current recommended doses and potentially twice the number of visits. Administratively, they may be more difficult to implement by requiring that vaccine providers keep track of two vaccines. The costs of such schedules will be substantial, and implementation, at least in the beginning, may be complicated.

Current Status of the Vaccination Program

Dr. Edward Brink, DI, CPS, summarized information on vaccine coverage in the United States and presented results of the limited number of studies of polio antibody seroprevalence. Available immunization data suggest that less than 90% of children have received adequate OPV immunization at 2 years of age, and immunization coverage levels are lower among non-white than white children, at least until school entry. The cohorts of children entering school since 1978 have had coverage levels of at least 90%, and the cohorts of children and adolescents in school since 1978 are also likely to have markedly improved coverage levels. Seroprevalence studies generally indicate that approximately 90% of adults are protected against each poliovirus type.

Prospects for New Vaccines

Dr. Gerald Quinnan, FDA, discussed the current status and future prospects for IPV production.

A general discussion followed, and the meeting adjourned for the day.

On day two, the Chairman began the meeting at 8:30 a.m. and called for a slight modification in the agenda to receive the reports of "DTP-associated adverse reactions" earlier in the afternoon than previously scheduled.

Dr. Hinman presented poliomyelitis vaccine policy alternatives and decision analysis. He presented six polio vaccine policy options and discussed the pros and cons for each:

- Option #1 - Continue with present policy: (1) OPV as the principal vaccine for primary immunization; and (2) IPV reserved for immunocompromised persons and their family members, for adults receiving initial vaccination, and for persons who, for whatever reason, prefer IPV.

- Option #2 - Option #1 (above) plus IPV (one or more doses) for unimmunized family members and other close contacts of intended OPV recipient prior to administering OPV to the recipient.

- Option #3 - Use only the currently available IPV.

- Option #4 - Use only a more potent IPV.

- Option #5 - Combined OPV/IPV schedule with one or more doses of IPV administered prior to OPV for recipients and contacts.

- Option #6 - Free choice of OPV or IPV by the recipient or by the responsible guardian.

The Committee discussed the options, whether there is justification to revise the current statement, and length of time required to gear up to produce vaccine. The Committee agreed that there is a need for more data before a major change in approach would be warranted and that surveillance should be maintained. Dr. Katz suggested that the Committee members take the new data home and continue to look at the options. In the meantime, it was agreed that Dr. Hinman would draft an update on the relative risks and benefits of vaccines against poliomyelitis and circulate the draft to the Committee for their comments.

Reporting of DTP-Associated Adverse Reactions

Representing the Ad Hoc Committee of Parents and Physicians for Safe Immunization, Mrs. Karen Cline, from Haskell, Oklahoma, and Mrs. Judith Glomb, from Aston, Pennsylvania, spoke on behalf of themselves and other parents whose infants had died after receiving DTP vaccinations and whose deaths were recorded as SIDS. Kevin C. Geraghty, M.D., from El Cerrito, California, spoke on "DTP Vaccine."

Use of MMR/DTP/OPV at 15 months

Dr. Adamadia Deforest, Associate Professor in Pediatrics at Temple University School of Medicine, and Chief of the Virology Section, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania, presented results of a randomized, double-blind study that demonstrated the safety and efficacy of simultaneous administration of MMR with a 4th dose of DTP and a 3rd dose of OPV in children between 14 and 23 months of age (under CDC contract No. 200-81-0624). Serological responses and clinical reaction rates following

primary immunization with MMR vaccine were compared in a test group of 405 children given MMR simultaneously with doses of DTP and OPV and a control group of 410 children given MMR, followed by doses of DTP and OPV vaccines 2 months later. Seroconversion rates to MMR exceeded 96% in both groups. Antitoxin levels of at least 0.1 international units (IU) to diphtheria and 0.01 IU to tetanus, neutralization antibody levels of at least 1.0 IU to all three poliovirus serotypes, and an agglutinin titer of at least 1:16 to pertussis were demonstrated in greater than 97% of subjects in both groups. Rates of vaccine-associated clinical reactions to DTP were not augmented by simultaneous administration of MMR, nor were rates of vaccine-associated clinical reactions to MMR augmented by simultaneous administration of DTP.

Dr. Roger Bernier reviewed the current recommended schedule for active immunization of normal infants and children: combined measles-mumps-rubella (MMR) vaccine at 15 months, with the 4th dose of diphtheria and tetanus-toxoids and pertussis vaccine (DTP) and the 3rd dose of OPV at 18 months. He then led a discussion on a new recommended schedule for active immunization of normal infants and children. It is anticipated that implementation of the new schedule would result in an increase in the percentage of children fully or partially immunized by 24 months of age. After discussing the new proposed recommendation, each Committee member was asked to send their comments to Dr. Koplan within 2 weeks.

Updates: Adult Immunization, MR, and Pertussis Vaccine Development

Dr. Alan Hinman summarized recent activities in adult immunization. Staff have been added to the Division of Immunization to work full time on the issue, requests for proposals for contracts to allow purchase of vaccines at reduced prices have been issued, and Important Information Statements for the adult vaccines are being developed. In addition, two contract studies are underway to develop approaches (1) to improve acceptance of hepatitis B vaccine and (2) to improve acceptance of Td, influenza, and pneumococcal vaccines.

Measles incidence in 1985 continues at about the same levels as in 1984. A meeting is to be held in early November to discuss remaining impediments to the elimination of measles and any modifications in strategy that might be warranted to accelerate elimination. Rubella is presently at record low levels, and no cases of congenital rubella syndrome (CRS) have been reported yet this year.

Considerable effort is underway in pertussis vaccine development. Under contract with the National Institute of Allergy and Infectious Diseases (NIAID), the Michigan State Department of Health is preparing an acellular vaccine which is near the stage of initial clinical trial. Preparations are nearly complete for the large-scale trial of clinical efficacy of two Japanese products in Sweden--one containing equal concentrations of LPF and FHA and the other representing purified toxoided LPF. The Public Health Service (PHS) is providing both technical and financial support to this trial. In addition, NIAID-funded vaccine evaluation units have been studying a Japanese acellular vaccine combined with U.S.-produced diphtheria and tetanus toxoids. Finally, a group of PHS scientists will travel to Japan for 2 weeks in early December to obtain as much information as possible about the Japanese experience with acellular DTP vaccines.

Influenza Update

Ms. Nancy Arden, DVD, CID, reported that surveillance since last season indicates continued circulation of influenza virus types A(H3N2), A(H1N1), and B. Type A(H3N2) viruses have been isolated most frequently, followed by type B. Influenza type A(H3N2) caused widespread outbreaks in parts of the Southern Hemisphere, with type B activity increasing toward the end of the season. Type A(H1N1) viruses have circulated at low levels and have usually been associated only with sporadic cases. Antigenic analysis of more recently isolated viruses is incomplete; however, preliminary indications are that they are similar to strains which circulated in the United States last winter. Strains representative of recently isolated types A(H3N2) and B viruses have been sent to the vaccine manufactures, through the FDA.

Varicella Zoster Vaccine

Drs. Philip Brunell and Stephen Preblud summarized the material presented at a symposium on varicella-zoster (VZ) vaccine held in San Antonio, Texas, on October 21, 1985. The latest summary data from Merck Sharp & Dohme were also presented. Studies from Japan and the United States involving approximately 8,000 vaccinees continue to show that the vaccine is safe and effective in both normal and leukemic children. While vaccination of leukemic children does not necessarily prevent infection, it does prevent serious complications. Data from the NIAID collaborative study suggest that yearly doses of vaccine may be necessary for leukemic children who are on chemotherapy. Studies of children with solid tumors are now underway. Seroconversion rates in normal adults do not seem to be as high as those in normal children. Studies are continuing to further investigate this situation. Finally, Dr. Quinnan announced that there would be an FDA workshop on VZ vaccine in January 1986.

Haemophilus influenzae Type b

Dr. Theodore Mortimer reported from the subcommittee (Drs. Mortimer, Katz, Leavitt, and Pruitt) on chemoprophylaxis for prevention of secondary Haemophilus influenzae disease. After assessing data from the various investigators, the committee felt that unexplained disparities remained in the estimates of the risk of secondary disease following a single case in day-care. However, contacts less than 24 months of age were at increased risk in several areas for extended periods of time. Therefore, day-care classrooms in which a child less than 24 months of age is exposed to a case of Haemophilus disease should be considered for chemoprophylaxis. In such a classroom, children who have received the vaccine should still receive chemoprophylaxis, since the vaccine probably does not prevent carriage of the organism.

Children who have had invasive Haemophilus b disease at less than 24 months of age should receive the vaccine according to the usual recommendations, since most young children fail to mount an immune response to the disease. An estimated 2 million doses of the vaccine have been given to date; 11 cases have been reported in children who have received the vaccine, substantially fewer cases than expected in 2 million children of the age group receiving the vaccine. Adverse reactions reported have been similar in type and frequency to those noted prior to licensure.

Other ACIP Business

The Committee reviewed the risks and benefits of continuing to store the swine influenza vaccine manufactured for the National Influenza Immunization Program of 1976. Dr. Koplan asked each member to give him their recommendation for course of action for disposition of the swine flu vaccine within 2 weeks.

The winter ACIP meeting was scheduled for February 3-4, 1986.

With the thanks of the Chairman, the meeting was adjourned about 3:30 p.m.

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

Samuel L. Katz MD — 13 Feb. 1986

Samuel L. Katz, M.D., Chairman — Date