Department of Health and Human Services

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Centers for Disease Control and Prevention

Advisory Committee on Immunization Practices

Minutes of the Meeting

October 23-24, 1996

Atlanta, Georgia

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GEORGIA
AUDITORIUM A
OCTOBER 23-24, 1996

OCTOBER 23

8:30	Welcome		Dr. J. Davis Dr. D. Snider
9:00	Updates National Vaccine Program Vaccine Injury Compensation Program	Information	 Dr. R. Breiman Dr. G. Evans
9:15	Measles, Mumps, and Rubella (MMR)	Draft Statement	Dr. J. Modlin Dr. J. Watson
10:45	**BREAK**		
11:15	Polio Vaccination Recommendation Vote on Sequential IPV/OPV Schedule for the Vaccines for Children Program	Implementation Plan VFC Vote	Ms. S. Crawford Dr. R. Prevots
12:15	**LUNCH**		
1:15	Acellular Pertussis Vaccines	Draft Statement	Dr. M. Griffin Dr. D. Guris Dr. M. Pichichero Dr. M. Rennels Dr. H. Six Connaught Dr. P. Strebel Dr. M. Wharton
3:30	**BREAK**		
4:00	COMVAX® - Combined Hib and Hepatitis B Vaccines	Discussion	Dr. G. Euler Dr. O. Levine Dr. F. Mahoney Dr. T. Vernon Merck Dr. D. West Merck
5:30	Varicella Vaccine Update	Information	Dr. T. Vernon Merck
6:00	**ADJOURN**		

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OCTOBER 24

8:30	Recommendation for Vaccination of Health Care Workers	Draft Statement	Dr. R. Strikas Dr. W. Williams
~~9:00~~	~~Programmatic Strategies to Increase Immunization Coverage – Reminder/Recall~~	Draft Statement	Dr. E. Maes cancelled
9:30	Immunization Working Group of the U.S./Mexico Bi-National Commission	Information	Dr. J. Cordero Dr. R. Tapia
9:40	Assessment and Feedback of Practice-based Immunization Coverage Data	Discussion	Dr. E. Hoekstra
10:00	**BREAK**		
10:30	Harmonization of Childhood Immunization	Draft Schedule	Dr. J. Gindler
11:15	Rabies Postexposure Prophylaxis (PEP)	Draft Statement	Dr. C. Rupprecht
11:45	Public Health Service Opportunistic Infections Work Group	Information	Dr. J. Kaplan
12:00	**LUNCH**		
1:00	Status of SmithKline Beecham Biological's Candidate Herpes Simplex Virus Vaccine	Information	Dr. G. Dubin SmithKline Beecham Pharmaceuticals
1:30	Update on Clinical Developement of DTaP and Hep B Clinical Vaccine	Information	Dr. D. Krause SmithKline Beecham Pharmaceuticals
1:45	Results and Analysis Study of Influenza in Pregnant Women	Discussion	Dr. N. Arden Dr. M. Griffin
2:15	Unfinished Business		Dr. J. Davis
2:45	Public Comment		
3:00	ADJOURN		

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ATTENDEES:

Committee Members
Dr. Jeffrey Davis (Chair)
Dr. Barbara Ann DeBuono
Dr. Mary Glode
Dr. Marie Griffin
Dr. Fernando Guerra
Dr. John Modlin
Dr. Jessie Sherrod
Dr. Steve Schoenbaum
Dr. F. E. Thompson
Dr. Joel Ward

Ex Officio Members
Dr. Robert Breiman (NVPO)
Dr. Geoffrey Evans (VICP)
Dr. Carolyn Hardegree (FDA)
Mr. Randolf Graydon (HCFA)
Dr. Kristin Nichol (VA)
Col. Relford Patterson (DOD)
Dr. G. Rabinovich (NIAID)

Liaison Representatives
Dr. Richard Clover (ATPM)
Dr. David Fleming (HICPAC)
Dr. Stanley Gall (ACOG)
Dr. Pierce Gardner (ACP)
Dr. William Glezen (IDSA)
Dr. Gregory Gelmet (AAHP)
Dr. Neal Halsey (AAP)
Dr. Kristin Nichol (VA)
Dr. Georges Peter (AAP)
Dr. William Schaffner (AHA)
Dr. David Scheiffle (NACI)
Mr. Howard Six (PhARMA)
Dr. Richard Zimmerman (AAFP)

Executive Secretary
Dr. Dixie Snider

Office of the Director
Dr. Claire Broome
Tremayne Mackey (Student)
Dr. Gladys Reynolds

Office of the General Counsel
Kevin Malone

Office of Public Affairs
Barbara Reynolds

Epidemiology Program Office
Robert Black

National Center for Infectious Diseases
Dr. Farhad Ahmed
Dr. Louise Barden
Dr. Joseph Bresee
Dr. Scott Campbell
Dr. Terry Comans
Dr. Rita Helfand
Dr. William Heyward

National Immunization Program
Dr. William Atkinson
Dr. Louise Barden
Dr. Kris Bisgard
Dr. Bob Chen
Dr. Steve Cochi
Dr. Jose Cordero
Ms. Roz Dewart
Dr. Clare Dykewicz
Dr. Don Ekwueme
Ms. Judy Gantt
Dr. Jacqueline Gindler
Dr. Steve Hadler
Dr. Beth Hibbs
Dr. Edward Hoekstra
Dr. Sonja Hutchins
Ms. Tamara Kicera
Dr. Charles LeBaron
Dr. John Livengood
Dr. Cortland Luhff
Dr. Mehran Massoudi
Dr. Walt Orenstein
Dr. Gary Rhyne
Dr. Sandy Roush
Dr. Jane Seward

National Immunization Program - Continued
Dr. Jim Singleton
Dr. Vishnu-Priya Sneller
Dr. Ray Strikas
Dr. Peter Strebel
Dr. Roland Sutter
Dr. Gina Terraceiano
Dr. Sherrilyn Wainwright
Dr. Jay Watson
Dr. Bruce Weniger
Dr. Melinda Wharton
Dr. Walter Williams
Dr. Wiliam Williams

Other Government Attendees
Dr. Bruce Gellen, NIH
Dr. Peter Patriarca, FDA

Others Present
Ann Bostrom, Georgia Tech
Raul Montesano Castellanos, M.D., Mexico Ministry of Health
Jill Chamberlain, Vaccine Bulletin
Paul Coplan, Merck & Co. Inc.
Donna Cory, Merck
Dee Czaykowski
Dack Dalrymple, Bailey and Robinson
Corry Dekker, Chiron Biocene
Jose-Luis Diaz-Ortega, Mexico Ministry of Health
Gary Dubin, M.D., SmithKline Beecham Pharmaceuticals
Joseph Eiden, Chiron Biocine
Vidor Emmanuel, Pasteur Merieu, Connaught
Elizabeth Goss, Fox, Bennett & Turner
Dan Granoff, Chiron Corp.
Kelley Gray, Chiron Vaccines
Jesse Greene, S.C. Department of Health
Daniel Gregory, SmithKleine, Beecham
Jeff Hackman, Connaught Laboratories
Valerie Hayes, Merck
Barbara Howe, SmithKlein, Beecham
Clifton Irby, Christian Science Committee on Publication
Rudolph Jackson, M.D., Morehouse School of Medicine
Cheryl Jones, Infectious Diseases in Children
Samuel L. Katz, M.D., Duke University Medical Center
Stephen Keith, North American Vaccine
David Krause, M.D., SmithKlein, Beecham

Others Present - Continued

Corry LaBarge, Merck
Chinh Le, Kaiser Permanente
Dr. Yvonne McHugh, Chiron Biocine
Dennis Parenti, SmithKlein, Beecham
Steve Perkins, SmithKline, Beecham
Jeff Peterson, Connaught Laboratories
M. Pichichero, M.D., Univeristy of Rochester Medical Center
Stanley Plotkin, M.D., Pasteur Merieux
Robin Pollini, ASTHO
Geoffrey Porges, M.D., Merck
Jane Quinn, Merck
Margaret Rennels, M.D., University of Maryland
Kristine Severyn, Ph.D., Ohio Parents for Vaccine Safety
Howard R. Six, Connaught Laboratories Inc.
Dan Soland, SmithKline Beecham
Dale Spriggs, VRI Inc.
Ling Su, Merck Research Labs
Roberto Tapia-Conyer, Mexico Ministry of Health
Julie Todd, JTC
Miriam Tucker, Pediatric News
Margaret Vaillancourt, IAC
Thomas M. Vernon, Merck Vaccine Division
Peggy Wang, Wyeth-Lederle
David Weeda, Olsson, Frank & Weeda
David West, Merck Research Laboratories
Deborah Wexler, M.D., Immunization Action Coalition
Ellen Wila

CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
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Opening Comments
The Advisory Committee on Immunization Practices (ACIP) was convened in Atlanta, Georgia by the Centers for Disease Control and Prevention (CDC) on October 23-23, 1996. Chairman Dr. Jeffrey Davis began the meeting at 8:34 A.M., welcoming Dr. Gregory Gilmet, the new liaison from the American Association of Health Plans (AAHP), and Dr. Howard Six, the acting liaison for the Pharmaceutical Research and Manufacturers of American (PhARMA). Dr. Six attended for Mr. David Williams; at the next meeting, Dr. Gordon Douglas would join as the official PhARMA representative. Dr. Snider asked the members who had to updated their disclosure form and had not received a signed copy, to see Gloria. He emphasized that honoraria (excluding travel) of up to $1000 do not constitute a conflict of interest in voting matters, particularly on such safety matters as adverse vaccine effects. Dr. Davis announced that travel expense reimbursements would now be by direct deposit; the members should completed the direct deposit forms for reimbursement. The 1997 meeting dates were announced: February 12-13, June 25-26, and October 22-23. Also distributed was the ACIP recommendation on adverse reactions to vaccines published in the *MMWR*.

The Committee members and attenders then introduced themselves, and the members declared any conflicts of interest. As Director of the Center for Vaccine Research, Dr. Ward received grants from Merck Sharpe and Dohme, SKB and Chiron Corporation, but he does not consult with any of them. Drs. DeBuono, Thompson, and Davis had no conflicts of interest. Dr. Glode had proposed a study on an unrelated vaccine with Chiron Corporation. Dr. Griffin had consulted with Merck on vaccines unrelated to ACIP discussions.

Dr. Guerra's department had recently completed a field trial on an acellular pertussis product, funded by a North American Vaccine Company grant. He also reported on past grants to the San Antonio Department of Public Health from Merck's Vaccine Division to enhance their computer tracking program of immunization levels. They are also soon to begin a demonstration project with support from SmithKline Beecham on a community-based hepatitis A vaccination program. Finally, there is a pending proposal with the MedImmune Company to do surveillance for the use of Respigam, a prophylactic treatment to prevent respiratory syncytial virus (RSV) infection in at-risk newborn infants.

Dr. Schoenbaum's wife owns stock in Amgen, Squibb, Bristol Myers, Glaxo and Proctor & Gamble, none of which make vaccines under ACIP discussion. Dr. Modlin's wife has some stock in Merck, Glaxo-Wellcome, and Chiron. He has consulted to and participated in educational programs funded

by Pasteur Merieux-Connaught, and his group at Dartmouth is working with MedImmune to study immunoglobulin and monoclonal antibody to prevent RSV infection. As Chair of the Pediatric Section of the National Medical Association, Dr. Sherrod solicited funds for an educational symposium at their July convention, resulting in potential conflict with North American Vaccine, Connaught, Merck and Lederle.

National Vaccine Program Update

Dr. Robert Breiman updated the ACIP members on the National Vaccine Program Office (NVPO). He reported a new high-level Department of Health and Human Services (DHHS) effort to promote adult immunizations, particularly with existing but underutilized vaccines. There is also discussion about improving adult vaccines and developing new ones. A functional strategy leading to measurable outcomes is planned by December 31.

The National Vaccine Advisory Council (NVAC) has participated in three papers. One describes a public health, industry and academia partnership to increase optimal vaccine development and use; another on registry confidentiality was prepared by NIP and endorsed by NVAC; and one by their Vaccine Coverage Subcommittee explores the various levels of responsibility for children's immunization. With currently stable funding for surveillance, NVAC is exploring improved surveillance options for vaccine-related adverse events. In mid-November, they plan to assemble interested parties at the Sabin Foundation's next Cold Spring Harbor meeting to discuss vaccine research and development. The NVPO Interagency workgroup is planning for post-licensure evaluation of acellular pertussis vaccine, as well as to fund unmet vaccine research needs in federal government. Proposals will be accepted, but current focus is on issues of adult immunization, pertussis in combination vaccines, and safety issues of long-term adverse events. Naming liaisons between NVPO and ACIP for mutual support has been discussed.

Dr. Snider added that the Adult Immunization Workgroup had met, chaired by Dr. Jo Ivey Bouford, the Principal Deputy Assistant Secretary of Health. Its liaison members addressed how to engage those outside the DHHS in these discussions. Dr. Breiman acknowledged the superb work by Gloria Kovach and Felicia Pearson in supporting both committees. Dr. Davis thought the delineation of NVAC/ACIP functions was important, and looked to NVAC to generate documents to support the ACIP's work.

Dr. Sherrod asked if the NVPO's partners included the public? Dr. Snider confirmed that for Adult Immunization Workgroup. However, an ongoing challenge for public health managers is to identify the proper representatives for the various segments of the community (he solicited help in doing so) within a still effectively-sized committee.

Dr. Sherrod was concerned that the ACIP meeting's agenda scheduled public comment at its end, after all deliberations and decisions were made. Dr. Snider suggested this be considered by the ACIP's Policies and Procedures workgroup. Dr. Davis pointed out that he calls on those attending during the meeting as well, though as Chair he must ensure that the meeting moves along.

Vaccine Injury Compensation Program Report

Dr. Jeffrey Evans noted that the September 30 report on all 1996 compensation program claims showed an average of nine claims per month. Nearly 90% of the pre-1988 claims had been adjudicated, disbursing about $700 million. About $125 million of that came from the Trust Fund, which again holds over $1 billion. He reported that the Senate Finance Committee had reviewed the proposed flat tax of 51 cents per antigen disease for the vaccine, applicable to all present and future vaccines covered under the program. The Vaccine Injury Table is being changed to add coverage for hepatitis B, Hib and varicella vaccines. He expected that to be published in the Federal Register in the next six months, but not funded until the excise tax is passed, anticipated in 1997. The compensation program's information is on the Internet through DHHS' Web page. This prompted Dr. Snider to ask the Committee's interest in posting the ACIP's meeting minutes on the Internet, to nods around the table. CDC will pursue this. Dr. Guerra asked if influenza vaccine was covered by the program, but it is not; only those vaccines recommended by CDC to be administered to children are included.

MMR Workgroup Report

Dr. John Modlin updated the Committee on the measles, mumps and rubella (MMR) statement, the first attempt to combine a number of statements. A number of changes were discussed at length by the workgroup. Editing is still needed, but most of the work was complete pending the ACIP/liaison comments. He hoped for a vote on the final statement during the February meeting.

Adverse Events of MMR in Adults

Dr. Ann Thomas stated the current relevant literature on adverse events of MMR in adults falls into three categories: common events following dosage in large campaigns of MMR in adults with unknown serostatus, and studies of occurrence of acute arthopathy in both rubella-seronegative adult women and chronic arthropathy in adult women receiving rubella vaccine (the RA27/3 strain, the only one licensed in the U.S. since 1979). Chen (1991) found no significant differences in documented fever, any rash, joint swelling or ache and injection site redness among MMR and monovalent vaccinees and unvaccinated controls at two colleges. Seager (1994) investigated adverse events (joint swelling, arthralgia, myalgia and other events) to monovalent measles or measles/rubella (MR) vaccine in a mass vaccination campaign. The only difference to the Chen study was fewer vaccinees experienced joint symptoms. These two studies were limited by lack of information on vaccinees, low response rates, long period of follow-up in the Seager study, and unknown susceptibility of vaccinees. However, they did confirm that MMR is well tolerated by adults. Polk (1982) examined acute arthritis/arthralgia in a prospective double-blinded, controlled trial of adult female seronegative health care workers aged 19-58 (median 30) years, vaccinated with MMR. This showed little illness or days lost. Fogel (1971) studied adult females (aged 21-39 years) in a prospective controlled study of rubella vaccine. Mild joint pain was reported by 32%. Orenstein (1981) followed 38 adult female seronegative health care workers (mean age 31 years), who received rubella vaccine. Again, 32% had any joint pain versus 3% of the seropositive controls, and only 8% (0% controls) had joint swelling. Only two persons missed any days from work. The conclusions regarding acute arthritis/arthralgia were that joint manifestations ranged in rates from 26-32%, joint reactions were mild and transient, and absenteeism was minimal. However the study limitations

included small sample sizes limiting the ability to stratify by age, and the limited duration of follow-up.

Next, Dr. Thomas addressed the risks of chronic arthropathy. She summarized the 1991 Institute of Medicine (IOM) report on studies by Tingle (1983, 1985, 1986) and Chandler (1981, 1982). They reported cases of persistent arthritis or arthralgia following rubella vaccine in six seronegative women. Both researchers isolated rubella virus from the peripheral blood of patients with persistent post-rubella vaccine arthritis. IOM concluded a causal relation between the rubella vaccine strain and chronic arthritis in adult women, although the evidence was limited in scope.

IOM suggested further studies, which were conducted by Slater (1995), Frenkel (1996) and Ray and Tingle (submissions expected December 1996). Slater studied chronic arthropathy of postpartum women aged 16-43 years (mean age 29) in a retrospective cohort, showing no statistically significant differences. Ray's chart focused on women aged 15-59 years, matched in age to controls, with a one-year follow-up period. There were no significant difference in rates (per 1000 person-years) for either rheumatoid arthritis or other conditions. Tingle studied postpartum women aged 18-42 years. He found a a significantly increased incidence of acute arthropathy in all the vaccinees relative to the placebo group; for combined symptoms, the rate was 30% versus 20%. While there was no evidence of increased incidence of recurrent or persistent nephropathy (arthralgia or arthritis 5-15 weeks post-vaccination) among the vaccinees, there was a high rate of joint complaints in the preceding ten years. Frenkel looked for persistent rubella infection in persons with chronic symptoms after rubella infection and immunization, and in patients with juvenile rheumatoid arthritis (JRA). Rubella virus was isolated in four of the 18 controls, but no cases. A PCR assay found rubella virus in the blood of two controls, but not in that of two of the six vaccinated cases, or three of the 11 JRA cases. It was concluded that the large controlled cohort studies did not support a link between chronic arthopathy and rubella vaccination, and that rubella virus in the peripheral blood of subjects with persistent arthropathy. The studies' limitations included Slater's potential underestimation of joint symptoms, and an insufficient sample size to detect differences in rates of persistent arthritis/arthralgia. Overall, the risk of any acute joint manifestations was 26-32% in seronegative adult females, and 0-3% in seropositive adult females. There was minimal absenteeism due to adverse events, and the evidence did not support a causal role for rubella vaccine in the development of chronic arthropathy.

Discussion

Dr. Rabinovich asked about study power. Dr. Thomas reported that while Tingle's power calculation was unknown, his study showed a higher background rate than in the other studies (NHANES' is 5%). However, this could stem from his definition (recurrent or persistent arthralgia from 5-52 weeks postpartum). However, there were amply large populations in other studies, like Kaiser in California. But Dr. Halsey appreciated this point, advising examination of power in the studies cited. He thought CDC's presentation of rubella vaccination in pregnancy a good example of prospective studies lacking optimal data power, citing as well the data presented on secondary vaccine failure and waning immunity. Though he was not convinced that MMR causes arthropathy, he thought the

study power insufficient to rule out a possible causal relationship. He advised in any statement to say that the arthropathy occurs at a rate lower than some specific point.

MMR Workgroup Report on Recommendations

Dr. Modlin then reviewed a chart summarizing and comparing the ACIP recommendation on health care workers (HCW) discussed in June (Option A), and the MMR workgroup's current proposal (Option B). The current acceptable evidence of immunity for measles and mumps is to be born before 1957, to have documentation of physician-diagnosed measles and mumps and laboratory evidence of immunity, or to have received two doses of measles and one dose of mumps vaccine. Evidence of rubella immunity is appropriate laboratory data or one dose of vaccine.

A small number of measles cases occurred in HCWs born prior to 1957, and about 5% are assumed to have no measles antibody. Therefore, in the absence of physician-diagnosed measles or laboratory evidence of immunity, Option A was strengthened to include at least one dose of measles vaccine for those HCWs born before 1957, and two doses of measles vaccine for those born during or after 1957. The mumps evidence of immunity did not change. However, the workgroup subsequently decided that this was overzealous, and recommended going back to the existing standard for acceptable evidence of immunity.

The current implementation recommendation distinguishes between those born before and after 1957 for measles and rubella, as well as by employment status and occupation. Beginning workers are to have evidence of immunity, but this may or may not be required of existing workers. The June draft strengthened this to require implementation among all employment status settings, occupations, and years of birth for measles, mumps and rubella. The October draft called for all medical facilities to ensure their HCWs' immunity, but returned to the birth year distinctions. All HCWs born before 1957 could be considered immune to measles and mumps, but not to rubella; all facilities should ensure rubella immunity. It was likely that most HCWs born before 1957, if employed according to the existing recommendations, would have been screened or immunized against rubella, and could be considered immune to all three. Option B proposed that existing HCWs born before 1957 who do not have laboratory evidence of rubella immunity, or who had not received one dose of rubella vaccine, should be fully immunized whether they are existing or new employees.

Discussion

Dr. Glode asked why Option B did not combine birth before 1957, a history of measles, and documentation of physician-diagnosed mumps, or laboratory evidence of immunity or two doses of vaccine. Without that, one would not be considered immune. Dr. Modlin responded that the problem arises in determining whether a person actually had measles, since memory and personal history are not reliable. And, it was not appropriate to base the recommendation on birth year alone, since about 4%-5% born before 1957 are seronegative for measles.

Dr. Schoenbaum noted that 4% of measles cases are trasmitted in medical facilities, not the greatest site of transmission. There is no evidence that congenital rubella in the U.S. is related to HCWs. While the ACIP might want to recommend rubella immunity among HCWs or adult women

considering childbearing, he noted the difference between mandated action and informed consent made with available data.

Similar concerns were expressed about the expansive definition of "health care worker". While in some offices this recommendation may make sense (e.g., pediatric), in others it may not (e.g., urologists treating adults beyond child-bearing age). Dr. Gardner noted that HCWs are only one quarter of the problem in hospital cases; the other 75% involve patient-to-patient transmission. He also observed that the figure chart basically states that all HCWs must show evidence of having received one dose of rubella vaccine or laboratory evidence of immunity.

Dr. Halsey also was concerned at potentially overzealous implementation regarding mumps. The draft's text (page 20, lines 24/25) advises vaccination for persons born before 1957 who are unsure of their history of mumps disease or vaccination. He thought that only about 50% of these would have had clinical mumps, and offered to provide clearer rewording to avoid immunizing up to 50% of HCWs. Next, he addressed the referenced "indeterminant" test. Reviewed EIA tests showed that most adults with indeterminant tests had neutralizing antibody and were considered immune. He was particularly concerned about pregnant women with indeterminant tests. He recommended a change to say that previous immunization negates the need for additional doses.

Dr. Chinh Le commented that most physicians do not know how to diagnose mumps, especially illness that could be associated with CMV, HIV, etc. And, noting the zealousness of employee health services to follow CDC recommendations, he warned against equating mumps with measles and rubella. While mumps can be transferred nosocomially, mumps has a very different impact than measles. Since seroscreening for mumps adds to costs, perhaps without as great a need, he recommended removing mumps from the recommendation.

Dr. Griffin recalled the members' discomfort at the last meeting with the idea of inoculating with MMR all HCWs born before 1957. That requirement was removed for measles, but slipped back in for rubella. This will require that employee health services recall all employees born before 1957, few of whom will have documentation of immunity. When Dr. Modlin responded that this is based on data that older adults are more susceptible to rubella than measles or mumps, Dr. Griffin agreed, but asked if the incidence requires such an extreme response. Dr. Modlin stated that although the numbers of HCW case transmissions are small, they have persisted over time.

Dr. Hadler said that the elevated risk of measles in HCWs was shown in 1989 to be four- to ten-fold higher in HCWs than in same-aged adult populations. There is no need to risk the transmission of measles by susceptible HCWs to immunocompromised patients. He also noted the long-standing character of the rubella recommendation; 22% of rubella occurs in persons born before 1957, versus about 5% for measles and mumps and 5-10% among the older population. Immunity could be required only of those likely to expose women in early stages of pregnancy, but identifying either would be impossible. Dr. Orenstein also was reluctant to retract a long-standing recommendation such as this one, and raised CDC's bigger concern about measles, due to its resurgence.

Dr. Schoenbaum was concerned with the underlying ethical issue of whether wishing to prevent diseases in certain settings justifies required immunizations in those with a probably small but unknown risk. He questioned imposing a mandate when most of what is desired can be done on a voluntary basis with informed consent. Dr. Thompson, however, thought that any increased risk in HCWs is peripheral to their ethical obligation to not trasmit rubella to patients. Since only a small proportion of workers would not have contact with susceptible populations, he advocated a standard of immunity.

Dr. Hardegree wished to ensure the clarity of the draft's proposed rubella recommendation that all employees of a facility will be included, as opposed to the present delineation of those with patient contact. Dr. Modlin agreed, in terms of implementation of the change; there is no recommended change regarding evidence of immunity. Dr. Guerra also raised consideration of paramedics and EMTs, as HCWs.

Dr. Peter asked if there is evidence to prove that those born before 1957 would remain a reservoir of transmission, and therefore support the need for proof of immunity. He also advocated an emphasis to ensure that hospitals adopt policies for those born after 1957, including new and current employees, to address most of those susceptible. But that still leaves the group born after 1957, and involves questions of where a hospital should place its resources. He also noted that perhaps improving implementation for those born after 1957 should supersede efforts to address those born before 1957.

Dr. Walter Williams reported that CDC's 1993 survey of hospital policies on vaccinating HCWs showed only a 42% implementation of the measles recommendation for new staff , and 38% in current staff. Only 29% of hospitals implemented the two-dose recommendation, and <50% implemented the rubella recommendations. His point was that less than half the hospitals do anything at all, and some are affected by state hospital code laws requiring certain vaccines. Dr. Orenstein suggested replacing "should be required" to "should be immune" in the text for measles (page 26, line 19). Dr. Modlin added that the table text under implementation for Option B could read "all medical facilities should take steps to ensure their employees' immunity".

VOTE. Dr. Modlin moved to accept the Option B recommendation. Dr. Thompson seconded the motion. Those in favor of Option B were Thompson, Davis, Guerra, Sherrod, Modlin and Glode. Voting against were Ward and Griffin. Drs. Hadler, Schoenbaum and DeBuono abstained, and the motion carried. To address those members who wished to soften the language on page 26, a straw vote was taken, with seven affirming the wish to do so.

Link Between Measles and Crohn's Disease

Dr. Gina Terracciano updated the ACIP members on recent reports from Sweden and the U.K. suggesting that exposure to measles virus or vaccine might be a risk factor for development of Crohn's disease (CD). Inflammatory bowel disease (IBD) includes both Crohn's disease and ulcerative colitis (UC).

British researchers stated that measles virus is present in GI tract lymphoid tissue during primary infection, producing a vasculitis and necrosis of the intestinal epithelium and development of lymphoid aggregates. The virus can cause ulceration of the entire GI tract, and its ability to persist in cerebral tissues infers that it also can do so in the GI tract. Therefore, they hypothesized that Crohn's disease many be a chronic granulomatous vasculitis following persistent infection with measles virus within the vascular endothelium. Wakefield studied intestinal tissue specimens of 24 IBD patients and 22 controls. He concluded that measles virus can cause persistent GI infection, and that it is a common and consistent feature of CD-infected tissues. PCR-analysis of DNA also revealed Epstein-Barr virus and human herpes virus 6. However, Wakefield's findings have not been replicated by other investigators. Liu studied 21 patients with CD and 28 controls. Using histochemical methods similar to Wakefield's, they did not detect measles virus, though they did find *e coli*, streptococci and listeria. In Japan, Iizuka examined intestinal tissue from 15 patients with CD, six with UC and ten with non-IBD. Using PCR, they did not detect measles virus. In 1995, MacDonald also expressed concern in *Lancet* about the selection of control tissues examined by Wakefield.

In epidemiologic studies of the perinatal period, Ekbom conducted a case-control study of perinatal risk factors for IBD by reviewing birth records for 257 known IBD cases and 514 controls delivered between 1924-1957. He showed an increased risk of IBD after perinatal infectious events (odds ratio of 3.8) and noninfectious events (odds ratio 3.5). Two of the 18 infectious events in IBD cases were maternal measles infection. Based on that, he studied all persons born 1945-54 in four Swedish counties and diagnosed with CD before 30 years of age. This time period included one influenza and five measles epidemics. Of children born during the three-month period after the peaks of the measles epidemics, they observed 57 cases of CD rather than the expected 39, with a standardized incidence ratio of 1.46.

Ekbom thought this strengthened Wakefield's hypothesis of a CD-measles relationship and a vulnerable perinatal period. He and Wakefield then studied CD after in-utero virus exposure, reviewing about 25,000 births from 1940-1949. Of these, four women developed measles infection, and three of their four children developed CD. Immunohistochemistry and electron microscopy methods showed their intestinal tissues to be positive for measles virus nucleoprotein antigen. They concluded that the mothers' exposure to measles virus risks CD later in life in utero children, and that such exposure may lead to persistent infection or modify the response to infection in later life, leading to persistence of measles virus.

Thompson and Wakefield also retrospectively studied three populations to see why IBD had increased in the three decades since the introduction of measles vaccine. The cohort of cases (3545 children) were vaccinated at 10-24 months of age in the measles vaccination trial. One comparison group (11,407) participated in the National Childhood Development Study (NCDS) of 98% of children born in one week in 1958. The other comparison group consisted of the partners of the measles vaccinees (2541 persons). They found an increased risk for CD of 2.0-3.0 and for UC (1.58 to 2.53) in measles vaccinees compared to both control groups.

There were many published responses to the resulting Thompson and Wakefield article. Patriarca and Beeler noted differences in recruitment and interviewing of cohorts, invalid comparability of cohorts, and different verification of IBD and vaccination status. Farrington and Miller cited biases from differential loss to follow-up and case ascertainment. Miller and Renton cited recall bias, and Baxter and Radford thought this study should have been a case-control study. Another *Lancet* letter noted that CD incidence in Great Britain had been increasing for two decades prior to the introduction of measles vaccine.

CDC looked at the study's case ascertainment to draw their own calculations. The authors had stated that since IBD prevalence in the NCDS group was higher than previous studies, they had not under-ascertained cases. But CDC found that they had compared cumulative IBD incidence in their study groups followed over time to point prevalence in all age groups of other studies. CDC compared cumulative incidence in the study groups to that expected based on age-specific IBD incidence rates, and duration of follow-up based on a large population-based Swedish study. Their calculations revealed that Thompson's 25 expected cases was close to that ascertained (22), but in the comparison groups (NCDS, partners) they had only ascertained 39 of their expected 91 cases.

Dr. Terracciano summarized CDC's concerns on the research done to date. No other researchers have been able to duplicate Wakefield's laboratory findings, and there are concerns about the specificity of his laboratory methods as well as concerns about the study design, methods and analyses used in Thompson's epidemiologic study.

Discussion

Dr. Terracciano reported that CDC's Dr. Bellini had offered to work with Wakefield's group to recover the viral genome through PCR analysis, but that offer was not followed up. Dr. Katz suggested coordination with the North American Gastroenterological Pediatric Association for follow-up. Dr. Modlin reported the workgroup's feeling that the data are insufficient to prove or disapprove an association between CD and prior measles infection, but sufficient to add a line to the statement as follows (page 46): "Therefore, available evidence does not support a causal association between measles virus or vaccination with measles vaccine and the subsequent development of Crohn's disease."

VOTE: Dr. Modlin moved to approve this language. Dr. Sherrod suggested editing the language relating to causal association as opposed to causal relation, but Dr. Rabinovich noted that neither has been demonstrated. The committee voted unanimously to approve the text's intent, with editing to be done to refine it.

Dr. Modlin welcomed committee member's suggestions for edits to the adopted Option B.

In recognition of their now-concluding service to the ACIP, Dr. Snider presented Dr. Thompson and Dr. Ward with a certificate and letter of appreciation from Dr. Satcher, as well as the book *Sentinel for Health*, a history of CDC's first fifty years.

Dr. Snider then noted the conclusion of the long and unusual polio immunization schedule recommendation process, marked by the ACIP's open and committed approach in dealing with the associated complex issues. After careful consideration of the situation, review of the literature, and consultation with experts and organizations in the field, Dr. Satcher decided to accept the ACIP's recommendation. CDC is now ready to move forward with all three schedules (IPV, OPV and sequential) as acceptable, and one (sequential) recommended. The agency is actively pursuing implementation. However, this process raised questions on how the ACIP responds to changing situations of public interest. Dr. Davis chairs a committee to investigate how procedures could be modified to optimize the committee's functions.

Polio Vaccination Recommendation Implementation Plan

Ms. Shaunette Crawford described for the members the National Immunization Program's (NIP) polio vaccination recommendation implementation plan. Member comments were solicited to be received by November 1. Completed activities include Dr. Satcher's approval and a signed contract for adequate IPV supply. Contract negotiations for OPV are ongoing and the polio Vaccine Information Statement (VIS) is in revision.

The Communications plan includes a Dear Colleague letter mailed to 262 partner organizations and a Polio Vaccine Update letter to over 16,000 partners and providers. Also planned are letters to editors of magazines and professional journals, public service announcements (PSAs), and on-line information. Meetings are scheduled, one with partners in October to refine the plan (parent and provider education, monitoring impact on vaccine coverage and monitoring polio and adverse events) and in November with the state Immunization Program managers and directors.

The Training/Education plan uses culturally- and language-specific materials to educate families, caregivers and health care providers about polio, and to promote regular parent consultations with physicians on their children's appropriate immunizations. Outreach about the new schedule included 16 focus groups, satellite training to over 27,000 public and private providers, the imminent release of a an updated training video, and increased grand rounds lectures to providers. Audience-specific updated educational materials about IPV/OPV and general immunization information are in development.

The Monitoring plan will assess the impact of the policy changes in the public/private sectors and the impact on coverage of polio and other vaccines in the first two years of life. It is also designed to enhance surveillance for the resurgence of wild/vaccine polioviruses and other vaccine-preventable diseases, and to monitor vaccine safety for adverse events after expanded use of IPV. Monthly monitoring will be done through surveys of VACMAN (the state vaccine ordering database) and of state immunization grantees, as well as through the Clinic Assessment Software Application (CASA), which monitors implementation impediments in U.S. public clinics. Also to be tapped are the immunization registries' real-time data, the National Health Interview Survey and the National Immunization Survey, which can differentiate between IPV and OPV at national and state levels. Polio and vaccine safety will be monitored through enhanced communication with pediatric and adult neurologists, consultation with the Vaccine Compensation Program, review of weekly reports

of vaccine-preventable diseases and monthly reviews of data from the Vaccine Adverse Events Reporting System (VAERS). Immediate action will result if needed. Gradual implementation of the IPV/OPV schedules will begin in early 1997, after the states distribute the new VIS to parents and providers, stock IPV and OPV, provide training to providers and assure operational vaccine contracts.

Discussion

Dr. Halsey noted that a change in CDC's surveillance for adverse reactions would reflect an increase in events not necessarily due to any change in the schedule. Public education should include how to interpret those data. Dr. Davis also advised comparison of the previous surveillance systems to that now planned. Dr. Orenstein commented that CDC's Vaccine Safety Data Link, covering about 2% of the U.S. birth cohort, will be the major part of the past/present surveillance for adverse events. The most active surveillance will be accomplished through collaborations with neurologists, perhaps uncovering previously undetected cases of vaccine-associated paralytic polio (VAPP).

Dr. Sherrod asked about CDC's current and planned monitoring of wild virus resurgence. Dr. Hadler said that the traditionally passive polio reporting was supplemented by the collaborative studies of CDC's enterovirus laboratory. It now would also be strongly stimulated by collaboration with pediatric and adult neurologists to better detect cases. Wishing to capitalize on the public health infrastructure in place, Dr. Sherrod asked if public health labs automatically reported isolated poliovirus to CDC. Dr. Hadler responded that polio disease is reportable, but the enterovirus reporting is voluntary and non-comprehensive.

Dr. Thompson reported that the Council of State and Territorial Epidemiologists (CSTE) also recommends physician reporting of isolated polio virus in those states where lab reporting is mandatory. Although he thought it very unlikely that a U.S. viral lab isolating wild polio virus would not report it, he also noted that very few labs can distinguish between wild and vaccine poliovirus. When found, common poliovirus is automatically assumed to be vaccine-related and is not routinely forwarded to the state or CDC labs. His lab is unusual in typing enteroviruses, and finds about 20% to be poliovirus. Sequencing or hybridization could be done, but he thought hat typing all polio isolates would be an impractical request. Dr. Glode asked if the samples from those laboratories collaborating with CDC's enterovirus lab would be sufficient to comprise a sample, and Dr. Hadler responded yes, theoretically; several hundred arrived each year.

Dr. Katz advised expanding surveillance of acute flaccid paralysis beyond neurologists, since many physicians may not seek such a consultant, and urged that stool samples be obtained from patients with acute flaccid paralysis. Dr. Modlin also thought most physicians or neurologists would be more likely to diagnose Guillain-Barré Syndrome, tick paralysis, neural abscess, etc. than polio. The diagnosis of acute flaccid paralysis must be very clear. Dr. Hadler solicited suggestions of physicians to contact for reports during CDC's planned surveillance expansion. Dr. Ward commented that sampling could help find wild poliovirus and maintain a measure of how much a vaccine strain is circulating at any point in time. He wondered if this could be piggybacked onto the sampling done for respiratory viruses.

The committee agreed to the importance of differentiating between wild and vaccine virus. The use of CSF specimens for virus isolation was suggested because of the large number of attenuated viruses isolated from stool specimens by labs. Those isolates will provide a natural selection, and potentially provide a higher yield of wild virus.

Because of the difficulty in distinguishing between wild and vaccine virus, Dr. Sherrod asked how CDC concluded there has been no wild polio since 1979. Dr. Hadler clarified that this refers to cases of indigenously-acquired paralytic polio. Although importation of wild viruses in the U.S. is at about 100-150 per year. The sensitive surveillance associated with VAPP cases has not detected any wild virus disease, and sustained transmission of wild virus would result in more than 5 per 100,000 cases of paralytic diesease.

Dr. Plotkin asked if sampling could be confined to identified high-risk populations, and maintained at a relatively low cost of sample collection and processing. Dr. Modlin suggested targeting surveillance to areas most likely to produce problems; e.g., by examining the sewage of airplanes arriving from polio-endemic areas. Even informational data could be useful, such as virus isolation data from surveyed clinical and public health laboratories. Dr. Davis noted that laboratory submissions were successfully sampled at a specific time each month to assess bacterial enteric pathogens associated human health effects, perhaps similar sampling methods could be used.

Dr. Sherrod concluded that CDC does not know the current status of wild polio, which must be known to ensure realistic outcome measures. She also asked how CDC plans to include all the options in a published harmonized schedule. Though reassured by Dr. Davis that the Working Group on a Harmonized Schedule had addressed this, she found the schedule complex even without options. She advocated an ACIP approach within an overall strategic plan. This is particularly necessary in light of the emerging combination vaccines, some of which should perhaps not be included in the schedule. Dr. Hadler said that some thought had been given to a strategy, particularly regarding in the Committee's decision to publish the schedule only once a year in January.

Update on Polio Surveillance

Dr. Rebecca Prevots reported that since the June 1996 meeting, reports of 14 suspected polio cases had been received by CDC for review, and 13 reviews were completed. Onsets of polio cases occurred in 1986 (1 case), 1989 (1 case), 1994 (3 cases), 1995 (4 cases) and 1996 (1 case). There were five recipient cases, three immunologically abnormal and two contact/community acquired cases. Cases of VAPP by year are eight cases in 19994, seven in 1995, and one in 1996. Recent recipient cases are stable, and contact cases have declined somewhat. Dr. Prevots also showed the statement's updated risk estimate table for VAPP from OPV (1980-1994). The 124 total cases equated to one case per 2.4 million doses distributed. The VAPP risk from the first dose is one case per 1.5 million distributed doses, for an overall excess risk of one case per 760,000 first doses.

The implementation plan includes monitoring of enhanced polio surveillance and the impact of the schedule change. The plan goals are (1) improved timeliness of polio case surveillance through a quarterly case review, (2) increased feedback and physician awareness through newsletters to

professional organizations of medical specialties (e.g., child and adult neurologists, pediatricians, immunologists, infectious disease specialists) in addition to planned meetings. Planned 1997 publications include a March *MMWR* polio surveillance update and the update on ACIP polio statements. Dr. revots reported that the published VFC vote produced only one comment, which was in favor of the vote.

Dr. Prevots outlined the VFC vote components. The ACIP recommended a schedule of two doses of IPV vaccine at 2 and 4 months, and two doses of OPV at 12-18 months and at 4-6 years. The resolution also found acceptable four doses of IPV at 2,4, 12-18 months and 4-6 years, and 4 doses of OPV at 2, 4, 6-18 months and 4-6 years. Footnotes and text clarify these recommendations. The first dose of the polio vaccine series may be given as early as six weeks of age. The recommended schedule may vary for infants and children who do not begin the vaccination series at the recommended time or who are more than one month behind in the immunization schedule. Completion of polio vaccination with any of the options is acceptable, but four doses of any combination of IPV or OPV by four years of age is considered equivalent to a complete polio vaccination series when administered according to the licensed indications for minimum ages and intervals between doses. Finally, the contraindications and precautions to use of OPV and IPV in the VFC program had been previously defined in the ACIP resolution 6/94-8. This proposed recommendation included a contraindication for those who experienced an anaphylactic reaction to a previous dose of OPV.

The proposed ACIP resolution, which also rescinded ACIP Resolution 2/94-11, was:

> "The ACIP recommends the number of doses, schedules, qualifications and contraindications as noted above and in the text of the new ACIP recommendations on poliomyelitis prevention ("Recommendations of the Advisory Committee on Immunization Practices: Poliomyelitis Prevention in the United States: Introduction of a Sequential Schedule of Inactivated Poliovirus Vaccine (IPV) Followed by Oral Poliovirus Vaccine (OPV)" - *MMWR*, in press) for the Vaccines for Children Program. This recommendation will become effective on February 1, 1997."

Discussion

Dr. Thompson asked why a vote was needed, since VFC already covers these vaccines. Dr. Hadler clarified that since the previous recommendation dealt explicitly with OPV or IPV alone and only implicitly addressed combinations, this must be explicitly stated. Mr. Kevin Malone of CDC's General Counsel also noted that the 2/94.11 resolution also specifically endorsed an all-OPV schedule; this is to reverse that.

Dr. Ward re-raised harmonizing OPV and IPV at 6-18 months for the third IPV dose, though there is some conflict with the package insert. Dr. Hardegree responded that the current FDA labeling is 12-18 months, not six months; an ACIP asterisk was inserted to provide that option. Dr. Sherrod supported this to ensure that children receive at least one OPV dose in year one (for intestinal immunity) and for greater provider ease. But Dr. Glode cited the schedule's intent to avoid OPV administration to an immunodeficient child. Dr. Sherrod disagreed with that from a public health

point of view, comparing a potentially lowering herd immunity to wild polio to the risk of a rare immune event.

Dr. Davis noted for Dr. Sherrod the ACIP's years of discussion on this, and Dr. Snider raised the practical fact that Dr. Satcher had accepted the ACIP's recommendation of the first dose of OPV at 12-18 months, with the 6-month OPV footnote. He would have to be notified of any ACIP change to therefore change his decision. Dr. Thompson commented that the public health point of view was well represented during these discussions, and the existing recommendation meets all those needs. Dr. Orenstein also observed that the harmonized schedule allows OPV use during the sequential schedule as early as 6 months. Dr. Carlton Meschievitz of Pasteur-Merrieux observed that their package insert revision application is at FDA, with data to support the use of IPV at six months, the sequential schedule of IPV at 2,4 months and the first OPV dose at either 12-18 months 6-12 months.

Dr. Sherrod asked for a risk-benefit analysis and summary of the last two years of discussion, since she had seen no algorithm to indicate how the ACIP arrived at its recommendation. Dr. Ward thought it would not be possible to provide an algorithm of three years of discussion.

VOTE. Dr. Thompson moved to accept the resolution as amended (showing an effective date of February 1, 1997 rather than January 15). The motion was seconded. In support were Davis, Ward, Glode, Griffin, Thompson, Guerra, DeBuono, and Schoenbaum. None were opposed; Modlin and Sherrod abstained and none absent. The motion carried, and the Committee adjourned for a lunch break.

Acellular Pertussis Vaccine Draft Statement

Upon reconvening, Dr. Emanuel Vidor, Director of Clinical Research for PMC, USA, reported on the clinical trials and recent licensure of combined acellular and Hemophilus influenza B (Hib/Tripedia™) vaccine for use as a fourth dose. The first trial was a comparative immunogenicity study comparing the combined Hib/Tripedia™ vaccine given as a booster dose to both vaccines given at separate sites. Children from 15-20 months of age participated who had received three prior doses of whole-cell pertussis (DTP) and Hib vaccines.

Both groups had strong antibody responses to PRP with high GMTs. A strong booster response to PT and FHA also was shown in both groups, except for a lower percentage of fourfold rises in the combined group. Diphtheria and tetanus also showed a strong booster response to the fourth dose, again with no differences between the groups. The study also assessed the antibody titers and percent of seroconversion to MMR antigens, before and 4-6 weeks after MMR vaccine, for those children who received it at the same time as the combined Hib/Tripedia vaccination. The 40 children had a high (96-98%) seroconversion rate. The conclusion was that Hib/Tripedia™ given as a fourth dose to children 15-20 months of age is as immunogenic as the two vaccines administered concurrently but at separate sites.

Dr. Vidor described three vaccine safety studies of about 2000 children at 13 U.S. sites. Again, they compared the combined vaccine to the two vaccines given separately, and evaluated the concomitant use of MMR. There were no differences between the combination group and the separate group for either local or systemic reactions. The pooled Hib/Tripedia™ safety profile data was compared to historical data of DTaP given as a booster, showing adverse events of <1% for fever >40 , persistent inconsolable crying, seizures, etc. Thirteen hospitalizations were unrelated to vaccine. The same safety profiles emerged for children who also received MMR, except that these children had a higher and more frequently delayed fever than in children who received the combined vaccine.

They concluded that there is no difference in safety profile between the combination vaccine of Hib/Tripedia™ and both vaccines given separately.

Dr. Vidor also reported on immunogenicity to PRP in subjects who completed the study. The infants who received three doses of the combination vaccine at 2,4, and 6 months were statistically significantly different than the infants receiving both vaccines at separate sites. There was a decrease of PRP GMT in the infants with the combination vaccine, but none in the other group. And, after three doses, there were no differences between the groups in pertussis antibody response except for a higher anti-FHA response in the combined group. These levels were comparable with those previously seen with Tripedia™ alone given for the primary series.

Discussion

Dr. Halsey asked if the data would be published, and Dr. Vidor reported one paper in process for publication. Dr. Orenstein was interested in the intensity of fevers in the 10-20 day interval and earlier. Dr. Meschievitz reported that first trial showed 2.9% of the combination vaccine group and 1.9% in the separate administration group to have fevers between 39-39.9°C; the efficacy trial showed this for 1.8%. Dr. Ward reconfirmed that this vaccine was reconstituted Tripedia.™ He noted that 5% did not respond after three doses to Haemophilus influenza, and asked if this was a concern or if it reflected a trend. Dr. Meschievitz noted that antibody was detected in the subjects not responding at the .15 μg/mL level, but that the upper 90% of the cohorts achieving that level did respond. When Dr. Orenstein asked if this study was being replicated, Dr. Meschievitz expected seven-month data later this year on another cohort. This could be shared with the committee.

<u>Acellular Pertussis Workgroup Report</u>

Dr. Marie Griffin reported on the acellular pertussis working group discussions of the fourth and fifth doses. Due to the paucity of safety data, Tripedia™ is licensed for four doses, but not for the fifth, in children who received four doses of Tripedia™. However, confusion arises because it is allowed for doses 4 and 5 in those who received three doses of whole-cell vaccine. Since the current recommendations allow whole-cell at 12 months, the workgroup favored a permissive statement about acellular vaccines at 12 months, even without much supporting data.

NIAID Multicenter VTEU Acellular Pertussis Fifth-Dose Trial Report

Dr. Michael Pichichero is the principal investigator for a NIAID multicenter VTEU acellular pertussis trial which compared six acellular pertussis vaccine with the Lederle whole-cell DPT as

a fifth dose in four- to six-year old children. This prospective, double-blind, randomized trial sought to assess the reactions and immunogenicity following the administration of DTaP or DTwP vaccination as a fifth dose, and looked at antibody persistence and evidence of immunologic memory in 2300 children. All the children had already received three primary doses of DTaP or DTwP at 2,4, and 6 months. The primary series trial included two vaccines, Lederle's and one produced by the Massachusetts Biologic Labs.

Thirteen hundred children continued in a fourth dose trial, and about 350 participated in the (unplanned) fifth dose trial. All had remained healthy, and received the same DTaP or DTwP as a fifth dose as they received in the first doses. If the child received a DTaP for the primary series later withdrawn by the manufacturer, he or she received one of the six participating DTaPs as a fifth dose.

Dr. Pichichero began by sharing the data from the primary series and fourth inoculations. They examined 1000 children after the fourth dose of vaccine for reactions including temperature, irritability, redness, swelling and pain. The primary series had already shown a significant increase in reactogenicity from the first to the third dose. They found minimal changes in fever after the fourth dose, except for a drop in those children who were whole-cell primed and then DTaP-boosted. There was little change in the fourth dose for irritability; there was a small drop with the Lederle vaccine, and in those who switched from a third dose DTwP to a fourth dose of DTaP. Local reactions were scored as 1-20 mm and >20 mm of redness/swelling, and pain was scored on cry/protest to touch (moderate) and cry when an extremity was moved (severe). The same trends were shown: a small increase in the larger swelling and redness with the fourth dose booster. The whole-cell vaccine showed a decline in the smaller swelling but an increase in the larger swelling. The same local reaction trends appeared with acellular boosting of whole-cell primed children: a drop from what was seen in the third inoculation reactions.

Dr. Pichichero presented the fifth dose booster reaction data on 125 children with five doses of the same DTaP, compared to ten children with five doses of DTwP. Few children had any fever or fever >102 F, and few had moderate or severe irritability. He showed a trend in temperature for the third and fourth doses, and for fever/irritability in the fifth dose. A drop was evident for the latter regardless of the vaccine used. He then showed data for local reactions of children receiving five doses of DTaP, showing significantly less redness of 1-20 mm in children who had received five doses of acellular versus five doses of whole-cell vaccine, and significantly less swelling of 1-20 mm and moderate pain. But, compared to the primary series and the fourth dose booster, there was a clear increase for acellular vaccines in local reactogenicity from the fourth to the fifth dose for redness, swelling and pain.

Dr. Halsey asked if they had compared children with no previous acellular or only one prior acellular dose, or if whole-cell was only used for dose five. He also asked if acellular reactogenicity was higher than if the whole series used acellular vaccine. Dr. Pichichero reported that some children received whole-cell for the fourth doses and then received DTaP. Those who received four doses of whole-cell then were randomized for the fifth dose. When five doses of DTaP with various

priming schedules were compared for local reactions, there was no significant difference between them regarding the fifth-dose DTaP booster reactogenicity data. He then compared DTwP with various mixes/matches. Only one comparison showed any statistical significance, and may not have been clinically relevant.

Dr. Rabinovich asked how the studies were adjusted for statistical variances. Dr. Pichichero responded that these data were analyzed by NIAID's Biometry Section, and had not been adjusted for multiple comparisons. In comparing children who received five doses of DTwP to those in various cohorts, there was some statistically significant increase in local reactions in relation to whether the cohorts were DTaP primed with one, two, three or four components, as long as they were boosted with DTaP. And, initial information shows no statistically significant changes in the percentage of children with the five common reactions to the fifth dose booster. Dr. Meschievitz confirmed for Dr. Peter that the package insert's data addressed the local reactions following the fifth dose of Tripedia™. When asked about power calculations, Dr. Rabinovich reminded the group that this was a follow-up, supplemental data study, and not powered as a clinical trial.

Dr. Pichichero then shared data showing low occurrence of on anorexia, drowsiness and vomiting, with no significant difference among the vaccines. To measure more severe systemic and local reactions, they examined fever (>104°), severe irritability, redness and swelling >30 mm or >50 mm, and severe pain. As a practicing pediatrician who has vaccinated 600-700 children with acellulars and >2000 children with various series, he was impressed at the absence of parents' reports of pain. Even the larger swellings with redness seem to be relatively painless, judging by the absence of parent feedback.

The Study Conclusions are:

1. When given as a fifth dose, the evaluated DTaP vaccines are associated with lower rates and severity of injection site reactions and similarly low rates of fever and irritability as compared to DTwP.
2. The DTaP-primed, DTaP-boosted groups show suggestions of variation in the reactions monitored, but no vaccine was most or least reactogenic regarding all the reaction categories.
3. Booster vaccinations for the fifth dose in this population showed a trend of intensifying reactions, but pre-booster vaccination levels (data not shown) were uniformly low and no correlation was found between the common reactions and the level of antibody.
4. Each of the vaccines produced significant increases in antibodies (data not shown) but there were differences among the vaccines reflecting their antigenic content.

Discussion

Dr. Glode recalled overimmunization with tetanus boosters in children that produced an Arthus reaction, associated with high anti-tetanus antibody levels. She asked if only pertussis pre-booster titers were low, or if diphtheria and tetanus titers were also low. Dr. Pichichero responded that the fifth-dose data did not show any correlation attributing local reactions to different diphtheria and tetanus antigenic content. He also noted that Arthus reactions are not only immune mediated but

also inflammatory, and the absence of pain seemed to contraindicate this. They do not behave like typical Arthus reactions.

Dr. Halsey wondered if an increase of reactogenicity would be seen in children who received all-acellular pertussis vaccine to that point. He also asked how the local reactions of such children to the fifth dose would compare to children getting whole-cell vaccine. Dr. Pichichero thought the data demonstrated no increase in fever or irritability to the fifth dose, but it is clear and statistically validated that five doses of acellular produce less local reactions than five of the whole-cellular vaccine. Parents can be assured that the reactions, are generally painless, and can expect an average 6-10% increase in reactions (especially local ones) with the fourth dose, and redness and swelling in as many as 20%-30% of children which is still three times better than whole-cell vaccine.

Dr. Paradiso noted that rare but dramatic reactions have been reported from the first three doses, and the fourth and fifth doses. He warned that one hazard of grouping data is that vaccine-specific events can be lost. He preferred to look at more children with five doses of the same vaccine.

Dr. Pichichero confirmed for Dr. Guerra that all the fourth doses were administered at 15-18 months, with a tight clustering around 18 months. Dr. Hardegree noted that more data will be available over time; the data on Tripedia™ was based on only 18 children, insufficient for an FDA response regarding the fifth dose. Dr. Pichichero agreed, but also wanted to avoid giving practicing physicians the impression that acellular vaccines should not be given for the fifth dose. A clear message is needed that these safer vaccines should be used and their series immediately begun.

Dr. Snider asked what data support four doses of DTaP and DTwP as the fifth dose, wondering if that would lead to a lower incidence of severe adverse reactions than using acellular vaccines. Dr. Pichichero responded that there were no such data from the NIAID VTEU trials. Dr. Zimmerman stated that the Tripedia™ package insert was only trying to accurately convey the data, not to discourage its use in five doses or to encourage one dose of whole-cell vaccine. He greatly regretted that this seems to have clouded the use of acellular vaccine.

Dr. Griffin summarized the situation. Tripedia™ is currently used for doses 4 and 5 following whole-cell, and is now licensed for the first four doses. There are little data on the safety of the fifth acellular dose after four acellular doses. The question was how much the statement should address this, particularly for infant use, without further confusing the situation. In a conference call, the workgroup agreed to the importance of using existing data, but they also wished to keep the statement simple and avoid weighing it down with multiple caveats. They decided to not dwell on the fifth dose, and were concerned that people may not want to start with acellular vaccines if they think they will have to switch back to whole-cell vaccines.

Dr. Griffin reviewed the contents of the draft statement. On page 13, it is stated under vaccine preference that DTaP is preferred for all doses in the vaccination schedule. The lack of FDA licensure for the fifth dose arises in Table 5 and in two statements. On page 11 (lines 16-21), it states:

"Data are insufficient to evaluate the safety of Tripedia™ when administered as a fifth dose to children 4 to 6 years of age who have received Tripedia™ for the prior four doses, but studies to collect information on the immunogenicity and safety of Tripedia™ in such circumstances are underway. Findings of these studies should be available before infants vaccinated according to the revised vaccination schedule require a fifth dose at 4 to 6 years of age."

There was also some workgroup discussion that the current wording (page 13, lines 7-9) that "data concerning safety are deemed insufficient, but do not constitute a contraindication", should perhaps be replaced with "data concerning the safety of this fifth dose are insufficient to date. However, such data should be available before infants vaccinated according to the revised vaccination schedule require a fifth dose at 4 to 6 years of age".

Dr. Zimmerman preferred to say that Tripedia™ can be used for the fifth dose rather than that FDA had not approved its use as the fifth dose. Dr. Hardegree approved of the revised wording, since the limited data make the contraindication an unknown. Dr. Glode endorsed the idea of keeping this simple, and expressed was concern that many physicians refer only to tables, thus an asterisked footnote by dose five should advise that while not a major issue, Tripedia™ is not yet licensed for this dose.

Dr. Halsey wished the statement to better address the concept that the reaction rate may be higher than now occurs with whole-cell vaccine. He suggested adding a sentence to the replacement text to the effect that "though data are limited, unpublished data indicate it to likely be less reactogenic for five doses than whole-cell vaccine". Dr. Zimmerman suggested also deleting the words "concerning safety". Dr. Griffin demurred that the concern is the lack of data regarding whether it is safe, and Dr. Hardegree agreed. Dr. Schoenbaum noted that only the lack of data have slowed FDA approval, which does not necessarily prejudice the case. Dr. Davis suggested stating that the ACIP would revisit this issue.

Dr. Griffin summarized that the draft's first statement under the safety section (page 11, line 18, "and safety") would simply be deleted, as would the second statement (page 13, line 9, "concerning safety"), and a statement would be added about limited unpublished data that five doses have a lower reactogenicity to whole-cell. She asked for a vote on the statement's intent with editing to follow, but also asked if an asterisk should be included in the table. Dr. Davis thought it should, to support what is stated elsewhere and to help those who only use tables.

Dr. Davis moved to accept this language, and was seconded by Dr. Guerra. In response to the request by Mr. Malone, he outlined the relevant companies that would cause a conflict of interest in this vote: Connaught, Wyeth-Ayerst Lederle, SmithKline Beecham, North American Vaccines, and Chiron-Virocine. However, as Dr. Modlin noted that this is an issue of vaccine safety, such conflicts may not apply. Dr. Davis also noted that this is a generic vaccine issue of DTaP versus DTwP, not of specific vaccines. Mr. Malone agreed, but advised caution on this very gray area, the

potentially significant increase in vaccine sales could raise conflict of interest. Dr. Snider reiterated that any member without significant financial interest could vote.

VOTE: Members if favor of the text as described were Davis, Thompson, Schoenbaum, DeBuono, and Griffin. None were opposed. Ward, Modlin, Glode, Sherrod, and Guerra abstained, and the motion carried.

Fourth Dose of DTaP

Dr. Griffin then addressed receiving the fourth dose of DTaP at 12-14 months. Factors supporting this include recently changed DTP recommendations allow a dose at 12 months if at least six months have elapsed since the third dose, and this might improve coverage rates and increase flexibility for children who may not return. Problems include DTaP is not licensed for this age, there are few data on immunogenicity and none for efficacy, giving the dose at 12 and 14 months this could increase the risk of short intervals between dose three and four, and confusion may rise since DTaP is currently administered at 15 months for the fourth dose.

In a conference call, the workgroup suggested adding to the draft's page 12 language that "When DTP is used, the fourth dose can be given as early as 12 months of age", and to add a footnote to the table that "DTP an be given as early as 12 months of age". An alternative proposal was to change this to:

> "At least 6 months should elapse after the third dose before the fourth dose is administered. If the interval between the third and fourth doses is at least 6 months and the child is unlikely to return for a visit at the recommended age, the fourth dose of either DTaP or DTP may be given as early as 12 months of age." And, the footnote would advise that "DTaP or DTP may be given as early as 12 months of age, provided that at least 6 months has elapsed since receipt of the third dose."

Lederle Presentation

Dr. M. Rennels presented the Lederle Takeda DTaP data sub-analysis of a four-center safety and immunogenicity trial. Vaccine from lots of the Lederle DTaP was given simultaneously versus combined with the conjugate Hib vaccine HbOC in younger (12-15 months) and older (15-18 months) toddlers. Participants in both age groups were randomized to receive the vaccines. Dr. Rennels described the serologic component of and participants in the study. Sixty-one were in the younger group (average age 12 months), 54 in the older one (about 15-16 months), with no gender or racial differences. There were no observed unusual or unexpected local reactions, incidence or severity of fever or other systemic reactions.

There were no significant differences regarding antibody to tetanus, typhoid, pertussis toxin (PT), FHA, pertactin (PRN), or FIM. All the children in both groups had 100% protective antibody levels against tetanus and diphtheria. Seroconversion, defined as at least a two-fold rise in antibody concentration, was outlined for PT, FHA, FIM and PRN. Dr. Rennels concluded that they had not found any differences in either safety or immunogenicity for the Lederle vaccines among these recipients.

Dr. Chin Le asked if the workgroup had looked at Hib titer. Dr. Rennels reported no difference between between the groups in post-vaccination geometric mean concentration of anti-PRP antibody. All children had >0.15 μg/ml, and 96-98% had >1.0 μg/ml. Dr. Le confirmed that all children had received whole-cell the first vaccination. They also could receive OPV, but did not receive MMR at the same time.

Dr. Paradiso emphasized that this was a study to compare the vaccines delivered in combination as opposed to separately, and that these are acellular pertussis vaccines licensed as booster doses after the administration of whole-cell vaccine. While the immune response and antibody response to the components was shown to be the same, the correlates of efficacy are not known under those conditions. The types and components will vary for different vaccines. While they are pleased with the data from this one lot, they areconducting studies with multiple lots and with an acellular rather than whole-cell prime vaccine.

Dr. Dan Brown noted that while the trial suggests efficacy after three doses, it also declines, and the booster dose is needed. The Italian efficacy study delivered the acellular vaccine at 2,4, and 6 months and still showed efficacy in the third year. While he thought the wording reasonable, he suggested that giving a booster at this age may not be as compelling, balanced with the lacking data on safety and immunogenicity. Dr. Griffin agreed there is no data on the fourth dose at 12 months; whether there may be a high local reaction rate is still unknown.

Dr. Fleming anticipated some problems in the public health sectors, since many health departments vaccinate children at 12- rather than 15 months, and this would invite a conflict on timing (e.g., with measles vaccination at 12 months). He advocated stronger language to allow children the dose at 12 months. Dr. Peter agreed, since increased reactions are unlikely at 12 months after a six-month interval, and there is the benefit of greater flexibility related to multiple injections. However, Dr. Ward recalled that one visit was desired to administer all vaccines, now almost impossible. Since two visits are and probably will continue to be needed, he saw no need to bring the timing down to 12 months.

Dr. Glode raised FDA and licensure issues versus the ACIP recommendations. She asked if there should not be a mention that this is not licensed for use at 12 months of age. Dr. Peter Strebel noted that there is a phrase in the statement regarding the package label; the question is whether the ACIP wishes to go further to address the ease of use in real-life situations. Dr. Modlin thought the bottom line to be the impact on immunization rates. Since it appears that a substantial number of children may miss the fourth dose if the 15-month visit is missed, and particularly since there seems to be no biologic difference in administering it at 12 or 15 months, he tended to agree with Dr. Peter. He supported inserting appropriate language that there is inadequate data for licensing at 12 months.

In response to Dr. Glode, Dr. Snider agreed that the ACIP must be consistent in identifying and explaining any disagreement in its recommendations with other guidelines. He also reported his and CDC Associate Director Dr. Claire Broome's recent meeting with high-level FDA staff to discuss

the manner of CDC and FDA collaboration, particularly regarding issuing statements and recommendations.

Dr. Thompson recalled moving the first MMR to 12 months to achieve an earlier measles immunity and he asked whether measles prevalence had decreased to a point where 15 months would again be an adequate age for first immunization. If so, a single visit at 15 months, would be compatible with the FDA recommendation for DTaP and provide MMR. Dr. Hadler said MMR is acceptable at 15 months and within the recommendatons, particularly with the current low measles incidence. He cited the declining prevalence of high-level measles antibody in mothers, providing a greater immune response to measles vaccine at 12 months. A survey of providers in 1995 indicated 60-70% of providers used two visits during the second year of life. Dr. hadler also noted, criticism of the government for off-label recommendations, and stated explicit language is necessary regarding use at 15 months and at 12 months, and the ACIP belief (based on immunogenicity and safety data with similar vaccines) was this vaccine could be used with similar efficacy at either time. Dr. Guerra and Dr. Clover noted potential barriers in managed care and in a perceived restriction on providers to watch for a child "unlikely to return".

VOTE. Dr. Ward moved to accept the alternative language shown on page 21 and was seconded. Since this was a safety issue, all the members could vote. Voting in favor were Griffin, Modlin, Schoenbaum, DeBuono, Guerra, Ward, and Davis. Opposed were Glode and Thompson; Sherrod abstained. The vote carried.

Other Issues

In other matters, Dr. Griffin noted the statement layout might be changed to separate the Tripedia™ and Hib/Tripedia™ information. Second, to address debate about anaphylactic reactions from DTaP, the workgroup discussed wording calling for no more doses of antigens (since the responsible dose would be unknown). Since immunity for tetanus had to be ensured, the wording changed to "should be referred for tetanus desensitization". But, since those risks/benefits were unknown, it was changed again to "may be referred for tetanus densensitization". There was no opposition voiced to this change.

Next, since immunogenicity data do not correlate to efficacy data, Dr. Griffin asked if they should be included at all. If included, should they be placed after the efficacy data, and should they be removed from the table in which DTP and DTaP immunogenicity are compared? Dr. Hardegree stated FDA's position that the joint presentation is inappropriate, particularly as other products arise which do not share the same antibody response to each of the antigens in the product. Dr. Modlin suggested stating that available information suggest a poor correlation between efficacy and immunogenicity, but provide a reference for the immunogenicity data. Dr. Griffin also suggested deleting Table 3 entirely, to de-emphasize that point. However, thought the comparisons may be irrelevant, Dr. Hadler noted that the data will be needed for future deliberations about extending ages or changing policy on combinations, to ensure no change in the basic characteristic on that vaccine. It was generally agreed to retain the immunogenicity data but to delete the table.

The fourth issue was the ACIP statement, which differs from the AAP recommendation, that there is no need to vaccinate a child with culture-confirmed pertussis. Dr. Peter had raised this issue. The Redbook Committee considered the possibility that immunity from natural infection is shorter than the accepted lifelong immunity (the basis of the current recommendation). It also is likely that many children who developed pertussis without a confirmed culture got DTP and that many children with probable pertussis are being vaccinated according to current recommendations. Therefore, they thought to continue with vaccination, despite of no data indicating increased risk in the period in which they receive pertussis vaccine. He solicited feedback. Dr. Griffin thought it rare for a child to develop culture-confirmed pertussis. Dr. Peter agreed, for the fourth dose, but those children who receive pertussis at six months and then receive no more for school entry may be sources of outbreaks. Dr. Halsey added that current data indicate high rates of pertussis illness associated with culture-confirmed pertussis in adults. Most adults with clinical pertussis probably had or were exposed to pertussis in childhood. There is suggestive data of waning immunity following clinical pertussis, and a single series in infancy does not protect against carriage of the organism or transmission to children. Dr. Griffin added that even those with the whole vaccine series have waning immunity. Dr. Halsey noted that less data than in the past suggest adverse events, the fear of which inspired a contraindication to vaccinating these children. Now, with acellular vaccines available, he thought this should be allowed.

Dr. Chen reported powerful German data presented at the Pediatric International Symposium demonstrating that pertussis could be developed twice, making possible a prolonged public health epidemic. He frequently sees culture-proven pertussis in his practice, and he urged the ACIP to resolve the issue. But Dr. Hadler cautioned regarding interpreting "absence of data". While the dogma that pertussis is a childhood disease only caught once may be wrong, there may have been other data to support the long-standing recommendation. Dr. Glezen thought there should be some data on the immune response of young infants with natural pertussis. He expected it to not produce a lasting antibody response, indicating immunization. Dr. Griffin suggested saying "there are no data on the persistence of antibody in children with pertussis disease", and that "some experts recommend vaccinating children even if they have had culture-proven pertussis". This would not go beyond the data. Dr. Peter noted there are no data on adverse reactions in children with documented pertussis who received the vaccine. He recommended to general agreement that the ACIP and Redbook develop mutually agreed language to avoid any confusion.

Dr. Thompson wished in general for all vaccines, to use the word "recommended" in the text rather than to state a preference, unless there was a specific reason to use preference. There was no objection voiced to this idea.

Dr. Snider recalled Dr. Satcher's request to include a section in statements about research needs, as done in the polio statement, and suggested doing this here. DTap issues similarly analogous to polio are the number of injections and the international issue . The latter suggests a statement that the ACIP does not encourage DTaP rather than DTP in resource-poor countries.

Dr. Halsey noted that one acellular pertussis vaccine had already been licensed for several months and one state wanted to use it widely. Dr. Davis requested comments on the statement by November 8. Comments would be provided in writing; there was no need at this time to vote. The modified statement would be faxed with the redlined comments received and then redistributed to the members. Dr. Halsey urged members to review the whole statement, and to quickly review and turnaround the language on new vaccines as they come in, so the NIP could publish them.

Dr. Sherrod feared that the timing of multiple new products' introduction could affect compliance, and called for hard data on introduction of new products. Dr. Davis cited substantial discussions on this issue, particularly on harmonization, but was mindful that this is a dynamic also of concern to NVAC. Dr. Snider noted that the IPV/OPV discussion assumed the inclusion of DTaP. Dr. Hadler reassured her that there would be real-time monitoring of the impact of the IPV/OPV policy change in four inner city areas, as well through registries for coverage. This will assess the impact on all antigens (including of DtaP) for multiple injections, and adverse events. With that, the Committee adjourned for a short break.

COMVAX® Discussion

Dr. Gary Euler introduced the discussion of COMVAX®, the combined Hib and Hepatitis B vaccine, just licensed on October 2. Dr. Frank Mahoney, of the NCID Hepatitis Branch, outlined four related issues:

1. The routine use of COMVAX®, specifically after a dose of hepatitis B at birth, and interchangeability issues with other Hib conjugates or Hep B vaccine.
2. The use of COMVAX® to complete the post-exposure Hep B vaccination schedule in infants of surface-antigen positive women.
3. Use of COMVAX® in infants whose mothers' HBsAg status is unknown or unavailable.
4. Determination of needed statements; e.g., a Notice to Readers with or without a stand-alone statement. The revised hepatitis B statement would include the materials in either case.

Merck Presentation

Dr. David West of Merck's Vaccine Division discussed vaccine performance. COMVAX® is a bivalent vaccine intended to immunize healthy infants against invasive *Hemophilus influenzae* type B (Hib) disease and hepatitis B (Hep B) infection. It was developed due to the ACIP/AAP recommendations for routine childhood immunization against Hib and Hep B. This would increase by 6-7 the number of monovalent injections needed in the first two years of life. COMVAX® provides this immunity through only three injections.

He described the composition of COMVAX®. The vaccine dosage contains 7.5 μg of PRP, the Hib component, the same Hib antigen as in the liquid formulation of monovalent PedvaxHIB®. The Hep B component has at least 5 μg of yeast-derived Hep B surface antigen (HBsAg), the same material as the Hep B vaccine Recombivax®. The routine administration schedule is 2,4,12-15 months, the same as for Pedvax®; this integrates well with other standard pediatric vaccines.

Dr. West outlined the COMVAX® clinical studies, the core one being an 11-center study with 882 healthy infants randomized (3:1) to received COMVAX® (CVX) or PedvaxHIB®. The vaccine was given in a 0.5 ml intramuscular injection, at 2,4, and either 12 or 15 months of age. One comparison group received monovalent Pedvax® and the other Recombivax® at the same time schedule.

The most clinically relevant immune responses for Hib was the percentage with >1μg/ml of anti-PRP after dose two at about six months of age. This was based on the theory that susceptible children are at significant risk of Hib early in life, supporting immunization as early as possible. For Hep B, the endpoint was the percentage with >10 mIU/ml (IU= international units) after the last dose in the series (dose three, at 13-16 months of age). Multiple studies have shown nearly total protection against clinically significant HBV infection in healthy subjects with >10 mIU/ml.

Two months after the second dose, at about 6 months, about 95% of the children had detectable Hib antibody (>0.15 g/ml); 72.4% had ≥1.0 g/ml and a GMT of 2.5. The COMVAX® group and comparison groups were very similar. For anti-HBs response after the last (third) dose, almost all the COMVAX® group children had detectable antibody; 98.4% had 10 mlU/ml and a GMT of 4468. All of the comparison groups had the same 10 mlU/ml response, and a GMT of 6944. Though there is statistical significance in the difference between the GMTs, he focused on the fact that both groups were higher than the licensed monovalent vaccine.

In studying safety, 6705 doses of COMVAX® was administered to 2612 healthy children aged 6 weeks to 15 months. In all, 22 children had serious adverse events within two weeks of vaccination, none related to COMVAX®. The common injection site reactions were pain/soreness, erythema (>1"), and swelling/induration. These were similar to the comparison group of monovalent vaccines. There were no trends of increases with successive doses of vaccine. There were a number of systemic complaints reported to occur at a frequency ≥1% in children given a 3-dose course of vaccine. The most common (which were prompted for on report cards given to parents) were irritability reported at frequencies of 29-57% and somnolence reported at frequencies of 21-50% after an injection of COMVAX® or concomitant injections of the monovalent vaccines PedvaxHib® and Recombivax HB®. There were no relevant differences in the frequency of the events between COMVAX® and the comparison monovalent groups. The vaccine was well tolerated. The low percentage of children who received injections 1-3 and who had a maximum temperature (103°F, rectal) also suggested no significant difference between the COMVAX® and monovalent groups.

Dr. West addressed the integration of COMVAX® to other pediatric vaccines' schedules, expecting it to be given with DTP or DTaP, IPV/OPV, and with M-M-R®II and VZV (varicella). They are continuing studies examining the immune response to other pediatric vaccines given to children concomitantly with COMVAX®. The clinical studies detected no impairment of immune response to any vaccine when COMVAX® was administered concurrently with DTP/DTaP (as a booster dose), OPV/IPV, M-M-R®II, and Varivax®.

He summarized the overall antibody responses to DTP given at 2,4, and 6 months concomitantly with the first two doses of COMVAX® at 2 and 4 months, which produced a four-fold rise in antibodies to all DTP vaccine antigen in ≥90% of the vaccinees. All the results were as high or higher than those in an historical study of those receiving DTP without any concomitant Hib or Hep B vaccine.

They now have data from 38 children who received COMVAX® with IPV at 2 and 4 months. At the second dose, all the children had polio antibodies. He also summarized postdose antibody responses to OPV at 2,4, and 6 months concomitant with COMVAX®, Pedvax® alone or Pedvax® with Recombivax HB®. High and similar percentages of antibody response and GMT were shown for the three polio types to both monovalents in each of these three treatment groups or Pedvax® alone. The same study, later in time, measured response to measles, mumps and rubella antigens. At 15 months, the children received M-M-R®II + Pedvax®, M-M-R®II + Pedvax® + COMVAX®; Pedvax Hib® + Recombivax® HB or Pedvax® Hib alone. They showed 93-100% seroconversion rates for the antibodies to the vaccine viruses, and similar responses across the comparison groups.

A large study in progress has 700-800 children receiving a variety of Hib and Hep B primary series. They received their last doses through COMVAX® at 12-15 months of age, with M-M-R®II + Varivax® or MMR + Varivax® deferred by six weeks. That study's results will be examined for the responses to concomitant or nonconcomitant administration. Currently, 100% of the Varivax® children have seroconverted for varicella antibody, and have similar GMTs.

Finally, Dr. West highlighted the standard dosage administration recommendations based on the current package insert: (1) administer a three-dose series of 0.5 ml of COMVAX® by intramuscular injection at 2,4, and 12-15 months of age; and (2) COMVAX® may be given to children who received one more of Hep B (HB) vaccine, in the 2,4, and 12-15 months series. The indication is that a three-dose course of COMVAX® may be given to infants who previously received one dose of HB vaccine at or shortly after birth. We do not have data on children given more than one prior dose of HB vaccine and are then given three doses of COMVAX®. A dose of COMVAX® can be given to finish the HB series in children who only need one more dose. For children not vaccinated according to the recommended 2,4, and 12-15 month schedule, (1) the number of doses of a PRP-OMPC vaccine (i.e., COMVAX®, Pedvax®, HIB) needed to immunize against Hib disease varies with age: for 2-10 months, 3 doses; for 11-14 months: 2 doses; for 15-71 months of age, 1 dose. But on the other hand, regardless of age, three doses of a HB surface antigen vaccine are necessary to immunize against HBV infection .

Dr. West stated that COMVAX® is interchangeable with licensed Hib and recombinant HB vaccines. Their studies show that the immune responses to Hib and HB components with COMVAX® are comparable to the monovalent vaccine. A recently completed study of healthy neonates also showed that a regimen begun with another HB vaccination can be successfully complete with Recombivax®. Finally, he itemized several issues to consider. Based on the package insert, COMVAX® is not recommended for use in infants <6 weeks of age, or infants born to

HBsAg-positive mothers; nor to persons who are hypersensitive to any component of the vaccine, and it may not induce the expected immune response to immunocompromised persons.

Discussion

Dr. Glode asked about adverse events. Dr. West reported 22 events reported and recorded without causation, 14 in the multi-center study, which are itemized in the product circular. They included vomiting, diarrhea, dehydration, etc.,and all required hospitalization. Dr. Glode then asked him to elaborate on the potential for suppression of the immune response to subsequent doses of the PRP/OMPC component. He cited past studies in which neonates younger than 6 weeks were given Pedvax®. They not only did not have a good response, but also had doses 2 and 3 muted.

Dr. Modlin learned that to date in the clinical studies, no one had received this vaccine with Hep B immune globulin concomitantly. Dr. Peter noted the similar 10% incidence of unusual crying in those who received COMVAX® and individual components. Dr. West confirmed that this is higher than in the literature reported, e.g., for DTP. The multi-center trial did not evaluate other vaccine responses, and many of the children did concomitantly receive other vaccines. They considered this an ascertainment artifact associated with the reporting form; another form without that prompt produced almost no such reports.

Dr. West was asked why children of surface antigen positive mothers could not get combined vaccine with 5 μg of HBsAg at the second and third dose. He theorized this evolved from the wish to ensure it was not used at birth, but since they have not studied COMVAX® in infants of carrier mothers there are no data to answer that question. Dr. Thompson asked if the schedule implies four doses. Dr. West confirmed that as they developed the schedule for 3 doses at 2,4, and 12-15 months, the implementation of the infant Hep B immunization using monovalent vaccines allowed most of the infants to receive a birth dose. They wanted to at least make sure that a three-dose series would do no harm; the "may give" means there is no contraindication to it. When Dr. Thompson asked if any infant given a series of Hep B vaccines would need a dose at adolescence, Dr. West responded that only future data will show the duration of the infant series Hep B vaccine immunity. It is becoming clear that loss of Hep B antibody has not produced a loss of immune memory, which sustains immunity well for Hep B. The ACIP will have to assess this regarding booster vaccinations.

Dr. Halsey wished that a FDA-licensed combined product could be given as needed to a child at an medical appointment. Regarding the harmonized schedule, multiple footnotes are not possible for all exceptions to rules. He asked why children of surface antigen positive mothers could not receive the product, in view of only a small decrease in the GMT titer. Dr. West responded that they were limited by the data from the clinical studies, which do not always reflect the reality of clinical practice. No cost in the public and private sectors. It was reported that no price had yet been set, but the product will be shipped at the end of the year to be available in January. Merck anticipated the supplies needed by their experience with other recently introduced vaccines; they believe supplies are sufficient.

Dr. David Kraus noted that COMVAX® was compared to liquid Pedvax HiB®, which has 7.5 μg of PRP. He asked if it was compared to the licensed Pedvax HiB® at 15 mg. Dr. West responded negatively, although that bridging was done for the Pedvax HiB® license study. When asked how the liquid Pedvax HiB® GMTs compare, he responded that the product circular table for liquid and lyophilized Pedvax HiB® showed a protection rate of about 80% and a GMT of about 3.2. That was a little higher than that seen in protocol 2, but subsequent studies revealed comparable across studies of 81% and 84% and GMTs at about 3.3 protection rates.

Dr. Hardegree went back to the issue of giving this to surface-antigen positive mothers, thinking those babies should have two doses of product before 2 months, at 0 and 1 months. That is in the footnote of the table for the 5 mg dose. She commented on the complexity of issues about that point. Dr. Halsey noted that the current recommendation is for administration at 0,1-2 months for infants born of surface-antigen mothers, so the second dose can be given up to 2 months. He emphasized emergence of new combination products is only beginning. To avoid creating problems for practitioners, he supported replicating the combination products' usage schedule from the schedule for their independently licensed component antigens.

Vaccine Performance Discussion

Dr. Frank Mahoney of the Childhood and Respiratory Diseases Branch, National Center for Infectious Diseases (NCID) introduced the issues related to the routine use of COMVAX® in infants of HBsAg-negative women. COMVAX® can potentially decrease the number of injections received by a child, as well as decrease the number of products a provider must choose and stock. It may result in some infants receiving four doses of vaccine, but even at four doses, Hep B vaccine remains cost effective. Finally, this combination may improve Hep B vaccine coverage.

Dr. Mahoney showed a bar chart of the National Immunization Survey (NIS) on Hep B vaccination coverage, showing a rapid improvement in coverage, with about 70% of children 19-24 months old vaccinated in the first and second quarter of 1995. There is some concern that there may be a plateau of coverage at that level, but there were no late data on this. Another chart compared vaccination coverage in the U.S. for Hep B (40-60% in 1994-1995) to Hib (90%). COMVAX® might help increase coverage for Hep B.

Studies evaluating the cost effects of administering Hep B at birth were shared. The birth coverage varied by area, but was 37% overall in the 1994 NIS survey. Dr.Mahoney reported a surprisingly high overall number of hospitals (40-50%) vaccinating infants nationwide. Though some would discourage birth vaccination, NCID approves of it. They wish to educate parents at birth of the importance of immunization, and this will perhaps improve Hep B coverage. An NCID analysis revealed that routine infant vaccination of three doses is highly cost-effective, with a low lifetime risk of infection (0.06). However, he solicited the Committee's views.

Hib Issues with Use of COMVAX®

Dr. Orin Levine noted the ongoing success of Hib vaccination. Since the licensure of Hib conjugate vaccines, the incidence of invasive Hib disease has decreased among children under five by more

than 99%, and there is an accompanying 90%+ immunization rate. When compared, the efficacy is comparable between PRP-OMP vaccine (the Pedvax HiB® component of COMVAX®) and HbOC and PRP-T. Its immunogenicity in a primary series was compared to the same vaccines given in routine Hib conjugate vaccinations, showing that better than 90% of infants developed ≥ 1.0 μg of anti-PRP antibody, the threshold level of antibody titer activity generally considered to correlate to protection.

One issue of using COMVAX® is the potentially increasing proportion of children receiving this vaccine who were partially immunized with other vaccines. Studies indicate such mixing did not reduce immunogenicity for any of the studied regimens; in fact, the GMT titer of PRP in infants with two doses of PRP-OMPC was lower than those who began with PRP-OMPC and completed the series with two doses of HbOC or tetanus toxoid. Interchangeability of Hib conjugate vaccines is not a concern.

Dr. Mahoney read the proposed language of recommendations for use of COMVAX®.

> "COMVAX® should be administered by intramuscular injection for routine vaccination at 2,4, and 12-15 months of age for infants born to HBsAg-negative women. The first dose of vaccine may be given at 6 weeks to 2 months of age, but must **NOT** be given before 6 weeks of age because of the potential for suppression of the immune response to subsequent does of the PRP-OMPC component of COMVAX®.
>
> "If vaccination is started after 2 months of age, the number of doses of a PRP-OMPC containing product (i.e., COMVAX®, PedvaxHIB®) depends on the age when vaccination is begun -- three doses if initiated no later than 10 months of age, two doses if started at 11-14 months of age or one dose if started at age 15-71 months. A 2-month interval is recommended for doses 1 and 2, although an interval of 1 month is acceptable. The recommended interval between dose 2 and 3 is 8-11 months. If less than 3 doses of COMVAX® are administered, recombinant Hep B vaccine should be administered at the previously recommended intervals in order to provide a total of three doses of an HBsAg-containing vaccine and achieve complete Hep B vaccination."

With no comments on these two paragraphs, Dr. Mahoney continued.

> "COMVAX® can be given at 2,4, and 12-15 months of age to complete the Hep B immunization series in infants who have received a dose of Hep B vaccine at birth. COMVAX® **MUST NOT** be administered before 6 weeks of age.
>
> "Preferably, the vaccine series should be completed with the same Hib conjugate vaccine. However, if different vaccines are administered (including COMVAX®), any combination of Hib conjugate vaccines licensed for administration to infants may be used to complete the primary series, a total of three doses being considered adequate. The Hib component of COMVAX® is similar in composition, safety and

immunogenicity to PedvaxHIB® and can be used interchangeably with this or other Hib conjugate vaccines.

"The HBsAg component of COMVAX® is similar in composition, safety and immunogenicity to Recombivax HB® and can be used interchangeably with this or other Hep B vaccines. Schedules that include more than one type of Hep B vaccine, including combined antigen vaccines and vaccines produced by different manufacturers, are expected to have safety and immunogenicity profiles comparable to those with single antigen Hep B vaccine."

A footnote added "Additional information concerning HBV infection, hepatitis B vaccine and Hep B vaccination is contained in *MMWR* 1991; 40(No.RR-13):1-25. Additional information concerning Hib disease, Hib conjugate vaccines and Hib vaccination is contained in *MMWR* 1993; 42 (No. RR-13):1-15.

Discussion

Dr. Halsey suggested language to address the child who received Hep B vaccine not at birth, but at 2-4 weeks of age during the first clinic visit, and he recommended some decision about minimum intervals. There are no studies looking at 2 or 4 weeks and 2,4, and 12 months, but he was inclined to be permissive, since there is no evidence of any harm from an extra dose. Dr. Katz noted the statement indicates that the surface antigen component is similar, but the composition adjuvant is twice as much in dosage. That should be clarified. Dr. Mahoney agreed that a specific statement that twice the amount and similar in composition could meet that need.

Dr. DeBuono worried about advancing a fourth (extra) dose public policy with no information on cost. She endorsed a recommendation to give only Hib at the third dose to a child vaccinated for Hib at birth. She also cautioned about a mixed message to hospitals and others routinely give Hep B vaccine at birth. Specifying something restricted before 4 and 6 weeks could lead to confusion and perhaps over-vaccination. She urged consideration of the implications of multiple vaccinations, an issue with other vaccines as well.

Dr. Mahoney responded that using a monovalent Hib presents two concerns: that a 0,2, and 4 month schedule is not encouraged for the Hep B component, and that the third Hib dose may be missed, since physicians using COMVAX® may no longer stock monovalent Hib vaccine. Dr. Schoenbaum asked about the similarities and differences between a COMVAX® statement and any other statement about single products. He thought that a statement is only needed when COMVAX® could not be used, but also to clearly encourage the use of combinations if they simplify the number of doses to be given and are cost-competitive. Dr. Hadler thought this an excellent generic issue, also applicable to the planned DTaP/Hib presentations from Lederle and Connaught. CDC wishes to be clear for clinics who must make vaccine stocking decisions. The uniqueness of this vaccine requires some special instructions, but generalizable ones are desirable.

Dr. Rabinovich stated that no new vaccines have been sufficiently generic to not require data review. She questioned how States will decide which vaccines to stock, perhaps one reason CDC must carefully assess how this interrelates with others. Dr. Davis agreed this is a provocative issue affecting contracts on supplies each year. He also noted the complexity involved, as contractual agreements with VFC are different than those for public health clinic immunization funds. Dr. Hadler reported that contracts are already in place for all the products, but NIP is beginning to discuss these issues.

Dr. Gall asked when the ACIP should go beyond FDA's work, such as addressing antigen-positive women. He also questioned this attention to the fourth dose in light of no data. Dr. Halsey reiterated that the language was permissive to address a child already beginning immunization to allow use of this product. Hep B vaccine has been well studied, showing no evidence of any harmful effect but a more rapid antibody response when extra doses are given earlier. With that potential benefit, he thought it was practical issue to encourage going beyond the data on which FDA relies. Dr. Davis noted another important issue was whether a family practitioner or pediatrician even counts the birth dose in the schedule.

However, Dr. Fleming worried that this language may be confusing. He advocated, stating the underlying principles to be made: (1) for children 6 weeks or older needing both Hep B and Hib, this vaccine is desirable, and (2) for children needing one or the other of those immunizations and the monovalent vaccine is not available, that use of this vaccine is acceptable.

Dr. Snider asked if the committee wished language crafted about combinations as a preamble to this recommendation. He acknowledged the downside on recommending for every combination to come, though each may have specific issues that would not be covered by a generic study. Addressing each could sound like a product endorsement rather than a recommendation on fitting it into a standard schedule. Dr. Ward suggested developing a document on combination vaccines to help practitioners collate them, although this would admittedly be hard to keep updated.

Dr. Bob Chen suggested a short statement in the *MMWR* describing issues pertinent to this specific combination product. He reported that Dr. Bruce Weniger is directing a study of over-immunization and polypharmacy, working with health economists to determine all the variables to optimize immunization strategies. They hoped this would provide some concrete data to inform such decisions. However, that will take 6-9 months to complete. Dr. Snider suggested announcing that fact in a discussion of the advantages and challenges of combinations. Dr. Davis added that the Canadian experience with reactions, given that they may be hyperimmunizing for several different antigens, could also be useful for this discussion.

Use of COMVAX® Vaccine for Antigen-Positive Mothers

Dr. Mahoney reported CDC's anticipation that all infants born of surface-antigen mothers would seroconvert, since 92% did so after two doses. Numerous studies show the vaccine and HBIG to be highly effective in a variety of schedules. There are 20,000 births to such women in the U.S. annually. There is a low prevalence of HBsAg in the U.S., so the risk of perinatal transmission is

low if given the appropriate prophylaxis. COMVAX® may improve the three-dose coverage for these infants early in life. Surveillance as well as post-vaccination serologic testing must be in place to monitor coverage of these infants, and provider education is needed on the schedule to defer giving this from the 1-month visit to the second month.

He showed the schedule to immunize such infants, with and without COMVAX®. Hep B and HBIG are given at birth; Hep B-2 can be given at 1-2 months of age, and Hep B-3 at 6 months. With Hep B and HBIG at birth, the provider can use COMVAX® at 2,4,6 and 12-15 months of age. He showed evaluations by state Hepatitis Program coordinators of immunoprophylaxis provided to infants of HBsAg-positive women from 1987-1995. Coverage has been improving; nationally, 89% of the 8252 identified infants received vaccine and HBIG at birth, and 61% completed the series by 6-8 months. The states that track this have about 95% coverage.

Dr. Mahoney then reviewed the efficacy of Hep B vaccine and HBIG for infants of e-antigen positive mothers (those who are highly infectious) by schedule. There was no difference in efficacy for COMVAX® at a 2, 4, and 12 month schedule compared to 0,1, and 6 months for Engerix. On another chart, he showed data on the post-vaccination serologic testing of infants born to HBsAg-positive mothers 1995-1996. Of 1819 infants, only 3% were surface-antigen positive, showing the high efficacy of the vaccination program as it is used under field conditions.

He then read two options to recommend use of COMVAX® for infants born to HBsAg-positive mothers:

A. "COMVAX® may be administered at 2,4, and 12 months of age to infants of HBsAg-positive mothers to complete postexposure vaccination as long as the infant received Hep B vaccine and Hep B immune globulin (HBIG) soon after birth. The first dose of vaccine may be given at 6 weeks to 2 months of age. COMVAX® **MUST NOT** be administered before 6 weeks of age because of the potential for suppression of the immune response to subsequent doses of the PRP-OMPC component of COMVAX®."

B. "Infants born to HBsAg-positive mothers should only receive Hep B Vaccine at birth (along with HBIG) at 1-2 months and 6 months of age. They should not receive COMVAX® to complete postexposure vaccination to prevent perinatal HBV infection. These infants should also be vaccinated with a single antigen Hib conjugate vaccine beginning at 2 months of age."

The issues involved are that there is no decrease of efficacy with option B; it is unlikely that there will be missed doses of Hep B at 2 or 3 months, nor that children will be vaccinated at one month of age with COMVAX®. There is no difference of adverse events with either option. If not allowed, there is no chance of giving COMVAX® at one month, but there are chances of missed vaccine doses if the provider does not start monovalent vaccine.

Discussion

Though Dr. Mahoney clarified that four doses are not recommended, Dr. Thompson demurred that he would interpret that, because four doses that include Hep B are cited. As written, this almost implies the need to give three more doses. He advised language to cite the need for atleast two more doses of Hep B vaccine; then if desired, the combination can be given with the fourth dose, even though more vaccine is not needed.

It was noted that the ACIP's attempts to ease difficulty for the practitioner will have to be balanced against the potential issues of adverse events and cost. The current government price for Hep B vaccine presents no cost issue, but this issue will rise as new combinations emerge. Dr. Mahoney though it impractical to ask a provider to track the individual doses for these children. Realistically speaking, tracking shows that these children receive the wrong product by getting the same routine vaccines with other children. Dr. Peter recommended simply stressing the most important point, that this vaccine not be given before 6 weeks of age.

In response to Dr. Gall, Dr. Mahoney confirmed that the anticipated decreased efficacy stemmed from a missed dose if the physician does not stock monovalent vaccine. Dr. Gall recalled that 5 μg dose was chosen because of a small decrease in the immunogenicity occurring with the product. Dr. West explained that in the clinical studies, slightly lower interim antibody responses were seen with the combination form than with the monovalent vaccine, indicating a higher dosage. But at the same time, the absolute response level was good, and the child's aging process leads to a more potent response.

Dr. DeBuono speculated that the next discussion of this committee would be to add COMVAX® to the VFC program. She expressed concern that the ACIP frequently considers the availability and access to vaccines without sufficient thought to the cost implications to states running Medicaid and VFC programs, managed care programs, etc. Therefore, she thought that the ACIP must clearly recommend how this product should be appropriately used in a cost-effective manner. She thought this present language to indicate a CDC acceptance of overvaccination, which she rejected as bad public policy.

However, Dr. Halsey observed that overvaccination has occurred for moe than 40 years; while not advocated, it is preferable to under-vaccinating. For example, three doses of OPV may be sufficient, but five doses produced good disease control. He cautioned that a fear of over-immunization may impede the onset of use of new products. Second, he observed that some infants are receiving 2.5 mg rather than the 5 μg they should have. Having this product available would preclude the need to stock both dosages, and a unified dose of 5 μg for all children will help to simplify this for physicians. Dr. DeBuono rejoined that the Committee cannot recommend one thing to hospitals (vaccinate at birth) and another to practitioners (continue with three doses thereafter). The recommendation must be very clear.

Dr. Halsey responded that, as in other cases, flexibility should be incorporated, warning for example that states with a 60% birth immunization coverage could not bring in a new product containing Hep B until stopping the birth dose. He also noted that since not all women are screened, the first birth

and subsequent doses prevent perinatal transmission of Hep B. Dr. Mahoney agreed that if anyone is overimmunized, it should be these children, because this actually is post-exposure prophylaxis. He felt strongly that permissive language for use of this product would have more of a positive impact than a negative one.

To move forward, Dr. Hadler suggested dropping the birth vaccination when new combinations are released. He also noted the time available before any VFC vote to determine the initial costs. Dr. Mahoney observed that the cost analysis used the higher contract combination dose (5μg) cost, but also the government cost. Dr. Peter raised the perspective that few children will be affected by this, and that the tradeoff will be the improved efficacy of the combination vaccines. He noted further that the birth dose was developed to free the schedule, and is alterable. He advocated a flexible approach, to avoid creating problems for other potentially better products.

The committee addressed the immediate problem of the licensed product, noting that its routine use is covered by the package insert. Dr. Modlin was a little concerned at a minimalist approach, because many practitioners use these statements as source of information as well as recommendations. When asked, Dr. Halsey did not anticipate a Redbook statement on every new combination drug due to their limited resources and staff. They will, however, address the harmonized schedule and insert some guiding principles on that.

Dr. Modlin suggested that the ACIP form a workgroup with the Redbook committee and re-address the issue in February. Dr. Hadler recalled past CDC issuance of a brief informative notice to *MMWR* readers on new products, consistent with the package insert and reviewed by the ACIP Chair. Such a draft is near completion on COMVAX®. He suggested also forming a workgroup. Future statements could begin with generic observations about combination vaccines followed by the specifics of those issued.

Dr. Schoenbaum advocated a general, minimalist statement, as he did not see this as a new vaccine but a combination of two old ones. Dr. Davis disagreed, finding these the same antigens, but not the same vaccines. Dr. Snider also commented that the workgroup's primary purpose is not to develop a statement on COMVAX®, but to use it as a model to discuss how to deal with combinations. Dr. Schoenbaum approved of that, urging that the workgroup determine the flexibilities. In some instances, that would involve using combinations; in others, open options would be better. Dr. Thompson encouraged the workgroup to help highlight the options for the fewest numbers of visits possible. Dr. Halsey offered to share the drafted guidelines of the AAP's Committee on Infectious Disease regarding simultaneous administration, which included some language regarding how new combination products could be used.

Dr. Davis summarized that these new vaccines involve cross-cutting issues, frustrating the hoped-for Committee's feedback to the program. Dr. Mahoney stressed the need to address other than routine usage, anticipating provider questions in addressing cases like the children of surface-antigen positive mothers. Dr. Snider stated CDC's need for internal discussion of its responsibility, but the ACIP and its work will be kept in mind when that occurs. It was agreed that no statement would be

released before the next meeting, except perhaps for a short *MMWR* article reiterating the FDA package insert which warns against use prior to six weeks.

Dr. Margolis mentioned that this may delay a hepatitis B statement, which annoyed Dr. Davis since two years had passed since the ACIP's approval of the hepatitis B statement. He stated emphatically that this must not happen with any other statement in which the ACIP participates. Dr. Snider responded that this is a complex issue, as new information often arrives before the statement's publication that must be considered for inclusion. Dr. Davis did not dispute that, but insisted that once the ACIP comes to closure on a statement, they should expect its publication within a reasonable period of time. Dr. Snider understood, and reported CDC discussion related to putting statements on line, such that minor modifications could be accomplished without a major ACIP agenda item to address the whole statement. He suggested that the agenda address this at some point. Dr. Hadler thought this appropriate for the hepatitis B statement, and perhaps with acellular pertussis. Any changes could be added to an online text and a notification to readers published in *MMWR*.

Varivax® Vaccine Presentation

Dr. Thomas Vernon of Merck introduced Dr. Robert Sharrar, the Director of their worldwide monitoring and adverse event surveillance program registry. Dr. Sharrar updated the committee on the safety profile of Varivax® in its first year of marketing. Due to the late hour of the day, he emphasized a few important facts. The data came from the routine post-marketing reporting (PMR) of adverse experiences following administration of vaccine, from two Merck disease surveillance programs and from the Merck/CDC Varivax® pregnancy registry.

Though both PMR and surveillance are spontaneous passive voluntary reporting systems with incomplete reporting, they differ. PMR has no standard case definitions as does disease surveillance (it is recorded as reported by the health care provider), and it counts multiple outcomes. This implies only a temporal association of the event to vaccine administration, not a causal one.

The VZV identification program was introduced during the chicken pox season, but PCR analysis can distinguish between vaccine and wild varicella strains. They established a program to gather selected specimens on certain adverse events of interest and typed them for strain. The time period of the spontaneous PMRs was May 1995 to April 1996, the first year of marketing, in which 2.6 million doses of vaccine were distributed. Of those, 1738 adverse event reports were received, only 57 serious, a reporting rate of 2.2 per 100,000 doses distributed.

The serious events included encephalitis and pneumonia. Most adverse events will probably be reflected in a population being monitored; some may be attributed to vaccine, but most probably are not. Of 7 reports of encephalitis, two of adults were excluded and five counted in patients aged 1-4 years old. Onset was in 7-19 days post-vaccination in four and 90 days in one. None had the characteristic chicken pox rash; four had neurologic sequelae. The etiology was unknown in four; one clinician thought encephalitis to stem from cat scratch fever. PCR showed one to be negative for VZV of any type.

He described two of the four pneumonia cases reported, all of which had underlying conditions. A three-year old girl with decreased appetite, fever and an atypical rash began acyclovir; she was hospitalized two weeks later because of increasing cough, dehydration and persistent fever and rash. A chest x-ray showed diffuse interstitial pneumonia. Later, a bronchial alveolar lavage revealed PCP, but not HIV. PCR showed a wild-type VZV. She died almost three months after vaccination. The second case was a one-year old male with a history of oral thrush who developed a rash on his right knee and groin about 15 days post-vaccination. The rash recurred 38 days after it resolved. He was hospitalized 85 days after vaccination for respiratory distress, hypertonia and lower extremity weakness. PCR analysis of the bronchoalveolar lavage showed the Oka/Merck strain of VZV. He was treated with acyclovir and IV immune globulin, and recovered.

The non-serious adverse event reports (67%) included fever, rash or local reactions. Of the rashes occurring within 42 days, 65% were varicella-like, 28% were non-specific, and 7% were hypersensitivity rashes. A graph showed 86% of the rashes occurring within three weeks. Nine wild-type and nine Oka/Merck VZV were identified. The wild type were in those 6-30 years of age, with onset 2-14 days post-vaccination (median 8 days) and four patients clearly had chicken pox (〉100 lesions). The Oka/Merck cases were 15-42 years old, with onset from 5-28 days post-vaccination (median 22 days). Only two had 〉100 lesions; one was clearly immunosuppressed.

The issues of concern to providers include breakthrough cases: 169 case reports occurring from 43-337 days after vaccination, 8 with two doses. Only 12 patients had temperature 〉100°F, and wild-type VZV was identified in two. There were 59 reported secondary transmission cases, but this was narrowed to 29 cases upon a case definition of onset 14-64 days post-vaccination. Of these, 21 were chicken pox, 4 were non-specific rashes, and four were herpes zoster. Most source cases were children, most secondary cases were adults. Only 12 source cases had a rash. Onset of illness was 11-28 days post-vaccination in the source rash cases, and 15-53 days in those without a rash.

The wild type VZV was identified in six patients, and Oka/Merck in only one, a 30-year old pregnant mother of a one-year boy. She developed 100 lesions 16 days after her son developed 30 lesions 24 days post-vaccination. This is the only documented case of secondary transmission between normal hosts. There were 24 cases reported of herpes zoster occurring from 24-148 days post-vaccination, all but two being ≤5 years of age and only one reporting a rash. Three cases of Oka/Merck strain were identified. Lack of response, which concerned providers, was attributed to their use of a commercial antibody test insensitive to the vaccine induced antibody.

The pregnancy registry is currently following 187 patients and has results on 94. The prospective reports of those who came to term showed a 16% spontaneous abortion rate, 20% elective termination of pregnancy, and 64% with live births with no identified congenital anomalies. All the women were inadvertently vaccinated before knowing they were pregnant. Dr. Chin Le asked if Merck followed up the 64% live births, but they did not. The infants were all normal and were not followed beyond delivery.

Dr. Sharrar summarized Merck's conclusions. There were 7.1 adverse events per 10,000 doses distributed. Except for anaphylaxis, varicella pneumonia, an HIV-infected child and chicken pox in a patient with chronic lymphopenia, there were no other serious vaccine-related adverse events. Secondary transmission from a normal child with vesicular lesions was documented, as was herpes zoster with a vaccine strain.

PMR Studies of Varivax®

Dr. Robert Copeland of Merck, who oversees the post-marketing surveillance in collaboration with NIH, Kaiser Permanente/Northern Colorado and Duke University, reviewed the special post-marketing studies. The objectives among vaccinees were to assess the short-term safety profile, any shifts in age of distribution of varicella over 15 years after licensure, the persistence of antibody for ten years after licensure; persistence of varicella immunity, and zoster incidence after 15 years. He outlined the studies to do so: a short-term safety study measuring adverse reactions, a 10-year persistence of antibody study to assess 2000 children and adults, a daycare center study to assess changing varicella antibody among 1200 children in 10 centers, and a 15-year follow-up study to assess varicella in herpes zoster incidence rates among 7000 children. Lastly, they are conducting a 15-year changing varicella epidemiology study among 40,000 subjects aged 5-19 years of age.

Dr. Copeland focused on the Kaiser short-term safety study and the Duke daycare study. The subjects (at least 25,000 children 12-23 months of age) served as their own controls, with a 30-day exposure period for certain outcomes and a 60-day period for hospitalizations or deaths after vaccination. They also looked at historical controls of age- and gender-matched children vaccinated in 1994 with routine pediatric vaccines. The study extended from June 1995-to January 1996. It included about 44,000 vaccinees among 1-year olds (34%), 2-12 year-olds (62%), and older (4%). About 60.8% received only Varivax®; MMR was the most common concomitant vaccine. Uptake analysis of Varivax® showed that 57% of children 12-18 months receiving MMR-2 also received Varivax® concomitantly.

The statistical analysis listed relative risks for all control periods and medical events as ascertained by medical records, regardless of relationship to vaccine. The investigators then calculated the relative risks for any adverse events (AEs) in relation to the control periods examined all the statistically significantly elevated risks and focused on adverse events that had at least one elevated control period relative risk and a biologically and clinically feasible vaccine association. They then placed all the vaccines' relative risks of AEs in summary tables to assess patterns of vaccine effect. There were no deaths during the sixty-day period after vaccination, no visits for ataxia, encephalitis or anaphylaxis. There were 3200 relative risks calculated, 34 of these were statistically significantly elevated and several not vaccine related (congenital anomaly, well-child assurance visits). The compiled vaccine AEs included febrile illness, afebrile seizures, and varicella.

Dr. Copeland showed rate comparisons of febrile illness AEs in Emergency Room visits of 1- and 2-12 year old children. The p values were significant for the before- and after- control periods, but not relative to the historical period in 1-year olds. Among the greater number of 2-12 year olds vaccinated, the p value was not significant. The indicator for 11 of the 13 cases reported in the risk period was felt to be concomitant vaccine administration.

A p value of ≤.05 was flagged for afebrile seizure resulting in outpatient visits (there were no ER visits). It was 2.1 in the before- control period, and null in the after- control period, producing an essentially relative risk and null p-value. The relative risk in 2-12 year-olds decreased in statistical significance, suggesting a multiple comparison issue, or one in which afebrile seizures may contraindicate DTP administration and delay Varivax® vaccination. If delayed, those children with afebrile seizures would not be in the study; hence the before- comparison group would have artificially lower in events.

The relative risks for varicella outpatient visits showed significant p-values in 2-12 year olds, but not so for 1-year olds. The increased relative risk could have been for visits due to varicella-like rash, known to occur in about 5% of vaccinees. The discrepancy may be because the 1-year olds are routinely vaccinated, while the 2-12 year olds may be vaccinated following exposure, and may actually have been coming down with wild varicella disease.

Dr. Copeland summarized that the ER visits for febrile illness in 1 year-olds was elevated compared to before- and after- control periods, but not relative to historical control periods and not in 2-12 year olds. This is consistent with concomitant MMR and DTP vaccination. Outpatient visits for varicella in 2-12 year-old was elevated, but not those for 1-year olds, consistent with mild varicella-like rash or exposure to varicella-prompted vaccination. Outpatient visits for afebrile seizure in 1-year olds was elevated versus before- but not after- control periods, perhaps due to delay in vaccination after seizure. The data suggest no serious adverse events as measured by health care visits, nor any adverse event considered vaccine-related by the principle investigators. Ongoing safety assessment with larger numbers continues. Merck has committed to FDA to conduct such a study of 5000 children vaccinated with COMVAX®. Since clinics are using over to COMVAX®, this study may allow a look at the safety of children who received more than three doses of Hep B vaccine.

Over 5-10 years, the Duke University Day Care study seeks to assess changing varicella antibody among 1200 children ≤5 years of age in 10 daycare centers and will compare among vaccinated and unvaccinated children the rate/severity of primary varicella, secondary varicella and zoster. The design is an observational open cohort study. The participants are primarily white, with about 9% African-American, and a range of ages. About 50% of unvaccinated children were susceptible versus 6% of those vaccinated. The varicella infection rate was almost 14% in unvaccinated children. Two day care centers had outbreaks, with an 84% varicella rate during the outbreak and 54% overall. There was a zero varicella rate in the vaccinees. The incidence of varicella with onset of symptoms >3 weeks after vaccination was followed. The study's data suggested no Varivax®-related serious adverse events as measured by health care visits, and a substantially lower varicella rate among vaccinees than in unvaccinated participants.

Discussion

Dr. Halsey raised the selection phenomenon as a factor in comparisons of febrile illnesses before and after immunization. Children before vaccination may be less likely to have had fever since parents might wait to bring children in for routine exams if they have been sick recently. Dr. Griffin thought

that vaccinated children are generally a healthier population, probably one reason why this study had three control groups.

Dr. Vernon reporting for Dr. Jeff Morges, showed the VFC ordering data as of this week. On a map, he contrasted the states which had ordered for more than 50% of their VFC cohort to date, to those ordering for less than 25% of theirs. He also noted the importance of consumer acceptance to varicella use; the physician's recommendation or neutrality about the vaccine was dominant in the parents' decision to immunize. The rate of uptake in the private sector by age group showed an increase each year, including that projected for 1997. He demonstrated pediatric vaccines' uptake in the period after their launch. One year after licensure, varicella vaccine use had reached 55%, only 5% behind that of the measles vaccine four years after its licensure. Finally, he outlined partnership efforts to encourage vaccine utilization.

Dr. Ward asked about further combination vaccine work, and Dr. Vernon reported on an MMRV vaccine, which may also not require a freezer for storage. However, its release is not imminent; 3-4 years was the estimate for release. With that, the meeting adjourned at 7:05 PM.

OCTOBER 24, 1996

The committee reconvened at 8:40 A.M. the following morning.

Recommendation for Immunization of Health Care Workers

Dr. Walter Williams presented the draft recommendations for vaccination of health care workers (HCWs), developed in consultation with the Hospital Infection Control Practices Advisory Committee (HICPAC), and reviewed and adopted during the 1995 ACIP meetings. This had not been published pending completion and issuance of the BCG and varicella recommendations, and clarification of issues related to hepatitis C infection. These were resolved and included in the updated draft. This draft's information and recommendations summarize existing ACIP policy regarding vaccinating HCWs.

The only open issues remaining had been those about MMR vaccine in HCWs, resolved on the previous day. During its last meeting, HICPAC resolved two recommendations on MMR use very similar to the Option A presented on the previous day: those born pre-1957 were considered immune if they could provide a self-report of measles, a physician diagnosis or laboratory evidence of immunity, or else they received at least one dose of vaccine. Those born during or since 1957 would have to document physician-diagnosed measles. Self-report would be acceptable, with a lab report, or they would have to receive two doses of measles vaccine. It was anticipated that HICPAC will review and probably adopt the ACIP recommendation so that CDC may publish only one recommendation for use of MMR.

Dr. Williams sought the committee's concurrence to publish it showing the participation of both the ACIP and HICPAC. The preface states clearly that this recommendation applies to hospitals as well as other health care settings such as health departments, physicians offices, nursing homes,

professional schools, labs, and first response staff -- all those personnel at increased risk of exposure to blood and blood products.

The first major category addressed diseases for which immunization is strongly recommended: Hep B, influenza, measles, mumps, rubella and varicella. There is a section on TB and BCG vaccination, with TB control strategies stressed over BCG vaccination, though the latter is discussed for individuals in specific settings. The next section details other diseases for which immunoprophylaxis is/may be indicated: hepatitis A and C, meningococcal disease, pertussis, typhoid fever, and vaccinia. Rabies vaccine was deliberately mentioned only in the context of foreign travel. On Dr. Halsey's question, Dr. Williams explained that vaccinia was included in the ACIP's recommendation to address HCWs who may be exposed to persons receiving recombinant vaccines. Other vaccine-preventable diseases discussed include tetanus, diphtheria and pneumococcal disease.

There is a section on immunizing immunocompromised HCWs which summarizes the ACIP document on use of immunobiologics in persons with severe immunosuppression. There is mention of congenital immunodeficiency in other situations, including use of high-dose cortiosteroids. Other issues include immunization records, "catch-up" vaccination programs (they were still searching for a better word), and work restrictions for non-immune workers after exposure. This included a detailed table with specific restrictions for those exposed to or infected with vaccine preventable disease. It briefly discusses outbreak control and the vaccines indicated for foreign travel.

There are strong recommendations for disease control, since HCWs are considered at substantial risk for transmitting disease in health care setting. The recommendation's contents follow the major headings of the document: immunization strongly recommended, TB and BCG vaccination for HCWs in high-risk settings, other diseases for which immunoprophylaxis is/may be indicated, other vaccine-preventable diseases, immunization of immunocompromised HCWs and "other issues".

The document includes five tables: (1) a summary of published ACIP statements, (2) immunizing agents/schedules for HCWs, (3) recommendations for post exposure prophylaxis for percutaneous or permucosal exposure for Hep B vaccine, (4) a summary of the recommendations for immunizing HCWs with special conditions, including immunocompromised states like HIV infection and severe immunosuppression from other causes. It also describes recommendations for immunizing agents in circumstances such as pregnancy. Table 5 summarizes the work restrictions for HCWs exposed to Hep B, upper respiratory infections (e.g. influenza), measles, mumps, pertussis, rubella, and zoster.

Discussion

Dr. Katz observed that neither in Table 4 nor on page 56 is the MMR discussion consistent with the last ACIP recommendation regarding CD4 count or level of immunosuppression in use of measles vaccine. He thought that Redbook and CDC were moving toward the recommendation that immunosuppressed individuals should not receive MMR. Dr. Halsey stated that the Redbook Committee reexamined the issues of steroid dose and live viral vaccines. He asked for additional

perspective (page 35, bottom paragraph) on the dose of steroids in live viral vaccines. The traditional daily adult dose of 20 mg/kg of prednisone is being challenged, for example, for children with resistant asthma. Other data on immunosuppression with long-term use of 1-2 mg/kg/day also indicate that such persons may tolerate live vaccine as well.

Dr. Snider observed that this topic has been in the TB literature for a long time. The 20 mg dose arose from experience in Chicago of persons with no recurrence of TB in that group; this also served as a basis of when a TB skin test could be used without a suppressed reaction. There were data that 40 or 60 mg/kg/day would be sufficiently suppressive to cause reactivation of TB, while 20 mg/kg/day did not.

Dr. Modlin thought defining a safe cutoff dose to be unlikely, due to the variables of a heterogeneous population (e.g., with different live viral vaccines and different underlying conditions). Some children developed fatal chicken pox on low or even inhaled steroid doses, while others on high doses did well. Dr. Halsey agreed with this assessment. He disliked the rigid rule of no live viral vaccines for those receiving 20 mg/kg and above. He felt this too restrictive for children with no other underlying immunocompromising condition like asthma, and asked for leeway to provide them varicella vaccine. Redbook may be re-examining this in Spring; and consistent rules about the use of steroids would be optimal. He also agreed to Dr. Snider's observation that the text in this draft is weak, and begins with an acknowledgement of the extreme limitations of the data.

However, Dr. Katz encouraged consideration of the risk-benefit ratio in considering whether to give live virus vaccine to someone on steroids. Dr. Schaffner agreed; medical staff often can change their locale at work. He preferred to open this up even more to give people information and let them make their own choice. He also suspected that some occupational health directors may prefer not to use live virus vaccines with low risk staff. Dr. Pierce Gardner suggested adding a statement to the page 42 text on screening that post-immunization serologies are not indicated. He also noted that the MMR and HIV populations involve different pediatric and adult approaches. He also felt that this was realistically such a low priority for practitioners that it did not require a strong recommendation.

Dr. Graydon complimented the workgroup on developing a document with useful information. She suggested adding on page 59 (foreign travel section) comments about hepatitis A and B vaccinations, perhaps the two most importantly indicated for travel. Dr. Griffin also applauded this good summary of diverse recommendations. She asked if there were more guidelines in the document addressing an e-antigen positive person performing invasive procedures, or whether only internal review boards (IRBs) reviewed such issues. Dr. Williams reported a generally less proscriptive approach, accepting antigen positivity as the marker rather than a person's is e-antigenicity status. Both the ACIP and HICPAC recognized this as an issue and resolved this as the best approach to prevent transmission of bloodborne pathogens. Dr. Margolis added that the guidelines were published in *MMWR* in July 1991.

Dr. Chin Le noted the Table 5's proscription for a chronically e-antigen positive worker to work until the e-antigen is negative, and objected that this could be the rest of this person's life. Dr. Williams responded that the phrasing gives the institution the option to recommend which procedures an individual can or cannot preform, as opposed to a CDC proscription. Dr. Davis thought it telling that persons at this meeting were confused, and advised making this clearer. Dr. Chin Le then suggested a reference to the the page 9 text stating that vaccine-induced Hep B antibodies decline over time. This would support that persons losing anti-HBs titers are truly protected from further exposure, a question frequently raised.

Dr. Halsey expressed his concern at the recommendation about upper respiratory infections. He was certain that most institutions do not have the policy to remove anyone with any minor upper respiratory infection from patient contact, particularly in outpatient centers, because this would decimate the staff of large institutions. Dr. Williams stated that this was closely and aggressively scrutinized by HICPAC, but he would raise it with them again. Dr. Margolis cited 15 years of recommendations affirming that those with acute hepatitis should not treat patients. Anecdotal evidence indicate that this is where many transmissions occur.

Dr. Hadler urged everyone to review this statement, which was almost ready to publish 18 months ago, to ensure it is still completely up to date. Dr. Davis requested comments to go to Dr. Williams, who stressed again that any change in recommendations would have to be revisited. Dr. Davis requested comments by November 8. Dr. Gardner asked to first review the original MMR recommendations which were summarized in this document. Dr. Peter also distinguished between a codification of committee recommendations and issuing up to date guidelines. The former requires only a re-reading of the statement; the latter, which he advocated, also required indentifying prior statements' issues. Dr. Snider related this to his point on the previous day about developing a mechanism to update statements without having to read through them completely. The current pace of developments is forcing CDC to rethink its processes.

Report on the Immunization Working Group of the US/Mexico Bi-National Commission

Dr. Jose Cordero, Deputy Director of the National Immunization Program, reported the formation last May of the U.S.-Mexico Bi-National Commission's Working Group on Health. This group addresses issues of tobacco use, migrant health, women's health, and immunization. Its first meeting was to take place on the following day. Its main activities would be measles elimination, addressing joint concerns on rubella, and how to ensure that Mexican immunizations are considered valid in the U.S. (not true in some states).

Dr. Ricardo Tapia, the coordinator for these working groups, then presented the successful general strategies implemented since 1990 to increase immunization coverage in Mexico:

(1) A national policy to have free and universal vaccines.
(2) A health sector of integrated health institutions, headed by the Ministry of Health and the Social Security system. A National Council coordinates the vaccination strategies, and state vaccination councils coordinating the local health, educational and other sectors.
(3) A social participation strategy involves the public, the social and private sector.

(4) Information is disseminated to the population through the mass and print media, mainly by the private sector (including posters, educational games, pamphlets, etc.).
(5) Health staff are intensively trained regarding all vaccines, procedures, etc., during three national immunization weeks, conducted by each state program.
(6) In addition to the three weeks/year, a permanent program provides weekly supervision on the amount of vaccines available, confirmation of record keeping, etc.
(7) Applied research includes seroepidemiological surveys; attention to missed immunization is done mostly at the hospital level.

Specific strategies include (1) basic vaccination schedules for all institutions of health; (2) a permanent vaccination program conducted by more that 15,000 units, as well as almost 9000 field-level "brigades" and over 114,000 schools); (3) intensive vaccination though the national health weeks at the units described above, plus about 53,000 vaccination stands. State health weeks and outbreak control strategies supplement these efforts. The work is divided (4) through operative regionalization, with private services covering about 15% of the population in a secondary process. Fifth, logistic support is provided not only nationally but locally; and (6) epidemiologic surveillance is achieved through the National Vaccination Card (over 90% of children have it at the interview), a nominal census at the local level to keep each child's immunization schedule; and a special information system (PROVAC) linking the local health unit to the national level, providing regular updates of the immunization coverage every three months.

Graphs showed high immunization rates of about 80% for children <1 year, and 96%+ for 1-4 years of age. Dr. Tapia noted that there has been no reported polio in Mexico since 1990, only one case of whooping cough since last year, and that TB cases are the lowest ever. Another graph showed similar gains since 1990. Finally, Dr. Tapia showed a video of the permanent Mexican program. All material is locally developed with the input of community focus groups. The various areas and populations are identified with colors and symbols. The approach stresses the inclusion of immunization issues to family values, and the success rates have reflected this.

Discussion

To applause, Dr. Davis congratulated the Mexican government on their extraordinary program. Dr. Tapia confirmed for Dr. Ward that Hib is a planned schedule addition in 1997, along with MMR (combination, as opposed to the separate measles), Hep B for workers, and Td vaccine for 12 year olds. Dr. Ward recommended a permanent liaison to the ACIP from Mexico, to address transborder issues. Dr. Tapia reported Mexico's mutual interest in doing so to improve coordination of efforts.

Dr. Gardner reported similar success in Columbia and other PAHO countries. He asked if Mexico has an adult booster Td policy, or plans for pneumococcal or influenza vaccine. Dr. Tapia reported that adult immunization is under discussion. With current funding, they want first to change the basic immunization program to include hemophilus, MMR and other vaccines. The booster Td vaccines will be implemented; while influenza is recommended, it is not under the government policy for reimbursement.

Dr. Halsey asked if Mexico had data on Hep B surface antigenemia prevalence rates, and if there were plans to incorporate a Hep B vaccine. Dr. Tapia reported they had just completed their Hep B survey, their first endeavor with the vaccine pharmaceutical industry. They will present that on November 3. The prevalence rate varies; it was 6% in 1987, but is up to 40% in HCWs. Hence, the plans to introduce Hep B vaccine. Dr. Wechsler asked whether the Mexican adults she sees in her practice would have had the tetanus series as children. Dr. Tapia thought this unlikely before 1990, when the program was greatly improved. The 1989-1990 survey showed that only 46% of Mexicans had the complete immunizations. Many did not have standard immunizations.

Dr. Tapia then showed videos broadcast on TV. Nurses are symbolic of the whole program, as they take the entire program into the community. The videos are in cartoon format to be attractive to children, one including a song well remembered by the children surveyed. The program also includes about 80,000 volunteers to provide logistical support and vaccinations.

Assessment and Feedback of Practice-based Immunization Coverage Data

Dr. Edward Hoekstra cited routine assessment and feedback of vaccination rates obtained at the provider's site as one of the most effective strategies to achieve high, sustainable vaccine coverage. Since 1995, all states receiving federal funds for vaccination programs have been required to conduct annual assessments of vaccination rates in public health clinics. In February 1996, the ACIP recommended expanding this to private practices as well.

NIP conducted two national surveys of immunization program managers to evaluate annual assessment implementation. In a single year (1994 to 1995), assessment of all public health clinics leaped from 11 states to 29, of which 10 assessed at least half their clinics. Nationwide, 75% of public health clinics were assessed, and median coverage rates for 4:3:1 (DPT:OPV:Hib) rose from 60% in 1994 to 68% in 1995. In 1995, 21 states assessed all community and migrant health clinics; 37% of these nationwide were assessed. Regarding private providers, 36 states began assessing private clinics in 1995, though most assessed less than 20. Only Maine assessed all private providers.

In the Georgia experience, the median coverage rates for 4:3:1 rose from 40% in 1986 to 89% in 1994, attributed to assessment and feedback. The percentage of clinics with coverage rates $\geq$90% rose from 0% in 1986 to 49% in 1994, and those with $\leq$60% dropping from 81% to 4%. In Iowa, half the birth cohort of 38,000 are seen by the public health sector, and all public health clinics have been assessed since 1993. A chart showed a similarly rising median 4:3:1 immunization rates from 49% in 1993 to 89% in 1996. Clinics with coverage rates $\geq$90% rose from 2% in 1993 to 49% in 1996, while those $\leq$60% dropped from 73% to 4%.

Seventy percent of Illinois' birth cohort of 131,000 children are seen by the public health sector, which since 1993 conducts biannual clinic assessments. Since January 1995, all public health providers receive a $10 incentive for each child up to date for 3:3:3:1 by 24 months; or, if the clinic has a >85% coverage, $15 for each child. By January 1995, the median coverage rate for 3:3:3:1 (DPT:OPV:Hib:MMR) was 75%, a year later it was 89%. The percentage of clinics with coverage

rates of over 90% increased from 12% in 1995 to 48% in 1996, while their percentage of clinics with coverage ≤60% decreased from 28% in 1995 to 7% in 1996.

Discussion

Dr. Davis appreciated the power of assessments and feedback to reinforce good practice. He asked if Illinois' incentives produced any staffing pattern changes, or how the dollars were used. Dr. Hoekstra reported that though each clinic could decide how to use the money, it would not be a large total. Dr. Hadler asked if any such dramatic data had been seen in urban areas, noting that Chicago was not included in the Illinois report. Dr. Hoekstra responded that Chicago's assessment had just been set up, but reported that within a year of working with the WIC program, all their clinics added personnel and are doing assessment of vaccine records. Since April 1996, they have offered voucher disincentives (only one month of vouchers if parents do not bring their child's vaccination records or they are not up to date). This had a major impact, though he did not have the data on hand. They are following all Chicago WIC clinics, both high-risk areas and for Chicago as a whole.

Dr. Gardner wished for assessment and feedback of adults on pneumococcus and influenza immunization. Dr. Breiman reported that this is being considered. Dr. Cordero noted that the FY97 grant guidance includes state funding for adult immunization strategies as part of the 317 category. Dr. Margolis asked of any data on the introduction of new vaccines, such as Hep B in 1992. Dr. Hoekstra said this is done; that data was just not yet included in the overall figure. However, state data indicate the Hep B implementation in the 90% range. The assessment and feedback program could include any number of vaccines. Dr. Margolis added that the CASA assessments should also show penetration of Hep B vaccine.

Dr. Thompson asked if this program had failed anywhere, and Dr. Hoekstra reported that data from every state collecting it in a systematic way (e.g., not changing their surveillance), showed the same improvement to parallel the clinic assessment process. Dr. Gardner observed that the most common vaccine-preventable reactive airway disease is influenza. Since influenza vaccine is covered by VFC, the ACIP should be alert to the increasing vaccine coverage of these high-risk children.

Dr. Peter asked what works (or does not) to get private practices to conform. Dr. Hoekstra responded that some states with universal vaccine distribution use those contracts with providers to help the physician implement this, particularly with the multiplicity of vaccines in last few years. Even managed care clinics are improving. Dr. Peter requested periodic update summaries of state data. Dr. Hadler asked if these data should also be sent to the AAP and AAFP to circulate among their constituents. To further acceptance of the new recommendations to come from the ACIP, he also wished to more widely publicize such information, and requested a few of Dr. Hoekstra's slides to show to pediatric audiences. Dr. Hoekstra was agreeable to do so.

<u>Continuation of COMVAX® Discussion</u>

After a short break, Dr. Davis apologized if some discussion of COMVAX® was cut short on the previous day, as it included a variety of issues relating to the ACIP's future direction. Dr. Harold Margolis summarized the vaccine-specific issues discussed on the previous day. First was the

routine use of the vaccine, or that in infants with surface-antigen positive mothers. The program proposed two wording options for these latter, one to allow vaccine use and the other advising against it (the current FDA-approved label). The third issue was use of the vaccine in areas where prenatal screening is not the norm.

Out of this discussion came a number of long-term programmatic issues: the use of multiple doses of the vaccine (vaccine overlap or "polypharmacy") which may disburse extra doses. This is applicable to the new recommendations on new vaccines. COMVAX® issues could perhaps guide the programmatic issues. Since the discussions resulted in no ACIP guidance, he asked to address questions specific to this vaccine either on this day or through a working group, as the program would be called upon for answers.

Dr. Gary Euler reiterated where the statements were needed regarding COMVAX®: inclusion in the revised Hep B statement; the expanded notice to readers to be published following consensus on the wording; the standard notice to readers published November 22, 1996; the short (7-10 page) statement "stand-alone" document".

He reviewed the advantages and disadvantages of each. Option A's expanded notice would allow fewer statements, the wording on issues would be published sooner, and it may provide a better precedent for handling new combination vaccines. Its disadvantages are a potentially lesser emphasis on the Hib component, and the lack of a stand-alone statement (it would be incorporated in the expanded notice). The notice would be delayed until consensus is achieved, and a revised Hib statement from that of 1993 will be needed. Option B, the "stand-alone" statement, is recommended because of the quicker notice to readers publication, an equal emphasis on antigens, and more room to present data and issues than in an expanded notice. On the other hand, the issues would be published later, and an extra statement may be a questionable precedent for handling new combination vaccines.

Discussion

Dr. Schoenbaum felt there were only two potentially public health issues related to this product: the proscription against giving Hep B or any other antigen with Hib prior to 6 weeks of age, and an extra dose. He saw no problem if the extra dose caused no harm and was priced equal to the lower priced-antigens. Dr. Davis commented that greater cost of additional doses could become one of those not-fully-understood ethical issues. Dr. Thompson said that the over-immunization issue is only valid if the child is given Hep B at birth rather than beginning immunization at two months. This vaccine removes most of the concerns about the new polio statements, by ensuring no more than three injections per visit. That important benefit should be realized quickly, though he agreed there still are cost issues to be addressed. Dr. Hadler stated that the program is now modifying the polio statement to note that one combination now is available as an option to reduce the number of injections.

Dr. Schaffner advised care in the wording presented. Since the ACIP would not have a VFC vote on this vaccine until next meeting, COMVAX® would not be available in public clinics. He advised

presenting it to providers such that in some circumstances COMVAX® could be substituted for the currently recommended immunizations. Until other issues like cost are worked out, more cannot be said. But Dr. Margolis re-raised the issues not addressed by the package insert, such as the options about vaccinating children of antigen-positive mothers. While it can be emphasized to not give COMVAC at birth or <6 weeks of age, other experts also could argue for four doses, especially in these populations. Also not covered in the insert is the question of whether this vaccine can be used for persons in those areas where surface-antigen screening is not done.

Dr. Plotkin advocated a generic document on combination vaccines, augmented as each vaccine is released. Dr. Davis agreed, but reiterated the need to get information out quickly and to address issues not in the package insert. Dr. Halsey recommended a simple statement in *MMWR* indicating that the product can be used, but not under 6 weeks age, and ignoring the issues of infants born to surface antigen-positive mothers. That would create some questions, but would answer immediate program needs in the absence of a committee statement at this time. Dr. Hardegree noted that manufacturers can always approach FDA for justified revisions.

Dr. Davis summarized that a conference call would be held on the following week to quickly develop an advisory. The working group would include Committee members, manufacturers, FDA, etc. The standard notice to readers would be issued with standard language addressing no issues of off-label use. Dr. Peter asked that it also identify the issues yet to be resolved, and state that they will be included in a revised Hep B statement. He recommended not issuing a stand alone statement to avoid that precedent, but rather a generic one on combination vaccines. Dr. Hadler recalled that these notices generally state that a full ACIP recommendation will follow.

Harmonization of Childhood Immunization

Dr. Jacqueline Gindler presented the January 1997 schedule as discussed by the schedule harmonization working group. Among the changes since the last schedule published in July 1996 were the licensure of Tripedia™ for the first four doses of the DTP vaccination series, as well as licensure of the DTaP-Hib combination for the fourth doses of DTP and Hib series among children ≥15 months of age; licensure of Hib-Hep B (COMVAX®) for use at 2,4, and 12-15 months of age, and acceptance by CDC of the ACIP's recommendation for a sequential polio vaccination schedule.

DTaP Issues

The DTaP vaccine (Tripedia™) is licensed for the first four doses of the DTP vaccination series; recommended at 2,4,6 and 15-20 months of age. It may be used to complete the primary series in children who received one or two doses of whole-cell DTP. Additional data is being collected on the safety and immunogenicity of the fifth dose among children who received four doses of DTaP. And, DTaP-Hib (Tripedia™-ActHIB®) is licensed for the fourth dose of DTP and Hib among children ≥15 months of age.

At issue was whether "DTaP or DTP", or "DTaP", should appear on the figure as the preferred vaccine; whether there are sufficient data to permit recommendation of DTaP as young as 12 months of age; and whether (if "DTaP or DTP" appears) the bar should show DTP4 at 12-18 months or 15-

18 months. Also discussed was whether the footnote should mention that DTaP is not licensed for the fifth dose among children who received four previous doses of DTaP, and whether the availability of DTaP-Hib should be mentioned in the footnote.

Dr. Gindler read the proposed language to the DTaP footnote for the pre-adolescent dose:

> "DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) is the preferred vaccine for all doses in the vaccination series, and may be used to complete the series in children who have received one or more doses of whole-cell DTP vaccine. Whole-cell DTP vaccine is an acceptable alternative to DTaP. If whole-cell DTP is used for the fourth dose, this dose may be administered at 12 months of age, provided at least 6 months have elapsed until the third dose."

Discussion

Dr. Griffin recalled an ACIP vote that DTP or DTaP could be used at 12 months, although not licensed for use at that age. To be consistent with the ACIP's recommendations, the figure must include both vaccines. Dr. Gindler recalled to agreement that this was recommended for children unlikely to return at the recommended age. When it was recalled that the use of "recommended" was desired over "preferred", Dr. Gindler cited the effort to keep the footnotes short and simply refer to the package insert and ACIP recommendations.

Dr. Griffin asked why the first sentence was inserted. Dr. Gindler reported the workgroup's consensus that the figure should include "DTaP or DTP" with DTaP listed first, and to extend the bar from 15-18 months since the preferred DtaP for dose 4 was licensed for use during that age range. In the footnote, they would identify DTaP as the preferred vaccine, though whole-cell is acceptable. They agreed not to include any statement about its lack of licensure for the fifth dose, nor mention the DTaP-Hib vaccine. She showed the table, with DTaP in a slightly larger font than DTP. Dr. Davis noted that this may be the final year that DTP would be on the figure.

Dr. Schoenbaum suggested, then, putting only DTaP in the figure with only the footnote referencing DTP. Dr. Sherrod commended this effort to simplify a complicated issue, but again questioned the recommendation of DTaP for all doses in the series, since the fifth dose is not yet licensed. Dr. Davis reported the workgroup's conclusion that by the time the children were eligible for the fifth dose (4-5 yrs of age) that issue will have been resolved. Dr. Griffin noted that DTaP is now recommended for the fifth dose for all children currently eligible. There is every expectation that the data will support its use over the next few years. When Dr. Sherrod asked what would happen if the data do not show that, Dr. Griffin responded that the alternative was to continue with whole-cell vaccine.

Dr. Halsey raised the liability issue for those still using DTP if it is removed from the schedule. For that reason, the group consensus was to include them both and emphasize DTaP, probably only for another year. He also noted that there was no termination date; an annual or semi-annual schedule should be decided on this day. Dr. Peter agreed, and added the need to ensure that the schedule includes the appropriate language of the involved organizations (e.g., for the AAP, DTaP is

'preferred' but DTP is acceptable). Dr. Glode suggested releasing a short vaccine update at six months, with a note that the full schedule is published each January. Dr. Cordero supported the annual schedule, to allow consideration of collateral material and activities such as media kits, and satellite and local courses.

VOTE. Dr. Thompson moved to accept the language as reflected in the table, with DTP in a slightly smaller typeface, and the footnote as described. In favor were Davis, Ward, Glode, Griffin, Thompson, Schoenbaum, Modlin and Sherrod. None were opposed.

Dr. Gindler wished to clarify whether the footnote would add a statement similar to the ACIP's that DTaP is acceptable at 12 months of age in certain circumstances. Dr. Hadler suggested simply stating that "if the child may not return for immunization, the fourth dose may be administered at twelve months of age, if at least 6 months has elapsed since the third dose". Though vague, this could address the issue in the space available. Dr. Davis summarized that this adopted the intent of the previous day's discussion to allow both DTaP or DPT.

VOTE. Dr. Thompson amended his motion to have the footnote in this described language, to be crafted. All were in favor of this, and the motion passed.

Polio Vaccination Schedule

Next, Dr. Gindler raised the polio vaccination issues. The ACIP recommends a sequential schedule with two doses of IPV at 2,4 months followed by two doses of OPV at 12-18 months and 4-6 years of age. The American Academy of Family Physicians (AAFP) recommends parent-provider choice among sequential, all-OPV or all-IPV schedules. The language submitted to the AAP executive board supports the first 2 doses of IPV, allowing an all-IPV or sequential schedule. Dr. Halsey expected to provide the final language in the next week.

Dr. Gindler then outlined the vaccination issues in the figure, again showing the schedule. One question was whether the polio immunizations should list IPV/OPV, or just "Polio". Another was where the bar indicating the third dose should appear, since the all-OPV schedule ranges from 6-18 months rather than IPV's 12-18 months.

The working group's consensus was to list only "Polio" on the schedule, at 2,4 months, 12-18 months and 4-6 years. She read two options for the proposed footnote on polio vaccination, both beginning with a statement that both OPV and IPV are currently licensed in the U.S. She also reported the working group's preference for Option 1.

I. "IPV is the only poliovirus vaccine recommended for immunocompromised persons and their household contacts. For other children, schedules using all OPV, all IPV or two doses of IPV followed by 2 doses of OPV are all acceptable:
   1. Two IPV at 2,4 months; two OPV at 12-18 months and 4-6 years.
   2. Four OPV at 2,4,6-18 months and 4-6 years.
   3. Four IPV at 2,4,12-18 months and 4-6 years.

"The ACIP recommends schedule 1; the AAP recommends a schedule with the first two doses being IPV (i.e., schedule 1 or 3), and the AAFP recommends a provider-parent choice of any of the schedules. However, all three schedules are acceptable to the ACIP, the AAFP, and the AAP."

II. "The ACIP, the AAP and the AAFP consider that schedules using all OPV (2,4, 6-18 months, 4-6 years), all IPV (2,4, 12-18 months, 4-6 years) are all acceptable. The AAP recommends a schedule with the initial two doses being IPV (i.e., either the sequential or all-IPV schedule), and the AAFP recommends that clinicians and parents discuss the three schedules and choose among them. IPV is the only poliovirus vaccine recommended for immunocompromised persons and their household contacts."

Discussion

Dr. Davis favored Option 1's delineation of the groups' positions. Dr. Peter thought the first sentence was well enough known to be deleted, but Dr. Snider noted that non-providers (parents) would use this table, too, not necessarily knowing there are two vaccines. Dr. Ward preferred Option 1, retaining the lead-in to elaborate on IPV/OPV (since the table now only indicates "polio" immunization), and liked the enumerated listing. Dr. Zimmerman accepted either option, preferred #1, but noted that #2 better reflected AAFP's language. He suggested Option #2's language with #1's format.

Dr. Schoenbaum moved that Option #1 be adopted, but incorporating the AAFP's language from Option #2. Dr. Halsey thought a formal vote to adopt specific language inappropriate, since it reflects positions of other organizations. Dr. Thompson just wished to ensure the inclusion of language specifying that all the organizations advocate parent-provider choice. The only distinction is AAFP's non-preference of a particular schedule.

Dr. Hadler suggested moving up the AAFP text in #2 to the end of the second sentence outlining each schedule. This can be done in both footnote versions. Dr. Griffin agreed, since the current version incorrectly implies that the ACIP does not recommend discussion or choice. Dr. Halsey agreed to work on the final wording. Dr. Zimmerman noted that a discussion of informed decision/choice is not in the VIS statement, which does not reflect the feeling about informed choice expressed here. He also stated that AAFP is willing to review any new language suggested, but it must be approved by their Board.

Dr. Schaffner was concerned, however, that the ACIP opinion was being diluted. Dr. Hadler suggested a vote to incorporate the intent of all 3 organizations to recommend discussion of the two schedules, and on the preferred format. Dr. Ward observed with interest that, after three years of debate produced a consensus recommendation wording, the harmonized schedule would become subject to the veto of collaborating agencies' Boards, requiring a change of wording. While the process is appropriate, he thought it inappropriate to request a re-writing of the statement at this point. Dr. Halsey responded that what the associations recommend must be written by their governing board, including the ACIP. He fully agreed that everything else need not be rewritten.

Dr. Gindler verified in closing the workgroup's consensus to have polio rather than IPV/OPV and to extent the bar from 12-18 months.

Hep B Vaccination

Dr. Gindler raised this issue of the infant vaccination because the management of infants whose mothers' HBsAg surface antigen status is unknown is currently unclear. The current wording calls for a higher dose of Hep B vaccine at birth, but make no recommendation for HBIG. The footnote calls for dose 2 at age 1 month, and dose 3 at 6 months. A frequent question from the field is why these infants are not treated the same as those who are known positive. In fact, the ACIP recommendations for Hep B vaccine state that blood from such women should be drawn at the time of delivery and subsequent management of the child be based on the Hepatitis B test results. Since this was not included in the footnote for the sake of brevity, she proposed a change (new text italicized) to the infant Hep B footnote section on infants of HBsAg-status unknown mothers.

> "Infants born to mothers whose HBsAg status is unknown should receive either 5 μg of Merck Vaccine (Recombivax HB®) or 10 μg of SKB vaccine (Engerix-B®) within 12 hours of birth. *Blood should be drawn at the time of delivery to determine the mother's HBsAg status, and the dose and timing of subsequent vaccine doses should be based upon the mother's HBsAg status; if the mother is found to be HBsAg-positive, the infant should receive HBIG as soon as possible (no later than 1 weeks of age).*"

The workgroup's consensus was to accept that, and the Committee had no further discussion.

Regarding adolescent Hep B vaccine, the current schedule indicates that Hep B should be initiated or completed during the 11-12 year-old visit. Providers have questioned whether these doses can be given earlier. The proposed text would be added to the beginning of the current Hep B footnote with the balance remaining the same:

> *"Children who have not been vaccinated against Hep B in infancy may begin the series at any childhood visit."*

Dr. Schoenbaum agreed, but noted the broader issue of the schedule itself, which raises the issue of the shaded bar. He advised being consistent that catch-up occur no later than 11-12 years for Hep B or varicella. Dr. Gilmet and Dr. Schoenbaum thought that applying the term "adolescents" to children aged 11-12 was incorrect, and Dr. Mahoney reported AAP's use of the word "children". However, Dr. Hadler noted that this term was referenced in the statement to be issued shortly.

Dr. Chin Le suggested a third version of a footnote. Since he felt that catch-up for Hep B or varicella should be done at any opportunity, he found the current shaded bar misleading. He proposed extending it from 4-16 years for both Hep B and varicella, since the 11-12 years visit is often missed due to a change of health care provider. A footnote for hepatitis would state *"Children and adolescents who have not been vaccinated against HBV in infancy may begin the series at any visit. All efforts should be made to address and complete the series by 11-12 years of age."* The footnote for varicella would say: *"Susceptible children who have not been immunized against varicella during*

early childhood are encouraged to receive the vaccine at any visits (if not contraindicated). Varicella immunity is strongly recommended before the child reaches adolescence."

Dr. Halsey agreed with his proposal, since the Academy has also been questioned whether Hep B can be given in between those ages. Dr. Margolis recalled that the Hep B schedule was adopted to suit programmatic needs, but he also warned that changing the bar would also change earlier ACIP recommendations. Dr. Halsey thought this would be consistent with current AAP policy, but might conflict with the ACIP due to the VFC policy. Dr. Ward saw no diminishment to a past focus on adolescents, and extending the bars would allow providers to take the opportunity to use Hepatitis B vaccine during more visits. The footnote clarifies that the adolescent visit is the last chance for immunization. Dr. Margolis, though, thought this risked dramatically changing the Hep B immunization. Extending the bar would also require a footnote to address the immunization issues of high-risk groups.

Dr. Peter liked the two proposed footnotes, as they address frequent questions for both Hep B and varicella. He suggested a compromise of adopting the footnotes, retaining the current bars, and consider extending the bar with the next schedule. Dr. Gall supported this. Dr. Hadler noted that the varicella language is more permissive language. NIP and he had some reservations about extending the bar, because that may imply funding that does not exist except for the adolescent cohort. He thought the footnotes dealt with the issues raised without giving them such force. The ACIP recommendations do not endorse vaccinating at any opportunity. Dr. Davis suggested a conference call to discuss this.

Dr. Wexler suggested shading the areas covered by VFC funding, but Dr. Cordero noted that 317 funding would also be an issue of concern, since its allotted coverage is now at maximum. Dr. Schaffner objected and noted that these are recommendations on the immunization schedule, not involving even important funding issues. Finally, the Committee generally approved Dr. Peter's suggestion, with wordsmithing to be done by the NIP.

Second Dose of MMR

Since the AAP and AAFP prefer the second MMR dose at 4-6 years, Dr. Gindler suggested amending the schedule chart to remove the "or" and to shade the 11-12 year dose as a catch-up recommendation. Dr. Halsey supported that and would seek Academy approval in the next few days. If not possible, it could be included in the mid-year report proposed by Dr. Glode.

Dr. Gardner stated that the document discussed yesterday specified a 4-6 year old MMR dose, and urged consistency. He suggested specifying these doses as MMR1 and MMR2, as for hepatitis. He also noted that the new MMR document states that waning immunity does not cause vaccine failure, plays little role in measles transmission, and that the major benefit of the second dose is to reduce the proportion of persons with primary vaccine failure. To be consistent with that, the MMR2 bar would be extended to include 18 month and 4-6 year brackets, then shading the 11-12 year visit as a catch up dose.

When Dr. Davis asked AAP's opinion, Dr. Halsey indicated that they generally follow the ACIP regarding MMR, but also advised sensitivity to the Redbook Committee as a partner in this process. A footnote similar to that just adopted for Hep B and varicella might be the answer to allow discretion in the MMR dose. However, Dr. Gindler noted that the language is already very permissive.

Dr. Hadler was concerned that issuing such a schedule change before the statement is complete may cause confusion. He noted that the policy does not formally change until a statement approved by the ACIP and CDC is published in *MMWR*, although recently is seems to be accepted when published in *Pediatric News*. He and Dr. Snider would discuss this with Mr. Malone to ensure it is acceptable. However, Dr. Modlin worried that if not published in January, an ACIP decision in June would be confusing. Though he understood Dr. Hadler's concern, he felt the need to make this a timely document to support an immediate change, particularly since the MMR statement is published. Dr. Glode demurred, though, since another footnote may be necessary if AAP cannot accept the harmonization. She preferred retaining the current schedule for 1997.

VOTE. Dr. Davis moved to retain the current language and chart. All members present voted in favor: Ward, Davis, Glode, Modlin and Griffin, Sherrod.

Combination Vaccines

Dr. Gindler raised the question of a footnote to address the new and emerging combination vaccines. At issue was that (1) as other combination vaccines are licensed, the schedule will become out of date; (2) there is no precedent for identifying specific products on the schedule unless their schedule of administration differs from routinely recommended vaccines. And finally, (3) the workgroup preferred a simple statement indicating that combination vaccines are available any may be used when indicated. They proposed a footnote:

> *"This schedule indicates the recommended age for administration of currently licensed childhood vaccines. Some combination vaccines are available and may be used whenever administration of all components of the vaccine is indicated. Providers should consult the manufacturers' package insert for detailed recommendations."*

Dr. Sherrod re-expressed her concern about the fifth DTaP dose. Dr. Snider responded that the text could say "licensed for the fifth dose after four whole-cell doses, but not four acellular doses". When Dr. Sherrod wished to indicate that in a footnote, it was noted that the package insert covers that. Dr. Snider obseved other dissonant aspects of the schedule to the package insert, such as OPV at six months.

VOTE. Five members were in favor of the proposed language: Ward, Davis, Glode, Modlin and Griffin. Sherrod was opposed.

January 1997 Schedule

Dr. Gindler provided the timetable to publish the 1997 schedule to no further committee comment.

Discussion

Dr. Wexler reported a problem in catching up 3-11 year-old Asian children, and suggested a footnote regarding Hep B vaccine. Physicians are not familiar with the recommendation of early immunization to catch up these children due to issues of horizontal transmission of hepatitis B. She noted that though over one million children from Asia, Africa, or certain endemic countries and now the U.S. are eligible, with vaccine available, they are not included on this schedule.

Dr. Snider thought this and other comments to raise issues of provider education and reference material, longer than this schedule but shorter than the recommendations. He would report back to the committee on CDC's consideration of this issue. This also has precedent in the modification of recommendations already done to make them more user-friendly for the Internet.

Dr. Vernon raised the central mission of the ACIP. He recalled fears, when the OBRA 93 legislation created the VFC, that the ACIP would become a fiscal rather than a scientific entity. At the time, he defended its ability to separate the two roles, to first be an organization recommending for the good of children and adults based on the best science, separate from funding decisions. He stressed the critical importance for the future of the Committee to maintain its integrity and credibility. Dr. Chin Le supported that comment, stating that ACIP decisions affect managed care decisions on what will be paid for immunizations. The Committee must avoid the risk of blocking out children migrating in and out of the managed care system every year by strictly defining limited periods during which vaccine administration will be reimbursed (e.g. Hep B at only 10-12 years of age).

With that, the Committee adjourned for lunch. On reconvening, Dr. Snider stated that CDC is considering with its General Counsel the issues related to the VFC program. An ACIP working group will participate in this work.

<u>Rabies PEP Presentation</u>

Dr. Charles Rupprecht noted that the final text of the bat rabies PEP recommendations, accepted with minor modifications during the last meeting, was in the members' meeting books. He noted the increasing trends of rabies in the 1980s and 1990s, and a relationship between PEP and the number of rabid animals in time and space. However, the correlations are not absolute, because the proportion of rabies varies regionally and by wildlife species. Since from 1980-1988 raccoon rabies declined from 4500 to an estimated 1800, Healthy People 2000 proposed to reduce that number by half by the year 2000. However, the raccoon rabies epizootic rebounded, now stretching along the east coast. Dr. Rupprecht expected an oscillating but average incidence of about 7-8000 annually over time. While stabilization of PEP is expected, spikes will probably occur.

Those few states with surveillance can show a rough correlation to overall animal incidence and PEP. A sixty-fold increase of rabies in two New Jersey counties reflected this; with the epizootic, PEP is expected to rise. However, few states report PEP. The last detailed study (Helmich, 1980-

81) was done when surveillance involved investigational vaccine use; surveillance occurred in at least 21 states. The raccoon epizootic was only entering Virginia at that time. At best, one can now only extrapolate based on Helmich's data of about 7200 diagnosed rabid animals. During 1995, 7881 rabid animals were reported. A range from 5000-57,000 estimated PEPs were extrapolated from the 1990 census data and regional rabies epidemiology. Sales of Human Rabies Immune Globulin (HRIG) also can support estimates, but variables include the unknown quantity not used or used as a booster of previous PEP. However, 24,000-43,000 people could have been treated during 1992-94 if all HRIG was used (but, again, the consumption varies based on the weight of those treated).

Helmich's data showed a preponderance of use of PEP in children and an overall incidence of 70-80 cases per 1 million population (about 34% in persons <14 years in those states with surveillance). The surveillance data of the 1990s showed those rough estimates to be close, with a range from a low of 19% <18 year old to high of 44%. However, the limitations were the limited number of PEP cases in those states with surveillance, casting doubt on the validity of extrapolating to higher incidence areas. But the foci of outbreaks are also of importance; they often reverse the 1980s ratios. In these, the one-third of background PEPs to children will probably rise as focal outbreaks occur, due to such factors as children's curiosity about animals and their appropriate size as targets to small carnivores. He cited a New York (Tioga county) outbreak of 350 exposures with rough ages showing 70% at <7 years of age.

However, some estimates of worst-case exposure rates, potential PEPs and their associated costs can be based even on these relatively poor data. There have been no PEP failures since cell culture vaccine and rabies immune globulin were utilized in the last decade. If a range of 5000-57,000 total PEPs are assumed (a mean of about 22,000), and a range from 19-44% represented by children, extremes of 1000-25,000 annually could receive PEP, or a mean of 5-10,000 children. There is no available information on the amount of third party payments. But, while there are no reports of children refused PEP, it also can be estimated that about 50% of the cost may not be recoverable. This yields a figure from 50-12,000 cases in children not covered by health care insurance (more likely 2500-5000 annually). Assuming estimated PEP costs based on current literature of about $1500, the extreme costs range from $1-18 million, or more likely $4-8 million not presently recoverable.

Discussion

Dr. Davis appreciated this analysis to the potential impact on VFC. Dr. Hadler asked if the $1500 included ancillary medical services, but Dr. Rupprecht said it was limited it to HRIG and vaccine alone. Most of these patients are seen in emergency rooms, and adding those costs makes these ranges even greater. Dr. Modlin asked if 100% vaccine success rate was for simple vaccine use or only for vaccine given according to recommendations. He responded that there were no failures at all.

Dr. Thompson thought the estimate of overall costs as nearly accurate as could be done with the scarce data, but noted that they worked from the number of instances of PEP measured. In the absence of public funding of PEP, physicians often advise parents of the cost; frequently, the PEP

is declined, and appropriately so. But he expected that including the vaccine in VFC would at least double the PEPs done.

Dr. Plotkin reported estimates that 90% of PEP occur in an Emergency Room or hospital, making a true estimation of costs difficult. He also noted that the Compassionate Use program ensured that no one has ever been denied HRIG. When Dr. Thompson asked how that program would deal with a patient unable to pay, but for whom PEP is questionable due to an unclear exposure, Dr. Plotkin responded that the physician decides. He thought about 20 cases were so provided this year, and Dr. Rupprecht noted this is on a denominator of about 20,000.

PHS Opportunistic Infections Workgroup

Dr. Jonathan Kaplan coordinates CDC activities to prevent opportunistic infections. He reported on a process to update the USPHS/IDSA guidelines to prevent opportunistic infections, which includes some vaccination activities. CDC, NIH, and IDSA cooperated on these guidelines focused on HIV-infected persons, a summary of which was published in *MMWR* in 1995. PCP, TB, were the primary focus, but vaccinations were included. He outlined the document's references to vaccinations and the rating scale for each (A=standard of care, B=immunization offered, but advantages and disadvantages discussed, etc.). A table offers prophylactic regimens and vaccines for not necessarily opportunistic diseases (e.g., pneumococcal vaccine, hepatitis B and annual influenza vaccination). There is a vaccination schedule for children, and another section provides recommendations for HIV-positive travelers. Paragraphs addressed live and killed-virus vaccines.

He reported an upcoming meeting at NIH to address those guidelines needing updating, with attention planned to influenza, pneumococcal, and measles vaccinations. Recommendations for influenza vaccinaton for HIV positive persons will probably be similar to the ACIP's influenza recommendations; pneumococcal vaccination may be upgraded from a B to an A category for HIV-infected persons; and they will discuss the adverse reaction to measles vaccination in an HIV-positive person. They may recommend an immunoglobulin vaccination over the live virus vaccine for immunocompromised travelers, and they will try make their pediatric vaccination schedule consistent with others. He offered to report on this meeting to the ACIP.

Dr. Kaplan also reported discussion at CDC about further addressing vaccinations in HIV-infected persons, perhaps forming a workgroup or issuing an *MMWR* supplement. He preferred ACIP's method as more efficient. Dr. Davis recalled the 1993 ACIP supplement statement on immunocompromised individuals, but it was not limited to HIV. Several protocols now underway regarding HIV were reported on one with varicella, one with measles vaccine, and work on a new conjugate vaccine in ACTG. In the latter, Dr. Kaplan reported that Dr. Russ Van Dyke is in charge of the pediatric ACTG issues, and is coordinating with the AAP as much as possible.

Finally, Dr. Kaplan reported work beyond HIV. Dr. Clare Dykewicz is working on issues related to bone marrow transplant recipients, similar to the work done on HIV. Vaccinations will be an important part of that work, which is only now beginning. He offered to share their progress with the Committee, particularly if the ACIP wishes to be actively involved.

Status of Herpes Simplex Virus Vaccine

Dr. Greg Dubin of SmithKline Beecham Pharmaceuticals noted the ubiquitous nature of herpes pathogens, which include oral, genital, and eye infections, and even life-threatening infections in newborn infants. Although antiviral therapy's is available, the HSV ability to establish latency and recurrent disease can involve lifelong consequences in infected persons. Vaccination offers the best prospect to prevent herpes infections.

He discussed two herpes viruses, HSV-1 and HSV-2, which differ in clinical manifestations and epidemiology. HSV-1 is usually transmitted by contact with infected oral secretions, and usually manifested as acute gingivstomatitis in children. As many as 95% of individuals in developing countries are infected by HSV-1 by the age of 15. In the U.S. the incidence has declined, presumably because of improved standards of living. In contrast, HSV-2 is transmitted mostly through genital secretions, and the most common manifestation is genital herpes.

There is a clinical overlap in each of these infections. On occasion, oropharyngeal infections can be caused by HSV-2, and 10-30% of genital herpes are caused by HSV-1. Ocular herpes is usually caused by HSV-1, and is the leading cause of infectious blindness in the U.S. HSV-1 can cause devastating neurologic sequelae from encephalitic nervous system disease. In the U.S., between 1000-3000 cases of neonatal herpes occur, acquired in passage through an infected birth canal, caused either by HSV-1 or HSV-2. Neonatal herpes has a 50% mortality rate, and survivors often have serious neurologic sequelae.

Dr. Dubin then focused on genital herpes, transmitted by mucosal secretions containing infectious virus. High-titer viral shedding may occur during occurrences of clinically apparent herpes. Many HSV-2 infected persons have unrecognized but symptomatic herpes recurrences, with atypical symptoms. Other individuals have completely asymptomatic viral reactivations associated with viral shedding. But in each situation, viral shedding has been associated with transmission.

Not surprisingly, seroprevalence studies suggest epidemiologic features consistent with sexual transmission. NHANES II involved serologic testing of samples of persons in a broad demographic range of ages, ethnicities, and age. HSV-2 was uncommon in children under 16, but rose rapidly in older adolescents and adults, plateauing at a little over 20% in adults over the age of 45. This data is relevant to possible vaccination strategies. NHANES III data included analyses of sera collected in 1989-1991. A comparison of prevalence from NHANES II and III suggested an increase of about 30% in prevalence of HSV-2 antibody. The annual seroconversion rates among certain risk groups was also estimated (college students, women of childbearing age, STD clinic patients, and sexual partners of herpes patients). The latter two groups showed a 5-10% seroconversion rate per year.

Given the high rates of HSV-2 prevalence and seroconversion, there is considerable impact of herpes in the U.S. on public health and considerable psychosocial consequences. Aside from neonatal herpes, there are about 1 million new HSV-2 infections annually, and about 500,000 recurrences of genital herpes. And, though there are no definitive data on this, it is suspected that a number of

genital lesions caused by various infectious agents may facilitate HIV transmission. Dr. Dubin reported an estimate (from a managed care database) of approximately $650 million annually in direct medical care. In addition, genital herpes causes significant psychosocial morbidity in that infection is lifelong and often stigmatizing.

After briefly reviewing the structure of HSV, Dr. Dubin described the vaccine formulation. Glycoprotein D is the most promising candidate vaccine antigen. It is immunodominant, includes type-common neutralizing antibodies that cross-react with HSV-1 and HSV-2, and it protects against HSV challenge in animals. The vaccine antigen is a carboxy terminal-truncated form of glycoprotein D, derived from an HSV-2 isolate, and expressed in transvectored Chinese hamster ovary cells. The adjuvant system contains aluminum and monophosphoro lipid A (MPL). This is a detoxified form of lipid A which retains potent adjuvant activity. MPL has been shown to augment defective T-cell responses in the PH-1 class, and may protect against HSV infections. Pre-clinical studies with this formulation induced antigen-specificity in humoral and cell-mediated immune responses, and protected animals against genital HSV-2 disease (guinea pigs).

He then reviewed the immunogenicity data from the Phase II trials. GMT titers were shown in subjects (healthy adults over 18, average age in the early 20s) who received three doses at 0,1,6 months by deltoid intramuscular injection. By month seven, 100% had seroconverted to anti-gD2, and most showed humoral responses as early as month two. Dr. Dubin also showed cell-mediated immune responses tested with several gD-specific assays measuring lymphoproliferation, and secretion of interleukin 2 and gamma interferon. Sustained increases were seen well over the baseline level and extending beyond the 12-month study period.

Another Phase II study evaluated the immunogenicity profile of HSV-1 seropositive subjects, with vaccine also administered intramuscularly at 1,2, and 6 months. At month seven, a seven-fold increase from the baseline GMT was shown, sustained six months beyond the last vaccine dose. He reported a similar pattern of boosted immune mediated response in seronegatives, though at higher levels.

Dr. Dubin then reviewed the local reactogenicity of the vaccines. Each of the Phase II studies solicited reports from volunteers (through diary cards) of symptoms in a four-day period after vaccination. Since there were no observed differences in reactogenicity between the three doses, they pooled the results. HSV-seronegatives commonly reported soreness (41%) and redness (23%) at the injection site; HSV-1 seropositives more frequently reported reactogenicity (81% soreness, 19% swelling), but most reactions were moderate. The most frequent report by both seronegatives and seropositives was of headache (15% of HSV-1 seronegatives and 12% seropositives). Fever and malaise were infrequently reported in either group. Only one severe headache was reported.

He then discussed the design of an efficacy study important in evaluating this vaccine to prevent genital herpes. This is a discordant couples study, evaluating genital herpes in healthy subjects whose partners had frequently recurring genital herpes. There are 55 participating study sites in Canada, the U.S. and New Zealand, to produce a sufficiently large population of discordant couples.

The design is double-blind, randomized and placebo controlled, with two groups. One receives gD2-SB AS4 vaccine; the other receives the adjuvant vaccine alone.

The study population is defined as a source partner with frequently recurring genital herpes disease, and the exposed partners (vaccinees) are HSV seronegative for both HSV-1 and HSV-2. The endpoints are the prevention of genital herpes disease and prevention of infection. The advantages of the study are the involvement of target individuals at relatively high risk of the disease. Another advantage is the ability to evaluate vaccine efficacy under stringent conditions (seronegativity for both HSV-1 and HSV-2), since the literature supports that HSV-1 prevents HSV-2 disease.

Dr. Dubin defined the issues to be addressed if this vaccine is developed and licensed: whether to target vaccination to high-risk groups, the partners of infected individuals, STD clinic patients, and adults with multiple sexual partners. However, one disadvantage of that approach is that by the time someone is identified as high risk, they may already have been infected with HSV-1 or HSV-2 as a genital infection. Another disadvantage of the targeted approach is its potentially limited public health impact on overall prevalence of disease in the general community. On the other hand, universal vaccination could target adolescents (11-12 years), infants and children since HSV-2 infection is uncommon before sexual activity.

Discussion

Dr. Ward asked if other vaccine candidates were being evaluated, and if HSV-2 provides cross-protection against HSV-1. Dr. Dubin responded that there are little data on the latter, since HSV-1 is acquired at an earlier age. But there are some serologic study data that HSV-1 provides protection, and most individuals are infected with HSV-1 before HSV-2. He also reported several other vaccines in development by Chiron (a subunit vaccine in Phase III clinical development), and one or two others entering human clinical trials that are either attenuated or inactivated whole viruses.

Dr. Modlin advised caution in deciding on this vaccine's use based on data suggesting one serotype may protect from the other. While antibody to type 1 can still allow infection with type 2, it may attenuate the clinical manifestations somewhat. He was not sure there was protection from a heterologous serotype. He also asked if there were any data from the animal model on duration of protection against clinical disease. Dr. Dubin reported none from the animal models, but there are some immunogenicity data to two years in a limited number of human subjects that suggests a sustained response at least in seronegatives, but the titer does decline over time. One issue regarding duration of protection is there is no established correlate of protection for humoral or cell-mediated responses. One endpoint of the efficacy study is to determine a correlate or surrogate of protection. He added that some limited published serologic data suggest that the incidence of HSV-2 infections may be lower in a subset of individuals that have prior HSV-1 antibody.

Dr. Dubin confirmed for Dr. Schaffner that neutralizing antibody tests were done as well as ELISA tests. In general, a consistent boost in neutralizing GMTs was seen from baseline levels; this can also be shown in most HSV seronegative individuals as well. Dr. Gardner asked how long the study would follow the prospective efficacy trial subjects' immunologic markers. Dr. Dubin reported

additional large-scale trials on vaccine immunogenicity and safety with extended five year follow-up planned. Some Phase II studies are also studying the duration of protection through five years. However, none of these data are available.

Dr. Katz asked if the study with seropositive individuals was following any reduction of recurrent infection. Dr. Dubin clarified that this was not addressed, as these were all healthy HSV-1 positive individuals with no clinical symptoms of disease. Dr. Snider noted the importance of the committee's feedback on the vaccination strategies, since this would affect the design of studies and decisions on labeling. While he appreciated the case for vaccinating adolescents at 11-12 years, he expected problems with vaccinating infants and children. The current immunization schedule may be an impediment, and parents could reject vaccinating an infant against a sexually transmitted disease that may occur years later, particularly without knowing the duration of protection. He also reported the recent formation of a CDC/NCI human papilloma virus (HPV) working group to discuss an HPV candidate vaccine.

Dr. Hadler suggested coordination with CDC's Division of Viral Diseases or the staff of CDC's National Center for HIV, STD and TB Prevention (NCHSTP) . He asked the timetable for efficacy data to estimate a product release, and if they were considering a combination vaccine like a hepatitis B-herpes simplex vaccine. This would be even more attractive for STD clinics. Dr. Dubin responded that this presentation was viewed as the first step in establishing a dialogue for CDC input to clinical development. Regarding the timetable, the company is well into their large scale studies, including the mentioned efficacy study. They hope to develop vaccines that might include this as an antigen. Dr. Glode asked about the predicted transmission rate per year in the placebo discordant couples. In the limited literature, Dr. Dubin cited prospective studies of discordant couples (some of placebo arms) estimating rates of 5-10% per year, with some groups as high as 30% a year.

Dr. Robert Chen expressed Dr. Michael St. Louis's interest in working with Dr. Dubin and other manufacturers conducting trials. Dr. Kristen Nichol agreed that universal adolescent immunization might have appeal, but hoped for further work on a cost-effectiveness model. Dr. Dubin reported that they are now studying adolescents for immunogenicity and other endpoints, but agreed that ultimately they will want to develop pharmacoeconomic data on vaccine use.

Clinical Development of a DTaP and Hep B Clinical Vaccine

Dr. David Krause, SmithKline Beecham, reported their strategy to simply the infant immunization schedule with combination vaccines. In 1993, the Children's Vaccine Initiative stated that combination vaccines of existing and improved vaccine were needed in both developing and industrialized countries. Their strategy is to develop, for example, a Hep B-IPV-Hib and perhaps HA vaccine in future, as well as booster doses for adults and adolescents. They are well into such work.

Dr. Krause described their development of Hep B. This would eliminate three injections, is well tolerated, is immunogenic and can be given simultaneous to other infant immunogens. The use of Hep B vaccine in infants and children is complicated in this country, partly due to the availability

of two currently licensed recombinant Hep B vaccines, one with the same dose in volume to age 19, the other changing dose but not volume depending on the surface antigen status of the mother or the patient's age.

He outlined the package inserts for Recombivax HB®, Engerix-B® and COMVAX®, all slightly differ from the ACIP's recommendations. He described the components of the DTaP-Hep B product, which consists of Infanrix® DTaP vaccine. The IND for this was filed in 1990, and in July passed the advisory committee. They hope for FDA approval as early as January 1997.

The efficacy clinical trials were described, one an observational household contact study in Germany nested in a large safety/immunogenicity trial. Infanrix® was shown to be 89% effective in eliminating WHO-defined pertussis. In Italy, where Infanrix® was compared to DTaP and a similar vaccine with the same antigens, Infanrix® showed an 84% efficacy rate, and was significantly more effective than a U.S.-licensed whole-cell vaccine. Another vaccine, with PT and FHA but without pertactin, was tested in Sweden and was less effective, indicating the importance of the pertactin component. Infanrix® was licensed as a primary vaccine in Germany in March 1995, and more than two million doses have been distributed.

The DTPa-Hep B product uses the same antigens as Infanrix®, plus the licensed dose of Hep B surface antigen used in Engerix, all absorbed onto .7 mg of aluminum. The IND was filed for this product in January 1995. More than 3000 children received this vaccine in clinical studies, and 6000 more received it in combination with another vaccine. They expect to apply for licensure in the first quarter of 1997.

The data are still coming in, but Dr. Krause described the clinical trials of DT-Hep B reactogenicity to date. He showed historical values and clinical trial data with DT-Hep B consistently performing better than whole-cell regarding swelling, fever, pain and redness. And with severe reactions, acellular products were very superior to whole-cell, except for fever, which is unusual with any product. DtaP-Hep B also performed better than Infanrix® with anti-D and anti-T responses, when both were given at 2,4, and 6 months of age. Anti-HB response when the product was given at 2,4,6 months of age produced a 97% protection rate with a mean GMT titer of about 800. This was mirrored by DtaP-Hep B given at the same schedule. A UCLA study giving Engerix with whole-cell vaccine on this schedule produced the same seroprotection rates but with a higher GMT antibody titer, perhaps due to the adjuvant effect of whole-cell vaccine.

Dr. Krause reported the opinion by some that DTaP should be a separate injection because there are no data on correlates of protection. However, an October 1995 FDA document stated with regard to combination vaccines that employ pertussis, that in some cases bridging immunogenicity data could be considered without a well-established correlate of protection.

He then showed a graph of pertussis antibody responses when Dtap-Hep B vaccine is given. They pooled data to compare it to Engerix when given at 2, 4, and 6 months of age. In every instance, for anti-PT, FHA and pertactin, the GMT was at least as high as when Engerix was given alone, and

there were similar seroconversion rates for each antigen. He outlined another study of the DTaP-HepB-IPV vaccine compared to the most- and least immunogenic but efficacious vaccine lots in the German household study. This demonstrated that large combination vaccines do not interfere with antibody development.

Their accomplished plans were to add IPV to, then replace, OPV and to supplant with DTaP the DTP whole-cell and Hib. They hope to add further combination vaccines in future, and expect them to be a necessity rather than a luxury. Such combination vaccines will benefit both patient and parent by decreasing the number of injections and needed visits in the first two years of life. Tangible public health benefits include lower costs of administration, improved compliance, ease of storage and transportation, and improved record keeping/tracking.

In discussion, Dr. Hadler asked about the planned schedule for the vaccine. Dr. Krause reported that current evaluation of DTP, DTaP-Hep B, and DTaP-Hib as boosters.

Closing Discussionn

Dr. Davis noted that the scheduled report on the study of influenza in pregnant women would be delayed, with more information on the proposed wording provided to the members before the next meeting. Dr. Schaffner asked to address safety when Dr. Griffin gives that presentation. Workgroups will be appointed after Dr. Davis reviews the large number currently in process. He encouraged more workgroup contact with the program.

Dr. Davis called for public comment, reiterating that attenders wishing to contribute during the meeting are generally provided that opportunity. No other public comment was forthcoming. When Dr. Sherrod asked about the procedure to put an item on the agenda, Dr. Davis directed the members to inform Gloria Kovach about . Dr. Snider stated that CDC is actively seeking both committee and manufacturers' agenda items, but that anyone can submit agenda items.

Dr. Davis again thanked Drs. Ward and Thompson again for their service, and invited them back at any time. With no further comment, the meeting adjourned at 2:50 P.M.

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

Jeffrey P. Davis, M.D., Chairman — Date 8/20/97

September 5, 1997

MEMORANDUM FOR THE RECORD

The following is a correction to the October 23-24, 1996 minutes of the Advisory Committee on Immunization Practices. This memorandum for the record is an official part of these minutes.

Page 37:

The presentation on Post-marketing Surveillance studies for Merck is Dr. Paul Coplan not Robert Copland.

The studies at Kaiser Permanente are in Northern California not Northern Colorado.

Page 39, first paragraph:

Dr. Tom Vernon reported for Dr. Geoff Porges not Jeff Morges.

Thomas M. Vernon, M.D.
Executive Director, Medical, Scientific and Public Health Affairs

Merck & Co., Inc.
P.O. Box 4, WP37A-301
West Point PA 19486-0004
Fax 215 652 8918
Tel 215 652 8664

September 3, 1997

MERCK
Vaccine Division

Dr. Dixie Snider
Centers For Disease Control
Executive Secretary, ACIP
1600 Clifton Road
Atlanta, Georgia 30333

Dear Dixie:

I request that several corrections be made to the minutes of the October 23 - 24, 1996, ACIP meeting.

Page 37:

1. Dr. Paul Coplan, not Robert Copland, made the presentation on Post-marketing Surveillance studies for Merck.

2. The acronym "PMR" is probably supposed to be "PMS" for post-marketing surveillance.

3. The studies are underway at Kaiser Permanente/Northern California, not Colorado.

Page 39, 1st paragraph:

I reported for Dr. Geoff Porges, not Jeff Morges.

Thank you.

Sincerely,