Department of Health and Human Services
Public Health Service
Centers for Disease Control and Prevention

Advisory Committee on Immunization Practices
October 22-23, 1997

Meeting Minutes

Atlanta, Georgia

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GEORGIA - AUDITORIUM B
October 22-23, 1997

	Agenda Item	Purpose/Action	Presider/Presenter(s)
October 22, 1997			
8:30	Welcome		Dr. J. Davis (Chair, ACIP) Dr. D. Snider (CDC, OD)
9:00	Updates	Information	
	National Vaccine Program		Dr. R. Breiman (CDC, NVPO)
	HHS Adult Immunization Action Plan		
	Vaccine Injury Compensation Program		Dr. G. Evans (HRSA)
	National Immunization Program		Dr. J. Cordero (NIP)
9:30	Rabies Postexposure Prophylaxis	Discussion	Dr. C. Rupprecht (NCID, VR)
	Is the suggested wording acceptable for changes to the local infiltration of HRIG at the site of bite exposure?	Decision Draft Statement	
	Due to recent publicity, do we need to clarify the previous wording on bat rabies exposures to reflect bite and to de-emphasize occult, cryptic and non-typical rabies exposures?		
10:15	BREAK		
10:45	Recommendations on the Use of Rotashield (Rotavirus Vaccine) as Part of the Routine Childhood Immunization Schedule	Draft Recommendation Information	Dr. J. Breese (NCID, VR) Dr. R. Glass (NCID, VR) Dr. J. Modlin (Dartmouth)
	Should we recommend a universal immunization schedule?		
	Discussion on approval of the proposed schedule.		
	What population of children should be excluded? [transmission of vaccine virus]		
12:30	LUNCH		
1:30	Combination Vaccines -- ACIP Guidelines	Discussion	Dr. R. Chen (NIP, ESD)
	Should the current combination vaccine draft statement be approved as is for MMWR publication?	Decision	Dr. M. Glode (Children's Hospital) Dr. B. Weniger (NIP, ESD)
	If not, what further revisions might be needed for eventual ACIP approval?		
2:15	Harmonized Immunization Schedule	Discussion	Dr. R. Prevots (NIP, ESD)
	Approve changes in harmonized schedule	Decision	Dr. M. Wharton (NIP, ESD)
2:45	BREAK		

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ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
October 22-23, 1997

	Agenda Item	Purpose/Action	Presider/Presenter(s)
October 22, 1997 - continued			
3:15	Immunization of Bone Marrow Transplant (BMT) Recipients Update the ACIP on the results of the working group meeting.	Information Discussion	Dr. C. Dykewicz (NCID, VR) Dr. J. Modlin (Dartmouth) Dr. S. Wainwright (NIP, ESD)
4:00	Report of Work Group on Algorithms for Immunization Registries Core data set for the specification of the ACIP recommendations Minimum interval definition	Discussion Decision	Mr. L. Blumen (NIP, DMD) Dr. F. Guerra (Texas Hlth Dept.) Dr. E. Kilbourne (NIP, DMD) Dr. R. Linkins (NIP, DMD)
5:00	ADJOURN		
October 23, 1997			
	Operational Considerations in the Implementation of VFC Resolutions	Discussion Decision	Dr. J. Livengood (NIP, ESD) Mr. D. Mason (NIP, ISD)
9:00	ACIP Adolescent Hepatitis B Recommendations Does ACIP want to revise the recommendation to be consistent with the AAP recommendations? Does the ACIP want to revise the VFC resolution to be consistent with the "new" recommendation?	Information Discussion Decision	Dr. F. Averhoff (NIP,ISD) Dr. N. Halsey (Johns Hopkins) Dr. H. Margolis (NCID, VR)
10:00	Isolation of Influenza Type A(H5N1) in Hong Kong An update on the findings of laboratory and epidemiologic studies on a strain of influenza that usually infects only birds. This strain was isolated from a child who died in Hong Kong. This is the first time influenza A(H5N1) has been isolated from a human.	Information Discussion	Dr. N. Cox (NCID, VR) Dr. K. Fukuda (NCID, VR)
10:30	Update on the Influenza Pandemic Preparedness Plan ACIP's role in the declaration of a pandemic and subsequent recommendation for vaccination.	Information Discussion	Dr. R. Strikas (NIP, ESD)

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
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	Agenda Item	Purpose/Action	Presider/Presenter(s)
October 23, 1997 - continued			
11:00	Meningococcal Vaccine Among College Students Endorsed time line for reconsideration of meningococcal Menigococcal vaccine among college students	Information	Dr. M. Collins (ACHA) Dr. B. Perkins (NCID, BMD) Dr. N. Rosenstein (NCID,BMD)
11:30	LUNCH		
12:30	Swedish Acellular Pertussis Mass Vaccination Project Presentation on the results from an acellular pertussis mass vaccination project conducted in Goteborg, Sweden	Information	Dr. J. Taranger (North American Vaccine)
1:00	Safety and Efficacy Results from Phase III Pivotal Trial on Lyme Disease Review and comments on data Discussion on recommendation for usage	Information	Dr. D. Dennis (NCID,VBD) Dr. D. Parenti(SmithKline Beecham)
1:30	Safety and Efficacy of An OspA Vaccine in Adults	Information	Dr. D. Dennis (NCID, VBD) Dr. J. Zahradnik (Connaught)
2:00	Unfinished Business		
2:30	Public Comment		
2:45	ADJOURN		

ATTENDEES:

Committee Members
Dr. Jeffrey Davis (Chair)
Dr. Barbara A. DeBuono
Dr. David Fleming
Dr. Mary Glode
Dr. Marie Griffin
Dr. Fernando Guerra
Dr. Chinh Le
Dr. John Modlin
Dr. Jessie Sherrod
Dr. Steve Schoenbaum

Ex Officio Members
Dr. Robert Breiman (NVPO)
Dr. Geoffrey Evans (VICP)
Mr. Randolph Graydon (HCFA)
Dr. Carolyn Hardegree (FDA)
Dr. David Trump (DOD)
Dr. Gina Rabinovich (NIAID)

Liaison Representatives
Dr. Richard Clover (ATPM)
Dr. Stanley Gall (ACOG)
Dr. Pierce Gardner (ACP)
Dr. William Glezen (IDSA)
Dr. Gregory Gilmet (AAHP)
Dr. Randolph Graydon (HCFA)
Dr. Neal Halsey (AAP)
Dr. Jose Luis Diaz-Ortega (Mexico)
Dr. Georges Peter (AAP)
Dr. William Schaffner (AHA)
Dr. David Scheifele, (NACI)
Dr. Jane Siegel (HICPAC)
Dr. Richard Zimmerman (AAFP)

Executive Secretary
Dr. Dixie Snider

Office of the Director, CDC
Mr. Bob Irwin

Associate Director for Science
Office, CDC
Mr. Bill DiGioia
Ms. Joan Redmond-Leonard
Ms. Jane Zanca

Office of the General Counsel
Mr. Kevin Malone

Office of Public Affairs
Ms. Barbara Reynolds

National Center for Infectious Diseases

Dr. Nancy Arden
Dr. Joseph Bresee
Dr. Michael Bruce
Dr. Nancy Cox
Dr. Catherine Denberger
Dr. David Dennis
Dr. Clare Dykewicz
Dr. Keiji Fukuda
Dr. Roger Glass
Dr. Ned Hayes
Dr. Rana Hajyh
Dr. Hector Izurieta
Dr. John Leake
Dr. Eric Mast
Dr. Umesh Parashar
Dr. Keith Sabin
Dr. Craig Shapiro
Dr. Tom Torok

National Immunization Program
Dr. Wm. Atkinson
Dr. F. Averhoff
Ms. Jennifer Ballew
Mr. Robert Black
Dr. Muireann Brennan

National Immunization Program - continued

Dr. Victor Caceres
Dr. Bob Chen
Dr. Steve Cochi
Dr. Jose Cordero
Dr. Sue D'Isabel
Mr. Gary Euler
Dr. Janice Greby
Dr. Dalya Guris
Dr. Beth Hibbs
Dr. Sonja Hutchins
Ms. Allison Johnson
Ms. Tamara Kicera
Dr. Paul Kilgore
Dr. Charles LeBarron
Dr. Carla Lee
Dr. John Livengood
Dr. Aun Lor
Mr. Dean Mason
Dr. Smita Mehta
Dr. Todd Mercer
Dr. Walt Orenstein
Dr. Mark Pletcher
Dr. Beth Pollard
Mr. Lance Rodewald
Dr. Sabouraud Sabine
Dr. Jim Singleton
Dr. Nicole Smith
Dr. Richard Spiegel
Dr. Vishnu-Priya Sneller
Dr. Ray Strikas
Mr. Robert Snyder
Ms. Sherrilyn Wainwright
Dr. Jay Watson
Dr. Melinda Wharton
Dr. Walter Williams

Other Government Attendees

Dr. Norman Baylor, FDA
Ms. Mary Ann Chafee, U.S. Senate
Dr. Karen Goldenthal, FDA
Dr. Karen Midthun, FDA
Dr. Peter Patriarca, FDA

Others Present

Lynn Bahta, Immunization Action News
Karen Biscardi, Pasteur, Merieux, Connaught
Sherrydon Braham-Forbes, Emory University
Jill Carleton, Cohn & Wolfe
Jill Chamberlain, Vaccine Bulletin
Helen Cicirello, NAVA
Neal Collins, Merck
Mike Cooper, Reutes
LaChenna Cromer, Westat
Dee Czaykowski, WLVP
Dack Dalrymple, Bailey and Robinson
Joe Daugherty, WBS Underwriters
Lauren Dobuski, ASTHO
Ruth Ann Dunn, Michigan State University
David Fedson, M.D., Pasteur Merieux Connaught
Alan Felton, Felton Medical
Dennis Foley, Wyeth-Lederle Vaccines
Joan Fusco, NAVA
Eugene Gangarosa
Ronan Gannor, Wyeth Ayerst

Others Present - continued

Jorge A. Gome, National Institute for Infectious Diseases, Buenos Aires, Argentina
Elizabeth Goss, Fox, Bennett & Turner
Chris Grant, Connaught Laboratories
Jesse Greene, S.C. Department of Health
Jessie Groothuis, Ross Products
Philip Hasegawa, Merck
Kim Haupt, Merck
Bill Hausdorff, Wyeth-Lederle Vaccines
Milo Hilty, Abbott Labs
Scott Howard, Smith Kline Beecham
John Hollister, Smith Kline Beecham
Barbara Howe, SmithKline Beecham
Clifton Neil Irby, Christian Science Committee on Publications
Rudolph Jackson, Morehouse University School of Medicine
Jeanne Jordan, Kaiser Permanente
Stephen Keith, North American Vaccine
Samuel L. Katz, M.D., Duke University Medical Center
David Krause, SmithKlein Beecham
Jacques Lapierre, Biochem Vaccine
Dagna S. Lawter, Wyeth Ayerst
Patty Leitch, C & W
Scott Litherland, Parallax Communications
Yvonne McHugh, Chiron
Peggy Monkus, Georgia Department of Health
Lisa Ohlandt, WLVP
Tom Ortiz
Peter Paradiso, Wyeth Lederle Vaccines
Stanley Plotkin, M.D., Pasteur Merieux
Margaret Rennels, University of Maryland
Cassandra Richards, Infectious Diseases in Children
Lisa Riddell, Merck
Ann Rogers, Parallax
D. Parenti, Smith Klein Beecham
J.B. Rosefsky, Wyeth Ayerst
Fred Ruben, Pasteur Merieux Connaught
Kristine Severyn, Ohio Parents for Vaccine Safety
Gary Schatz, Plexys Health Group
Florian Schodel, Merck
Frederick Shaw
Natalie Smith, California Department of Health Services
Dale Spriggs, VRI
Barbara Stoll, Emory University
John Taranger, North American Vaccine

Others Present - continued

Miriam Tucker, Pediatric News
Sam Turner, Fox, Bennett & Turner
Karen Vanderhoof-Forchner, Lyme Disease Foundation
Peter Viglirolo, Cooney-Waters
Ted Vigodsky, CBS News
Michelle Volansky, Westat
Annemarie Wasley, CSTE
Deborah Wexler, Needletips
Jo White, M.D., Aviron
John Zahradnik, Pasteur Merieux Connaught

CONTENTS

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

WELCOME

The Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention (CDC) on October 22, 1997. Dr. Jeffrey Davis, ACIP Chair, called the meeting to order at 8:40 a.m. Throughout the meeting, an Envision link was open with the Parklawn Building, in Rockville, Maryland.

Dr. Dixie Snider, Associate Director for Science, CDC, welcomed Dr. Jose Luis-Diaz (representing Dr. Jose Santos-Preciado, Secretario de Prevencion y Control de Enfermedades, Mexico) and Mr. David Williams (representing Dr. Gordon Douglas, Pharmaceutical Research and Manufacturers of America [PhRMA]). Dr. Snider also thanked Dr. Davis and Dr. Stephen Schoenbaum for agreeing to continue to serve on the Committee, pending the Secretary's signing of the member nomination package.

Dr. Snider informed the group of a new decision about Vaccines for Children (VFC) resolutions. Members with financial conflicts of interest not only must abstain from VFC voting but also are prohibited from introducing or seconding VFC resolutions. Dr. Snider made some procedural and housekeeping announcements and turned the meeting over to Dr. Davis.

Dr. Davis welcomed Dr. Luis-Diaz and Mr. Williams. He said that the minutes of the last two meetings will be completed by December 1, 1997. The next meeting will be held on February 11-12, 1998. Subsequent 1998 meetings are scheduled for June 24-25 and October 21-22.

The members then disclosed their potential conflicts of interest. Dr. Davis reminded them that all members could participate in discussions after this disclosure but could not vote with any conflict of interest. Ex-officio and liaison members were not required to disclose.

Drs. Jessie Sherrod, Marie Griffin, and David Fleming had no conflicts of interest. Dr. Chinh Le's employer, Northern California Kaiser Permanente, is conducting vaccine studies with Wyeth Lederle, Merck, and SmithKline Beecham. As Director of Health, San Antonio Metro Health District, Dr. Fernando Guerra served as principal investigator for a community-based acellular pertussis field trial with North American Vaccine; the health department also received funding from SmithKline Beecham for a hepatitis A vaccination project. Dr. Mary Glode is participating in discussions with Chiron on a planned clinical trial with a vaccine unrelated to discussions at this meeting. Dr. John Modlin reported that he and/or his wife and children hold stock in Merck, Chiron, and Glaxo Wellcome. He also participated in educational activities supported by Pasteur-Merieux Connaught. Dr. Davis received an honorarium from sponsors of a meeting supported by a grant from the Merck Vaccine Division.

Dr. Schoenbaum and Dr. Barbara DeBuono were not present for the initial disclosure but reported later. Dr. DeBuono had no conflicts of interest. Dr. Schoenbaum had no personal conflicts, but his wife holds stock in Amgen, Bristol Myers, Squibb, Glaxo Wellcome, and Proctor and Gamble. The liaisons and CDC staff introduced themselves.

UPDATES

National Vaccine Program Office: DHHS Adult Immunization Action Plan

Dr. Robert Breiman, National Vaccine Program Office (NVPO), reported on the Department of Health and Human Services (DHHS) *Adult Immunization Action Plan* (Draft: July 1, 1997).

As background, Dr. Breiman said that the Working Group on Adult Immunization of the National Vaccine Advisory Committee (NVAC) began a process to develop a report on adult immunization in 1992. In January 1994, NVAC approved a final report, DHHS printed and distributed the report, and a summary was published in the *Journal of the American Medical Association.* The report included five goals for adult immunization in the United States, recommendations for achieving the goals, and strategies for implementing the recommendations.

Dr. Breiman noted that, although federal agencies have carried out several of the strategies, there has been no systematic effort to address all of the report's components. A subsequent General Accounting Office document titled *DHHS Could Do More to Increase Vaccination among Older Adults* substantiated the need to focus more in this area. In October 1996, the Deputy Secretary therefore convened a working group to develop a Department-wide action plan. The working group members framed their deliberations around the goals delineated in the NVAC report. The resulting Adult Immunization Action Plan outlines a proposal for collaboration among DHHS, other federal departments, state health agencies, professional organizations, health-care purchasers and providers, vaccine companies, and the public.

The premises for the plan are that: 1) there is a large disease burden due to vaccine-preventable diseases in adults; 2) each year in the United States, at least 45,000 adults die of complications of influenza, pneumoccal infections, and hepatitis B; 3) the overall cost to society of these and other vaccine-preventable diseases in adults exceeds $10 billion each year; 4) vaccines to prevent these diseases are effective but are under-used; and 5) the use of vaccines has been improving, but greater coverage is needed, especially in particular groups.

Other areas of concern include: 1) the disparity between the low disease burden from measles, tetanus, mumps, rubella, and diphtheria, which have been controlled by effective childhood immunization programs, compared to the significant burden from pneumococcal infections, influenza, and hepatitis B, which could be better controlled if the nation had an equivalent program for adults; 2) the racial disparity in the risk for vaccine-preventable diseases (e.g., a 2.5-fold increased risk for pneumococcal bacteremia in blacks compared to whites in the United States); 3) the racial disparity in vaccine utilization and coverage; 4) the emergence of drug resistance; and 5) the relationship between infectious diseases and cancer. Worldwide, 16% of all cancers are estimated to be directly attributable to infectious diseases, including hepatitis B, human papillomaviruses, Epstein-Barr virus, human immunodeficiency virus (HIV) infection, *H. pylori* infection, and schistosomiasis. Worldwide, 285,000 cases of liver cancer, and, in the United States, 10% of liver cancer cases are attributable to hepatitis B.

The Adult Immunization Action Plan describes five main goals:

1. Increase the demand for adult vaccination by improving provider and public awareness
2. Enhance the capacity of the health-care delivery system to deliver vaccines to adults
3. Expand financing mechanisms to support the increased delivery of vaccines to adults
4. Monitor and improve the performance of the nation's immunization program
5. Enhance the capability and capacity to conduct research on vaccine-preventable diseases in adults, adult vaccines, adult immunization practices, new and improved vaccines, and international programs for adult immunization

In early November 1997, a meeting will be held with members of the National Coalition on Adult Immunization to devise strategies for implementing the plan beyond the government.

Discussion

Dr. Guerra asked about the experience with immunization in immigrants who are taking the qualifying medical examination for citizenship. Dr. Breiman knew of no information on adult immunization status in this group. Dr. Cordero noted that every person applying for citizenship must receive the immunizations on the official list of required vaccinations. Immunization requirements for immigrants are, however, complex. A current issue of contention centers on requirements for children who are being adopted from other countries.

In response to a question from Dr. Sherrod, Dr. Breiman said that requirements for adult immunizations in nursing homes and hospitals are a state-based issue. The NVAC Adult Immunization Working Group is holding a meeting on December 1-2, 1997, to discuss the use of non-traditional immunization sites, including pharmacies, churches, and nursing homes.

Dr. Le pointed out that, in the private sector and managed-care setting, many quality assurance groups are looking at immunization rates as a measure of performance. These groups would benefit from guidance and recommendations. Dr. Pierce Gardner added that an important step would be to encourage state legislatures to approve universal reimbursement of immunizations.

Vaccine Injury Compensation Program

Dr. Geoffrey Evans, Bureau of Health Professions, Division of Vaccine Injury Compensation, provided the group with handouts on monthly statistics, lawsuits filed against DTP manufacturers through 1996, and excise tax legislation signed into law in August 1997.

He explained that the Taxpayer Relief Act of 1997 includes amendments to revise the excise tax on vaccines covered under the National Vaccine Injury Compensation Program. The amendments revise the current excise tax structure to provide a flat rate of 75 cents per preventible disease (instead of 51 cents as proposed by the Secretary, DHHS, and 84 cents as included in the House and Senate versions of the bill). The Act also includes coverage for the three childhood vaccines recently added to the Vaccine Injury Table -- hepatitis B, *Hemophilus influenzae* type b (Hib),

and varicella -- at the 75-cent rate. The Act does not provide automatic taxation for new vaccines
recommended for routine administration to children. The revised tax structure and coverage of new vaccines took effect on August 6, 1997.

Dr. Evans characterized the excise tax legislation as a major development for the National Vaccine Injury Compensation Program. Others were the reauthorization in 1993 and the table changes in 1995 and 1997. He said that, as it enters the tenth year of operation, the program is in a "steady state," with marked progress in addressing its three public policy goals of individual compensation, liability protection, and stabilization of the marketplace.

Compensation of individuals -- The program's first priority was to compensate persons who were impeded by the tort system. Since the program's inception, more than 1,100 petitioners have received compensation via a streamlined mechanism outside the tort system. Although the first vaccine injury table was overly broad, subsequent changes have made it more scientifically sound.

Liability protection for vaccine manufacturers and administrators -- The program has succeeded in reducing the number of lawsuits filed against manufacturers and in successfully diverting claims away from the tort system. The number of claims filed against DTP manufacturers decreased from 255 in 1986 to 6 in 1996.

Stabilization of the marketplace -- Vaccine research and development are much more promising today, and the marketplace is "friendlier."

Discussion

Dr. Halsey noted that the 1997 Act does not provide for automatic inclusion of new antigens as they are added by ACIP vote and wondered what can be done to expedite the process to ensure coverage. According to Dr. Evans, little can be done except to work within the current rulemaking process. Dr. Halsey asked if changes in vaccines (e.g., live attenuated influenza vaccine) are automatically incorporated. Dr. Evans responded that the only vaccines covered by the program are those that CDC recommends for routine administration to children.

Replying to a question from Dr. Paul Glezen about why the relief from liability pressures has not decreased vaccine costs, Dr. Evans cited some continued liability and the need to maintain the liability fund. The good news is that prices are steady.

Dr. Le asked about adding alopecia as a side effect for hepatitis B vaccine, and Dr. Evans explained that changing the injury table is a long process but that, once an injury is added, compensation is retroactive for 8 years.

National Immunization Program

Dr. Jose Cordero, Acting Director of the National Immunization Program (NIP), had three comments. First, national immunization survey data for 1996, presented at the White House on July 23, 1997, provide much to celebrate. The nation exceeded the 1996 goals of at least 90%

coverage for DTP, polio, measles, and Hib, and 70% for hepatitis B. Case counts for most vaccine-preventable diseases are also at record or near-record lows.

National Immunization Survey data on race/ethnicity and poverty, released on October 17, 1997, are similarly positive. Most goals were met or exceeded for the five racial/ethnic groups; in cases where the goals were not met, the gap was within three percentage points. All goals were met for children living above poverty level. Three goals (for polio, measles, and Hib) were missed for children living below poverty level. Poverty therefore remains an important risk factor for under-immunization.

Dr. Cordero concluded with a reminder about three remaining challenges: sustaining current successes, ensuring that new babies are immunized, and developing and maintaining community-based registries.

RABIES POSTEXPOSURE PROPHYLAXIS

Dr. Charles Rupprecht, National Center for Infectious Diseases (NCID), presented two topics for discussion and decision: 1) local infiltration of human rabies immune globulin (HRIG) for rabies postexposure prophylaxis (PEP), and 2) PEP guidelines for non-bite exposures to bats.

Local infiltration of HRIG

At the last ACIP meeting, the members agreed on the need to amend the ACIP recommendation for local infiltration of HRIG, based on recent updates/suggestions from the World Health Organization (WHO) and the lack of scientific substantiation for infiltrating half the HRIG volume into the gluteus. CDC staff were asked to develop wording to emphasize local infiltration and to provide practitioners with discretion on the appropriate muscle mass for infiltration. Dr. Rupprecht presented the following amended statement on HRIG use:

> "If anatomically feasible, the full dose of HRIG should be thoroughly infiltrated in the area around and into the wound(s), and any remaining volume should be administered intramuscularly at a site distant from vaccine inoculation."

The statement will be included in context on page 6 and in Table 2 of the current ACIP document on rabies prevention.

Discussion

Dr. Fleming made a motion in favor of the following modification in wording:

> "If anatomically feasible, the full dose of HRIG should be thoroughly infiltrated in the area

around and into the wound(s). If not anatomically feasible, any remaining volume should be administered intramuscularly at a site distant from vaccine inoculation."

The motion was seconded and the modified language put to a vote.

VOTE: Nine members voted in favor of the modified statement on local infiltration of HRIG. None were opposed. The amended language was accepted.

Human rabies from apparent bat exposure

Dr. Rupprecht raised the need to revisit the issue of cryptic human rabies from apparent bat exposures, given evidence of new cases and the apparent misinterpretation of current recommendations for non-bite exposures. He noted that two human rabies cases, both due to bat exposures, were reported during the past weekend. He also called attention to a PROMED announcement, which appeared shortly after the last *MMWR* report on two human cases for 1997, stating that "CDC has recommended that all persons who touch a bat be treated for rabies whether they are bitten or not." This statement does not reflect the intention of either the ACIP or CDC with regard to rabies PEP.

NCID staff therefore drafted the following revised ACIP statement on rabies PEP for bat exposures. The intent was to emphasize the bite route, de-emphasize insignificant physical contacts, clarify exposures for which PEP is appropriate, and discourage inappropriate PEP.

> "Bats are increasingly implicated as significant wildlife reservoirs for variants of rabies virus transmitted to humans. Recent epidemiologic data suggest that transmission of rabies virus may occur from minor or seemingly insignificant bites from bats. The limited injury inflicted by a bat bite (in contrast to lesions caused by terrestrial carnivores) and an often inaccurate recall of the exact exposure history may limit the ability of health care providers to determine the risk of rabies resulting from an encounter with a bat. In all instances of potential human exposures involving bats, the bat in question should be safely collected, if possible, and submitted for rabies diagnosis. Rabies postexposure prophylaxis (PEP) is recommended for all persons with bite, scratch, or mucous membrane exposure to a bat, unless the bat is available for testing and is negative for evidence of rabies. PEP is also appropriate even in the absence of demonstrable bite, scratch or mucous membrane exposure, in situations in which there is reasonable probability that such exposure may have occurred (e.g., a sleeping individual awakes to find a bat in the room; an adult witnesses a bat in the room with a previously unattended child, mentally challenged person, intoxicated individual, etc.). This recommendation, used in conjunction with current ACIP guidelines, should maximize a provider's ability to respond to situations where accurate exposure histories may not always be obtainable, while still minimizing inappropriate PEP."

Discussion

Dr. William Schaffner commented on the difficulty of walking the fine line between bite and non-bite exposures. Although PEP recommendations center on bites, many bat-associated cases

have no history or manifestation of a bite and no history of bat contact. In his view, the concern about non-bite exposures is sufficient to justify PEP, especially when the only deciding factor is cost. Dr. Schaffner also recommended replacing "often inaccurate recall" with "history is not available or could not be obtained" -- to shift the burden from patient to provider.

Dr. Fleming asked the committee to consider modifying the language on non-bite exposures to make it more useful at the state level. The statement refers to "reasonable" probability for non-bite exposures when "reason is not operating" in this setting. Bat exposures have become an emotionally laden issue that has generated substantial public attention. In Oregon, concerns about bat exposures are the primary reason for calls to the health department, and the number of bats being tested for rabies has increased ten-fold in the last 6 months. Survey results showing that 1% of Oregon residents (30,000 persons) have found a bat in their homes in the last year suggest that bat exposures are fairly common.

Dr. Fleming therefore argued for more discretion at the local level. Practitioners are trying to follow the recommendations but feel that the ACIP language is forcing them to provide PEP against their clinical judgement. They have no flexibility from a medical-legal standpoint. He reminded the group that human rabies is very rare and that the increased workload generated by the provision of PEP for non-bite exposures is not likely to result in a decrease in cases; the number of cases is zero. He urged the committee to loosen the language to give providers some flexibility. His suggestion was to:

> Change the language for non-bite exposures from "PEP is also appropriate" to "PEP may be appropriate."
>
> Add the following sentence at the end of the statement:
>
> "The likely effectiveness of PEP in this setting needs to be balanced against the low risk that such exposures appear to present and thus the high cost per case prevented by the strategy."

Dr. Richard Zimmerman shared Dr. Fleming's concerns and agreed with his proposed revisions. He suggested supplementing the statement with a table for added clarity. Dr. Guerra encouraged the group to seek input from the field before any further action; three areas of concerns are: liability issues, compliance with PEP, and exposure to domestic animals in areas with a high prevalence of rabies in bats. Dr. Rabinovich understood the need for flexibility but was uncomfortable focusing on the cost of a public health intervention to prevent a very rare and severe disease for which an acceptable vaccine is available. In her view, cost per case is not the best discriminator for use of this technology.

Dr. Georges Peter agreed with Dr. Fleming's proposed language. He said that the real issue, however, is implementation in the field. Health departments need help in developing a process to share responsibility for the difficult decision for or against PEP for non-bite exposures. Dr. Rupprecht noted that more states are moving to a central source for PEP recommendations and administration; CDC is aware of the need for educational materials for health departments.

Dr. Schoenbaum supported the existing language. He felt that the statement already hedges enough; "appropriate" allows for discretion in medical care. Dr. Fleming countered that the vagueness of the current statement preludes appropriate translation in the field. He agreed that it would help to have a table listing situations in which PEP should "always be given," "not be given," or "given at the provider's discretion". In response to Dr. Rabinovich's comment, he stated that the ACIP routinely deals with the cost-effectiveness of vaccines.

Dr. Alison Mawle suggested adopting the revised statement minus the section on cost-effectiveness. Dr. Fleming made a motion to accept the following statement:

> "Bats are increasingly implicated as significant wildlife reservoirs for variants of rabies virus transmitted to humans. Recent epidemiologic data suggest that transmission of rabies virus may occur from minor or seemingly insignificant bites from bats. The limited injury inflicted by a bat bite (in contrast to lesions caused by terrestrial carnivores) and situations in which a history is not available or could not be obtained may limit the ability of health care providers to determine the risk of rabies resulting from an encounter with a bat. In all instances of potential human exposures involving bats, the bat in question should be safely collected, if possible, and submitted for rabies diagnosis. Rabies postexposure prophylaxis (PEP) is recommended for all persons with bite, scratch, or mucous membrane exposure to a bat, unless the bat is available for testing and is negative for evidence of rabies. PEP may be appropriate even in the absence of demonstrable bite, scratch or mucous membrane exposure, in situations in which there is reasonable probability that such exposure may have occurred (e.g., a sleeping individual awakes to find a bat in the room; an adult witnesses a bat in the room with a previously unattended child, mentally challenged person, intoxicated individual, etc.). This recommendation, used in conjunction with current ACIP guidelines, should maximize a provider's ability to respond to situations where accurate exposure histories may not always be obtainable, while still minimizing inappropriate PEP. The likely effectiveness of PEP in this setting needs to be balanced against the low risk that such exposures appear to present."

The motion was seconded. Dr. Guerra's alternative was to table the discussion pending a "straw vote" from the field on how to define low risk in complex settings. Dr. Davis felt that the current motion reflects the committee's position at this time and asked to proceed with the amended language. The motion was made, seconded, and put to a vote.

VOTE. Eight members voted in favor of the modified statement. No one was opposed. Dr. Schoenbaum abstained. The amended language was accepted.

Dr. Guerra recommended circulating the revised statement among the states. Dr. Fleming agreed, and added that states should also be polled about the usefulness of a table. Dr. Rabinovich worried that this might set a precedent for field testing of every ACIP statement. Dr. Davis felt that polling the states seemed prudent given the gravity of the decision-making process for rabies PEP.

The group had questions about a process, and some suggested working through the Council of

State and Territorial Epidemiologists (CSTE). Dr. Breiman also wondered about a process for sampling and data analysis. Dr. Davis said that the working group who initially considered this topic (Drs. Fleming, Griffin, and Modlin) could help the program staff develop a survey form and process. A motion was made and seconded to poll representatives of health departments via a survey on the proposed rabies PEP wording and the suggested explanatory table.

VOTE. Nine members voted in favor of the consultation; none were opposed.

Dr. Breiman raised some additional concerns for the working group's consideration, e.g., how to "collect" a bat safely, given the risk of non-bite exposures. Dr. Carolyn Hardegree, Food and Drug Administration (FDA), announced that FDA has licensed a new human rabies vaccine, manufactured by Chiron.

After a break, Dr. Davis announced that, given the gravity of the rabies PEP discussion and the licensing of a new vaccine, it would be prudent to revise the ACIP statement on rabies. The working group will address this task, assisted by any other interested volunteers. Dr. Davis also announced that another working group, chaired by Dr. Guerra, will be revising the influenza prevention statement.

RECOMMENDATIONS ON THE USE OF ROTASHIED (ROTAVIRUS VACCINE) AS PART OF THE ROUTINE CHILDHOOD IMMUNIZATION SCHEDULE

Dr. Roger Glass, NCID, introduced the discussion of the proposed ACIP recommendations on *Rotavirus Vaccines for Prevention of Rotavirus Diarrhea in Children* (Draft: October 19, 1997). At the June 1997 ACIP meeting, Dr. Glass and others presented supporting data for the recommendations. During the current meeting, they presented additional information and reviewed the recommendations for the committee's discussion. Dr. Glass noted that these deliberations are particularly timely because the American Academy of Pediatrics (AAP) Redbook Committee will soon be meeting to consider recommendations for rotavirus vaccine, and the FDA will be reviewing vaccine licensure and package inserts.

Background

Dr. Glass reported that rotavirus is the most common cause of infant gastroenteritis in the United States. Rotavirus diarrhea causes relatively few deaths (approximately 20 per year) but results in annual winter peaks of hospitalizations in children ages 6 months to 2 years. Each year, rotavirus accounts for more than 500,000 outpatient visits in children under age 5 (1 in 7 children) and approximately 55,000 hospitalizations (1 in 72 children). Rotavirus diarrhea results in $274 million in direct medical costs each year in the United States and more than $1 billion in total costs to society. Rotavirus vaccines were developed in response to this large burden of disease and have been shown to be safe and effective. The immunization goal is to prevent severe rotavirus diarrhea in children and to eliminate seasonal peaks in hospitalizations.

Dr. Glass then summarized some relevant studies by CDC to expand the national data base. The first, by Dr. Umesh Parashar, used National Hospital Discharge Survey data for 1990-1995. He

found that, in each year since a rotavirus-specific ICD-9 code was introduced in 1993, about 16% of diarrhea hospitalizations in children are coded as rotavirus. He concluded that hospital discharge data can be used as one measure of the impact of a rotavirus vaccine.

Second, surveys were conducted in two states (Connecticut and New York) that have a 100% sample of all hospital discharges. Data from New York show the same winter peak of hospitalizations for childhood diarrhea that is seen nationally. This data set is, however, ten times more robust than the national data set, which is a sample. Data from Connecticut are similar. A documented decline in rotavirus hospitalizations from 1986 to 1995 can likely be attributed to the large number of children who receive medical services in HMOs, where hospitalization rates are generally lower. Third, the HMO-Vaccine Safety Study showed that winter peaks of rotavirus infection also occur among HMO populations in southern California. Dr. Glass emphasized that data in all studies are limited by the lack of cases confirmed by laboratory diagnosis.

He then cited a series of vaccine cost-effectiveness studies, the first of which was conducted in 1993 by Smith et al. Updated estimates of the cost-effectiveness of a program of universal rotavirus vaccination were provided at the last ACIP meeting. Based on a $20/dose figure, it was estimated that a vaccine program would provide a savings of $340 million in societal costs and would cost the medical system about $100 million. The vaccine-breakeven cost from a medical care perspective would be $9 per dose; from a societal perspective, the breakeven cost would be about $56 per dose.

The rotavirus vaccine is well described in the literature. Multicenter studies show that it is about 50% protective against all rotavirus disease but is more protective against severe disease. The likely impact would therefore be a decrease in rotavirus hospitalizations; the impact is likely to occur rapidly and will be easy to monitor. Fever associated with vaccination is the primary adverse reaction of public health concern.

Vaccine safety and efficacy in premature and immunocompromised children

Dr. Glass said that the central issue for ACIP discussion is the recommendation for universal immunization. An unresolved question is, if infection with attenuated tetravalent rhesus rotavirus-based vaccine (RRV-TV) is less severe than a first infection with a naturally occurring strain, what recommendation should be made for premature and immunocompromised children? Should the recommendation be to exclude them from immunization, immunize them on the regular schedule, or neither, due to inadequate data?

Dr. Umesh Parashar, NCID, considered two issues regarding RRV-TV use in premature and immunocompromised children: 1) safety of the vaccine, and 2) efficacy in premature infants. There are no data on efficacy, but Dr. Parashar did present data on safety to document the higher rates of adverse reactions in children given the vaccine at 6-8 months and 4-12 months, compared to those who receive it at a younger age.

In a study in Sweden, children given the vaccine at 4-12 months had high rates of adverse

reactions, with fever and diarrhea reported in 79% and 42%, respectively. Reducing the age of vaccination reduced the number of adverse reactions. In a study by Dennehy et al, a 25% rate of fever after administration of RRV-TV to children ages 4-6 months was reduced to 3% when the vaccine was given to children ages 1.5-3 months. Rennels et al found no fever among children given vaccine before age 5 months. Among children older than 5 months, 71% had fever if their antibody was less than 1:40, but only 15% had febrile reactions if their pre-vaccine antibody was greater than or equal to 1:40. This suggests that maternal antibodies reduce the incidence of adverse reactions to the vaccine. Dr. Parashar concluded that, since older children appear to have higher rates of fever after RRV-TV immunization than young children, premature infants and children with late first immunization may also be likely to have fevers and other adverse reactions.

Draft recommendations for rotavirus vaccine

Dr. Joseph Bresee, NCID, presented the draft recommendations for use of rotavirus vaccine and the rationale for each.

1. The ACIP recommends universal immunization for all term infants (at least 37 weeks gestation) with three oral doses of rotavirus vaccine at ages 2, 4, and 6 months.

   The rationale for universal immunization centers on: the large burden of disease in U.S. children; the availability of a safe, effective vaccine; the likelihood that a vaccine program will yield a cost savings to society; and the likelihood that the timing and route of administration will yield high acceptance among health-care providers and parents.

2. The vaccine may be administered with DTaP, DTP, Hib, OPV/IPV, and hepatitis B vaccines.

   RRV-TV is safe and effective when administered with other vaccines. Evidence suggests that it does not interfere with the immune response to DTP, DTaP, and Hib vaccines. Children concurrently receiving RRV-TV and OPV may have slightly decreased immune responses to RRV-TV and serotype 1 poliovirus after the first dose of vaccine, but this is not evident after three doses. Data on IPV and hepatitis B vaccine are pending.

3. The vaccine can be administered to children who are being breastfed.

   Although breastfeeding may slightly decrease the humoral immune response to RRV-TV, no significant decrease in either immune response or overall efficacy has been observed among breastfed babies compared to non-breastfed babies after two or three doses.

4. The vaccine may be given to infants with transient respiratory illnesses, with or without low-grade fever.

   Trials with RRV-TV have been conducted without specific exclusions of these infants, and there are no data to suggest that they may be at higher risk for adverse events.

5. The vaccine is not recommended for: premature infants, infants with known or suspected immunodeficiency, infants with pre-existing chronic gastrointestinal disease, infants with hypersensitivity to any component of the vaccine, or infants with an acute illness, evolving neurologic condition, or persistent vomiting.

   Premature infants are excluded because: data on safety and efficacy are limited; the lack of maternally derived antibodies may make adverse reactions more common or severe; and the burden of disease in premature infants is not well established. The exclusion for immunodeficient infants was based on a similar rationale: no data on safety or efficacy, concerns about the effect of giving a live virus to immune-suppressed children, and lack of data on the burden of disease.

The recommendations also include two precautions:

1. Infants older than 6 months may have an increased risk of fever after vaccine administration.
2. Infants with ongoing diarrhea may have a diminished immune response to RRV-TV, and there is a theoretical risk that efficacy might be compromised.

Working group and AAP deliberations

Dr. Modlin summarized issues raised during the most recent working group conference call. First was universal immunization. The working group thinks that the vaccine is safe and effective and that universal immunization is a desirable goal. However, they agreed that a universal recommendation would be premature. They advocated delaying a recommendation until the vaccine has been considered by the FDA and more cost data are available. Their decision was based largely on credibility: 1) more precise cost data are needed before practitioners can be expected to accept the vaccine, and 2) many practitioners do not perceive rotavirus diarrhea to be a major threat to their patients, making the vaccine a hard sell.

The group's second concern centered on the recommendation for premature infants. In the absence of safety and efficacy data , they felt that additional discussion is needed about the content of the statement. They had similar concerns about the recommendation for immunocompromised infants. Immunocompromised 2-month-olds fall into three categories: babies with primary immunodeficiency disorders, babies who are born to HIV-infected mothers and who are also HIV infected, and infants on steroids. In the absence of data on safety or likely effectiveness in these groups, the statement needs to be explicit about management.

The group's final issue was consideration of children older than 6 months. The recommendation to immunize infants under 2 years of age will likely generate a large catch-up demand. Given that infants who receive the first vaccine dose after age 6 months have been shown to be at increased risk of febrile reactions, data on safety in older children will be important.

Dr. Halsey reported on the status of the AAP deliberations. The AAP's current draft is sketchier than the ACIP document but reflects the same thinking; the exclusion categories have not been

discussed. The Redbook Committee will meet on November 1-2, 1997, at which time Dr. Glass will summarize the current data. Dr. Halsey's personal view was that the recommendations should be more permissive in some situations. He agreed on the need for additional information before recommending universal immunization. Dr. Modlin moderated the ensuing discussion.

Discussion

Dr. Le noted the substantial societal costs resulting from the treatment of vaccine adverse events and asked if these had been considered in the cost analyses. Dr. Glass said that the lack of data on the cost of adverse effects precluded inclusion in the analyses. Dr. Modlin concurred with Dr. Le and added that: 1) the clinical approach to fever in 2-month-olds varies widely, and 2) adverse effects may obscure fevers due to other infections. He conceded that fever is not unique to rotavirus vaccine but pointed out that most vaccine-related fevers occur within the first 24 hours whereas rotavirus-vaccine-related fevers occur on day 3 to 5. Noting that vaccines are not always given at the recommended age, Dr. Halsey suggested supplementing the text with a table showing rates of fever in children at different ages.

Dr. Le questioned the efficacy of the vaccine in the real world; most U.S. studies were conducted in the summer, whereas rotavirus occurs throughout the year. He also noted that the vaccine does not require three doses for maximum benefit and asked about a decrease in the disease burden if fewer doses are given. He thought the statement could be more flexible, given the cost issues involved. Drs. Glass and Bresee said that the current lack of definitive data precludes such flexibility but thought that the wording could likely be softened later.

In response to a comment, Dr. Fleming agreed that the statement needs to be more precise about age limits and time of year for administration. Dr. Glezen favored including a definition of severe diarrhea and specifying the populations among whom hospitalizations are occurring. Dr. Deb Wexler felt strongly that the statement should address common questions about the safety of the live, oral rhesus RV-based vaccine. Dr. Hardegree added that the discussion of efficacy should address serotypes.

Dr. Le took issue with specifying the cost of universal immunization and advocated omitting the last two sentences in the section on cost-effectiveness (pages 10-11 of the draft). The point about societal benefits can be made without this specificity, which he felt gives an indirect "green light" to manufacturers to charge up to $56 per dose. Dr. Glass acknowledged that the figures were based on many assumptions and much variability and said that he, too, would prefer to omit these sentences. In Dr. Cordero's view, concern that data might be used in inappropriate ways is no argument for omitting data. Dr. Le was uncomfortable including data from a study that was neither peer reviewed nor published.

Dr. Katz asked if ACIP and AAP can still justify physician- and clinic-based delivery of vaccines. Administration of oral and mucosal vaccines by parents could eliminate substantial administrative costs.

Dr. Modlin asked the group to consider immunization of premature infants. He suspected that

the risk of increased adverse outcomes after vaccination is likely to occur only in infants with little passive acquired maternal antibody, i.e., infants born before 32 weeks' gestation. In the absence of data, however, what should be recommended? Dr. Peter P--- said that prematurity was not an exclusion criterion for the large efficacy trials and that he is reviewing the data to look at gestational age.

Dr. Halsey thought that the statement could be more permissive to provide leeway for vaccination of premature infants once parents are fully informed; he favored changing the language that vaccination is "not recommended" for premature infants. Dr. Modlin explained that the working group struggled with this issue but felt compelled to be explicit.

Dr. Peter agreed that practical points that affect implementation need to be resolved. He felt that the benefits of immunization will exceed the risks but called for data on risk factors in hospitalized children. Dr. Glass said that cohorts are needed for a case-control study. Dr. Guerra suggested that the RSV model might be helpful.

Dr. Glezen asked if it was an assumption that maternal antibodies protect babies who are less than 6 months of age or if a direct relationship had been measured and documented; susceptibility is not always clearcut. He was puzzled that the investigators did not know if premature babies are more susceptible; they may not be. He noted further that some physicians do not think that rotavirus vaccine is indicated for children; the preference might depend on the population under a physician's care.

Dr. Davis stated that the committee was clearly not ready to adopt the statement and asked the staff to incorporate the group's discussion points and written comments into a revised draft. All comments are due by November 7, 1997.

COMBINATION VACCINES -- ACIP GUIDELINES

Dr. Bruce Weniger, NIP, moderated the discussion on the proposed ACIP recommendations on *Combination Vaccines for Childhood Immunization* (Draft 008: October 10, 1997).

He first provided some background on the activities of the ACIP working group charged with developing the recommendations. A December 17, 1996, conference call was followed by a full-day meeting on January 28, 1997, attended by working group members, manufacturers, and providers. A draft statement was subsequently developed, circulated, discussed, and revised, with presentations at the February 1997 and June 1997 ACIP meetings. The draft provides recommendations for the optimal use of current and expected parenteral combination vaccines for childhood immunization, along with relevant rationale, background, and discussion of the complex and interrelated issues related to these products. The recommendations cover: 1) the preference for combination vaccines, 2) interchangeability of combination vaccines, 3) vaccine formularies, 4) administration of extra antigens, 5) vaccine history information, and 6) additional research priorities.

Dr. Weniger reported that the review of Draft 007 raised several unresolved issues about which

the working group was polled by mail. He summarized these issues, the working group's "votes" and comments on each, and the way in which they were resolved in the current draft.

1. Interchangeability of combination vaccines

   Issue: Should the boldfaced recommendation be divided into separate sections for vaccines with and without serologic correlates of immunity?

   Vote: Keep the categories separate -- 6
   Combine the categories -- 5

   Action: Delete the reference to serologic correlates from the boldfaced section, but maintain the distinction in the text.

2. Adult immunization focus

   Issue: Should the discussion of adult immunization be expanded and citations added?

   Vote: Yes -- 6
   No -- 5

   Action: Include some text/examples and related references as appropriate to reinforce an awareness of adult immunization issues.

3. Discussion of Hib interchangeability

   Issue: The discussion is not consistent with current ACIP and AAP recommendations. Should it be deleted and moved to another statement?

   Vote: Yes -- 1
   No -- 10

   Action: Include the discussion, but clarify that it represents a policy change that will be addressed in a future Hib statement.

4. Limited vaccine formularies

   Issue: Is the discussion of limited vaccine formularies appropriately balanced and neutral?

   Vote: Appropriately neutral -- 4
   Recommends, but OK -- 2

Recommends; make more neutral -- 4
Other -- 1 (Comment from working group member, Dr. Halsey -- This recommendation should be written: "*Immunization providers should maintain a stockpile of the vaccines that will provide all of the antigens recommended for children at each of the regularly scheduled visits. This responsibility may be fulfilled by stocking a variety of combination and individual products.*")

Action: Clarify ACIP's stance on this issue, and discuss pros and cons. Delete the term "limited formulary" from the section title.

5. Harmonization with AAP

Issue: Should the statement be deferred until AAP joins in?

Vote: Yes, delay for AAP/AAFP -- 6
No, publish by ACIP alone -- 1
No opinion -- 4

Action: Wait for AAP/AAFP, but impose a deadline to ensure timely publication.

6. Hepatitis B extravaccination

Issue: Should the statement include examples of situations appropriate for hepatitis B extravaccination?

Vote: Yes -- 5
No -- 5
No opinion -- 1

Action: Replace one example of Hib extravaccination with an example for hepatitis B.

7. Publication plan

Issue: What is the appropriate outcome for this document?

Vote: Publish in the *MMWR* as a recommendation from the ACIP -- 4
Publish in the *MMWR* as a guidance document from the ACIP -- 4
Publish in the *MMWR* as a background document from the ACIP -- 1
Action: Undecided

Dr. Glode led the discussion.

Discussion

Dr. Halsey confirmed that the AAP started on a draft statement on combination products but

tabled it on the assumption that there would be a joint statement. In his view, however, the joint development process seems to have slipped through the cracks. He favored a joint statement but felt that the process requires full participation by both committees, which has not been the case to this point. Dr. Zimmerman agreed with Dr. Halsey. The American Academy of Family Physicians (AAFP) is also interested in pursuing development of a joint statement but seeks more involvement in the process.

Dr. Glezen questioned the merits of a joint statement. Given ACIP's difficulty in reaching closure on its recommendations, he wondered if pursuing combined recommendations with two other groups is a good idea. Dr. Davis pointed out that, in this case, there was interest in a joint statement from the beginning. Dr. Livengood assured the group that publication problems can be addressed to facilitate timely dissemination. Dr. Glode suggested that the AAP and AAFP review the draft and let the ACIP know if they want to try to work toward a joint statement.

Dr. Zimmerman cited a recent survey showing that the Redbook is the most important reference source for primary care providers who serve children; documents other than the *MMWR* have a considerable influence among practitioners.

Dr. Hardegree pressed for more careful review of the statement. For example, the section on extra antigens implies a decreased frequency of local adverse events with acellular pertussis-containing vaccines, whereas the data suggest increasing local adverse events in some circumstances.

Mr. Tom Vernon commented on the vaccine formulary issue, on behalf of PhRMA. He referred to a letter dated October 21, 1997, to Dr. Cordero from PhRMA's Executive Vice President for Policy and Strategic Affairs. The letter states PhRMA's views about formularies and warns of possible unintended detrimental consequences related to Recommendation III in the draft. It explains that a "formulary" is customarily defined as a list of approved products whose availability is restricted, often on the basis of price. As used in the recommendation, however, the term seems to describe an inventory management system for physicians. PhRMA was unclear about whether the ACIP is recommending a restricted list of vaccine products for physician use or an inventory control system. In the former case, there are long-term implications for the viability of the vaccine industry and the development of new vaccine products that must be considered. In the latter case, PhRMA suggested that the level of micromanagement contemplated is unnecessary and inappropriate and urged ACIP to remove Recommendation III from the statement. Mr. Vernon suggested that an appropriate substitute might be the language submitted by Dr. Halsey in his comments to the working group.

Dr. DeBuono agreed that the discussion of formularies should be deleted. New York advocates maximum choice. Dr. Le felt that the discussion was adequately balanced. Formularies are common in the managed-care setting, and this statement provides a helpful framework and guidance. Dr. DeBuono argued that decisions on inventory management should be made by managed care organizations' medical directors, not the ACIP. Dr. Orenstein maintained that providing guidance to end-users is not micro-management but is part of the ACIP's role. The recommendations are directed to a broad audience. Dr. DeBuono feared that Medicaid managed

care organization will use this as an opportunity to limit their formularies, with the result that Medicaid patients will receive different vaccines. She believes in working toward a seamless system between commercial and Medicaid providers.

Dr. Fleming felt that the statement is too long and comes across as an endorsement. He favored a shorter statement that considers the pros and cons of both approaches. Dr. Zimmerman agreed on the move toward more neutrality. He was concerned about requiring all offices to stock all recommended antigens. Dr. Schoenbaum felt that the issue was handled by Dr. Halsey's proposed language.

After some discussion of the options (i.e., change nothing; create a more neutral statement; delete the statement; move the statement to another section and revise it), Dr. Fleming moved that the committee should not adopt the section on formularies in its current form; the motion was seconded.

VOTE. Nine members voted in favor of not adopting the section; one was opposed. The section will not be retained in its current form.

Dr. Davis asked the working group to develop a revised recommendation. He said that the group has been sensitized to the subtleties of the terminology (e.g., "formulary", "inventory") and should be able to come up with precise and reasonable language on which all can agree. Committee members have until November 14, 1997, to submit additional written comments.

HARMONIZED IMMUNIZATION SCHEDULE

Dr. Rebecca Prevots, NIP, moderated the next presentation, the goal of which was to review, discuss, and vote on three proposed changes to the Harmonized Childhood Immunization Schedule. She explained that the schedule lists vaccines under the routinely recommended ages. Bars indicate the range of acceptable ages for vaccination; shaded bars indicate catch-up vaccination at 11-12 years of age. The schedule is supplemented with a series of footnotes to provide additional information and to address exceptions and inconsistencies.

Polio vaccine

The proposal was to change the minimum recommended age for administration of the third dose of polio vaccine from 12 months to 6 months of age. Dr. Prevots explained that, in January 1997, FDA approved an amendment to the licensure of IPV manufactured by Pasteur-Merrieux Connaught, allowing the third dose in an all-IPV schedule to be given as early as 6 months of age. The fourth dose of IPV in an all-IPV schedule should still be given at 4-6 years of age. The change in the licensed indication for IPV administration has prompted reconsideration of the harmonized polio vaccine schedule.

Dr. Prevots also reviewed information related to the risk of VAPP among immunodeficient OPV recipients. This was information that had been presented to the polio working group in May

1996. At that time, a total of 20 cases of VAPP had been reported among immunologically abnormal recipients of OPV from 1980 through 1994, for an average of 1.3 per year. Of these, 12 occurred in children under 12 months of age. Differences in the reduction of immunodeficient VAPP cases by age of first dose of OPV were related to the age at which immunodeficiency was recognized.

The proposed change to the footnote for polio immunization is as follows:

> "Two poliovirus vaccines are currently licensed in the U.S.: IPV and OPV. The following schedules are all acceptable by the ACIP, the AAP, and the AAFP:
>
> 1. IPV at 2 and 4 months; OPV at **6**-18 months and 4-6 years
> 2. IPV at 2, 4, **6**-18 months and 4-6 years
> 3. OPV at 2, 4, 6-18 months and 4-6 years
>
> Parents and providers may choose among these schedules. The ACIP routinely recommends Schedule 1. IPV is the only poliovirus vaccine recommended for immunocompromised persons and their household contacts."

Discussion

Dr. Zimmerman said that the change in the all-IPV schedule to 6-18 months is clearly acceptable; the change will make the recommendation consistent with FDA package labeling. The more controversial issue is the sequential schedule.

Dr. Halsey supported changing the sequential schedule to allow the third dose of polio vaccine to be administered at 6 months. He argued that: 1) modifying the schedule to administer the first dose of OPV at 6 months in the sequential schedule would help induce optimal intestinal immunity early in life; 2) the third dose of OPV can currently be administered at 6 months in the all-OPV schedule; and 3) allowing for the third dose of IPV at 6 months would encourage manufacturers to develop combination products with IPV that could be used at 2, 4, and 6 months of age. Dr. Halsey also suggested positioning the word "polio" under the 6-month heading rather than in the middle of the bar to indicate a preference for the age for the third dose. Dr. Sherrod agreed with Dr. Halsey; the change will increase compliance in the first year.

Dr. Glezen was against the change on the grounds that it would increase the risk of vaccine-related polio. Allowing the administration of the first dose of OPV at 6 months places children with undiagnosed primary immune deficiency disorders at an avoidable risk of VAPP.

Dr. Modlin also preferred to leave the sequential schedule unchanged. He acknowledged that, in virtually all healthy infants, two doses of IPV will protect against vaccine-associated disease due to OPV when it is first given at 6 months of age. The only issue is for the very small cohort of immunodeficient children who are receiving OPV at 6 months and whose underlying immunodeficiency has not been diagnosed. For that group, two doses of IPV confers no

protection against vaccine-associated disease. The reason for the original change in the schedule was to decrease the rare occurrences of vaccine-associated disease. Dr. Modlin conceded that the number of at-risk infants is very small, but there will be a few for whom the change in policy will have a detrimental effect.

Dr. Peter observed that the focus of previous discussions was to work toward consistency among the three schedules. He supported allowing the third dose to be given as early as 6 months. Dr. Davis felt that the issue could be addressed with a statement of intent, such as: "Those who wish to administer a sequential schedule may choose to begin OPV administration at 12 months of age for the following reasons...." This gets at the issue without compromising the schedule.

Dr. Glode felt that the proposed change would weaken safety concerns. Dr. Katz agreed, but noted that, in all 20 cases cited by Dr. Prevots, OPV administration was the sentinel event that led to diagnosis. Dr. Modlin characterized this as a specious argument. Although most immunodeficient children at risk are not diagnosed until well beyond the age of first OPV by any schedule, ACIP should not relinquish an opportunity to reduce the risk in the very small number of children for whom this is not the case.

Dr. Glezen noted that CDC data refer to typical polio whereas many cases in immunodeficient infants are not typical polio and are not readily diagnosed. Delaying or eliminating OPV will improve the health of infants in general.

At this point, the committee had a series of votes. First, a motion was made and seconded to change the all-IPV schedule to be consistent with current FDA labeling: IPV immunization at 2, 4, and 6-18 months and 4-6 years.

VOTE. Eight members voted in favor; none were opposed; two abstained. The motion carried..

Next, they voted to change the sequential schedule: IPV at 2 and 4 months and OPV at 6-18 months and 4-6 years.

VOTE. Three members voted for the change; five were opposed; none abstained. The motion was rejected. The schedule will continue to read: IPV at 2 and 4 months, OPV at 12-18 months and 4-6 years.

Dr. Halsey reminded the committee that, since this is a harmonized schedule, the discussion and vote should have been preceded by a conference call with representatives from AAP, AAFP, and ACIP to develop consensus. Given the error in planning, he proposed that all decisions on the sequential schedule should be regarded as tentative pending discussions among the three groups. Dr. Davis said that the vote could be viewed as the ACIP's recommendation to the working group, for consideration by AAP and AAFP.

Dr. Zimmerman suggested extending the bar to 6 months for dose 3, and Dr. Halsey agreed. Dr. Sherrod also agreed and suggested a footnote reference about the 12-month dose. Dr. DeBuono

felt that the bar should reflect the recommendation and advocated placing the bar at 12 months and referencing the 6-month option in a footnote. Dr. Davis noted that two of three schedules recommend the third dose at 6 months and asked for a vote. A motion was made and seconded to extend the bar to 6 months for the third dose and to address inconsistencies in a footnote.

VOTE. Seven members voted for the motion; three voted against; none abstained. The motion carried.

The next issue was where the word "polio" should appear in the bar, given that its location generally signifies the recommended age of vaccine administration. A motion was made and seconded to keep the word "polio" centered in the bar.

VOTE. Eight members voted for the motion; none voted against; two abstained. The motion carried.

Measles vaccine

The next proposal was to change the shading in the 11- to 12-year visit to reflect catch-up vaccination versus routine administration of the second dose of MMR. Dr. Prevots explained that the ACIP has recommended routine administration of the second dose of MMR at 4-6 years of age, with the 11-12 year visit to be used for "catch-up" vaccination. The proposed change to the footnote in the harmonized schedule is as follows:

> "The second dose of MMR is routinely recommended at 4-6 years of age, ~~or at 11-12 years of age~~, but may be administered during any visit, provided at least 1 month has elapsed since receipt of the first dose and that both doses are administered at or after 12 months of age. **Those who have not previously received the second dose should complete the schedule during the 11-12 year visit.**"

The change would include shading the 11-12 year MMR dose to reflect catch-up vaccination.

Discussion

Dr. Fleming recommended changing "during the 11-12 year visit" to "no later than the 11-12 year visit". Dr. Halsey said that the proposed revision is consistent with the AAP recommendation, and he supported the change, with Dr. Fleming's amendment. Dr. Katz said that the 11- to 12-year age designation has nothing to do with immune response. The second dose was originally recommended nine years ago to fill a gap among the cohort reaching high school and college age. The 11- to 12-year designation has no meaning now. Dr. Halsey noted that the shaded bars for hepatitis B, varicella, and MMR vaccines are needed because of the emphasis on capturing children at the early adolescent visit.

Dr. Katz informed the committee of a paper, soon to be published in *Pediatrics,* that compares times for administering the second dose. Results show that adverse effects occur more commonly if the second dose is given at age 11-12. Dr. Halsey questioned the data and

maintained that there is a higher susceptibility rate at 11-12 years of age. Much of the increased adverse event rate can be explained by the higher proportion of vaccinees who are susceptible.

Dr. Peter argued to adopt the change because it is consistent with the final MMR statement; he contended that the group is revisiting issues that have already been resolved. There was a motion to adopt the proposed change, with the amended language. The motion was seconded. The amended language is as follows:

> "The second dose of MMR is routinely recommended at 4-6 years of age, but may be administered during any visit, provided at least 1 month has elapsed since receipt of the first dose and that both doses are administered at or after 12 months of age. Those who have not previously received the second dose should complete the schedule no later than the 11-12 year visit."

VOTE. Nine members voted in favor; none were against. One person was out of the room and was counted as an abstention. The motion carried.

Hepatitis B vaccine

The proposal was to change the wording of the footnote to emphasize adolescent vaccination:

> "Children and adolescents who have not been vaccinated against hepatitis B in infancy may begin the series during any ~~childhood~~ visit. Those who have not previously received three doses of hepatitis B vaccine should initiate or complete the series during the 11-12 year visit, **but unvaccinated older adolescents should be vaccinated whenever possible**..."

Dr. Prevots noted that a discussion of hepatitis B is on the agenda for Day 2. Since the language in the footnote is contingent on that discussion, she suggested that the committee defer their deliberations until Day 2. A motion to defer the discussion was made and seconded.

VOTE. Nine members voted for the postponement; none voted against.

IMMUNIZATION OF BONE MARROW TRANSPLANT RECIPIENTS

Dr. Clare Dykewicz, NCID, introduced the information session on the *Proposed Immunization Schedule for Bone Marrow Transplant (BMT) Recipients* (Draft 1). She reported that, when NCID began developing guidelines last year for the prevention of opportunistic infections in BMT recipients, a BMT Guidelines Immunization Working Group was formed to consider the inclusion of an immunization schedule. Despite the limited data on vaccine immunogenicity and safety in BMT recipients, the group agreed on the immediate need for even a preliminary national immunization schedule for BMT recipients. Providers are not sure how to manage the loss of titers to vaccine-preventable diseases in BMT recipients. As a result, the field is characterized by chaos and confusion. A recent nationwide survey of BMT centers showed that up to 11 different immunization schedules were being used per vaccine to immunize BMT patients and that immunization was underutilized.

At the last ACIP meeting, the committee members decided that they should be involved in developing the immunization schedule for BMT recipients. A working group was formed, and a meeting was held on October 6-7, 1997, to develop a draft schedule. The meeting was chaired by Dr. Modlin and included representatives from ACIP, AAP, the BMT Guidelines Immunization Working Group, FDA, and CDC.

Dr. Sherrilyn Wainwright, NIP, summarized the meeting discussions, provided background on immunization in BMT recipients, and presented a draft schedule. She also presented options for an ACIP role in the further development of the schedule.

Dr. Wainwright reported that the purpose of the October 1997 meeting was to develop a proposed immunization schedule for hematopoietic cell transplant recipients, including BMT patients. This population is not currently covered by ACIP immunization recommendations. The annual number of blood and marrow transplants worldwide is increasing dramatically, with an estimated 12,000 allogeneic and 18,000 autologous transplants performed in 1995 worldwide. A 1995 survey of U.S. transplant centers to assess current immunization practices found that, despite evidence that patients have diminished protection against immunizable diseases post-BMT, routine vaccines are underutilized by transplant programs.

BMT experts believe that national guidelines for optimal doses and timing of vaccines post-BMT are warranted. As more patients undergo BMT and as long-term survival improves, there is an increasing need to develop post-BMT vaccination strategies. Studies have shown that most previously immunized BMT patients become seronegative within a few months post-transplant. Most healthy post-BMT patients generate adequate antibody titers to vaccinations given 12 months after transplantation, but the presence of chronic graft-versus-host disease can diminish the response. Protein antigens and conjugate vaccines are more immunogenic than are polysaccharide antigens. Following BMT, the immune system of the BMT recipient becomes successively more normal during the first years after transplant. Cell-mediated responses also improve over time.

The proposed immunization schedule incorporates an evidence-based rating system to reflect the strength (A-E) and quality (I-III) of evidence to support each recommendation. The schedule includes five tables:

Vaccinations against common pathogens (pneumococcal, MMR, influenza, varicella)
Vaccinations against less common pathogens (DTP, DTaP, Td, IPV, Hib conjugate, hepatitis B, hepatitis A, meningococcal)
Vaccinations for household contacts and health-care workers (influenza, varicella, MMR, IPV, hepatitis A)
Vaccinations for foreign travel (hepatitis A, typhoid, cholera, yellow fever, BCG, IPV, rabies, meningococcal, Japanese B encephalitis)
Passive immunizing agents (varicella zoster immune globulin, tetanus immune globulin, human rabies immune globulin, hepatitis B immune globulin, IVIG, and IM).

Dr. Wainwright briefly reviewed the schedules and then proposed options for an ACIP role:

1. Develop a statement alone or in conjunction with AAP
2. Endorse a final version of a BMT immunization schedule with no formal ACIP statement
3. Review (with comment only)
4. Other

Discussion

ACIP members who participated in the working group deliberations were asked to comment first. Dr. Modlin stressed that the recommendations were based on an examination of the best available data and acknowledged the large gaps in knowledge. He also clarified that vaccines were assigned to either the "common" pathogen or "less common" pathogen group based on an examination of the impact of the particular vaccine-preventable disease in the BMT population. Prevention of influenza was determined to be the highest priority.

Dr. Le said that the statement should explain that the second dose of pneumococcal vaccine is not intended to be a booster dose. The statement should also strongly recommend chemoprophylaxis as an adjunct to pneumococcal vaccine.

Dr. David Fedson had a comment on the pneumococcal vaccine dose at 12 months. He was not aware of a problem until 2 years after BMT because patients are receiving 24 months of pneumocystis chemoprophylaxis, which prevents pneumococcal infection. Therefore, the 12-month vaccine dose may be of marginal or no benefit. The vaccine should be recommended at 24 months when patients stop prophylaxis for pneumocystis. Dr. Modlin said that, given the variation among sites, 1 year was a reasonable average for the duration of pneumocystis prophylaxis. Further, there are no data on the efficacy of chemoprophylaxis.

Dr. Gardner was uncomfortable with the categories of evidence given the paucity of clinical data. He felt that the group had stretched the categories beyond the comfort level.

Dr. Halsey suggested moving to a discussion of the ACIP role. He wondered about the legality of issuing ACIP recommendations for an off-label use of vaccines. Dr. Hardegree replied that the FDA would like all ACIP recommendations to be consistent with the data. Dr. Norman Baylor, the FDA representative at the working group meeting, agreed that the preference is for recommendations to be consistent with package inserts but noted that vaccines are clearly needed for the BMT population. The FDA will try to work with the committee to come up with compromise language that is both acceptable to the FDA and useful to providers. Dr. Halsey pressed Dr. Baylor to address whether ACIP can issue a statement without changes in labeling. Dr. Baylor stated that the FDA has no jurisdiction over ACIP recommendations. Although consistency is the goal, it may not always be possible.

Dr. Guerra asked about any overlap between recommendations for BMT recipients and those for organ transplant recipients. Dr. Modlin said that BMT patients are fundamentally different from

other organ recipients and require a separate schedule. Dr. Guerra thought it would be helpful to point out the differences.

Dr. Fleming asked for the working group's thoughts regarding an ACIP role. Dr. Modlin advocated an ACIP statement or a joint statement. Dr. Jon Kaplan, NCID, reminded the group of the development of guidelines for prevention of opportunistic infections in BMT patients, which was proceeding in a parallel process. The idea was to include an immunization component in this statement. The opportunistic infections document is much further along, however, and Dr. Kaplan was not sure if it could be held up for a formal ACIP statement.

Dr. Modlin felt that major changes in the current draft schedule are unlikely without additional data. He proposed bringing a revised version to the next ACIP meeting for a vote. This would work with Dr. Kaplan's timetable as well. Dr. Kaplan saw no problem with that suggestion and assured the committee members that they will have an opportunity to review and comment on the full document. Dr. Glezen contended that the lack of data precludes developing recommendations. He favored developing guidelines that will form a structure for pursuing and generating additional data.

In the ensuing discussion, Dr. Dykewicz clarified her preference for an AAP/ACIP-recommended schedule, and the group resolved some confusion about the process for finalizing, endorsing, and disseminating such a schedule. Dr. Halsey said that the AAP would be happy to have a role. Dr. Davis assured Dr. Dykewicz that proceeding with the current process will result in the desired product -- i.e., an immunization schedule for inclusion in the opportunistic infections document as well as the basis for a statement that several groups might eventually choose to endorse.

Dr. Modlin asked the committee members to submit their comments within the next month. The working group will revisit the guidelines via a conference call within 3 months. A revised schedule (not a proposed ACIP statement) will be presented at the next meeting for endorsement by the committee.

REPORT OF THE WORK GROUP ON ALGORITHMS FOR IMMUNIZATION REGISTRIES

Dr. Ed Kilbourne, NIP, led the session on computerized decision support mechanisms for ACIP recommendations. He reported that: 1) ACIP recommendations are increasingly being included in computerized clinical support systems, particularly immunization registries; 2) NIP is increasingly being consulted by systems developers for advice in interpreting ACIP recommendations; and 3) developers and users are encountering increasing numbers of problems with such systems.

At the last meeting, ACIP members were asked if they wanted to play a role in determining how

recommendations are translated into computer-given advice. Given the affirmative response, a working group chaired by Dr. Guerra was formed and has conducted informal discussions and one full meeting by conference call. A working paper has been drafted but is not ready for circulation. A shortened version was circulated to the ACIP members for their information.

The working group identified these issues for further deliberation:

Table-based versus rule-based algorithm design

Dr. Kilbourne explained that immunization algorithms are computerized sets of rules that evaluate immunization histories according to ACIP or other recommendations, resulting in a list of vaccines that are indicated at a given time. In one sense, all algorithms are rule-based, since they represent computerized translations of recommendations for immunizations. However, algorithms differ in the degree to which rules are embodied in data parameters that can be changed or updated without the intervention of programming.

In rule-based systems, rules are embodied in programmed code that are complex and difficult to understand. Changes and updates require a programming process and usually a new compilation of the computer system.

NIP staff and the working group members favor a tabular system whereby changeable aspects of algorithms are identified, isolated, and expressed as numbers (e.g., when to give a first dose, minimum interval until the next dose, total number of doses, age above which the vaccine should not be given, etc.). The parameters are ordered in a table and accessed by a program at appropriate points. An advantage is that tables can be updated under program control; changes become effective immediately when the parameters are updated, and updates do not require a new edition.

Dr. Kilbourne suggested that tables could be filled in as part of the process of developing or revising an ACIP recommendation. The required organization of concepts that constitute each recommendation will provide programmers with a definitive reference for the construction of their programs, simplify the programming task, and ensure that recommendations are consistent and complete.

Precision and choice of time units

Since most recommendations involve time intervals, the ease of interpretation and application can be affected by the choice of time units in which the recommendations are expressed (e.g., days, weeks, months, years). Computer routines can manipulate time intervals easily in any of these units. Frequently however, the application of time intervals by clinicians is easier in terms of months and years than days and weeks.

Dr. Kilbourne maintained that the choice of time units in the specification of ACIP

recommendations must be governed foremost by medical data. Units need not be made inflexible simply to ease the programmer's task. The working group encouraged the ACIP to address the question of precision in its recommendations and to take into account the selection of time units.

When is a vaccine dose "late"?

A value of an immunization registry is its ability to decide that a vaccine is due and to flag the need for reminders/recalls. Deciding when this should be done is a fundamental question for programmers. If the decision about when to consider a child overdue is mainly a scientific issue, then the ACIP may want to guide or prescribe late times. If not, the decision will become a management concern by default, and the programs will decide arbitrarily.

Quantifying the "gray zone"

Programmers also need to known how algorithms should deal with clinicians who want to vary from the recommendations. The issue comes down to strict adherence to recommended immunization times versus acceptable time intervals. Should the ACIP define the limits of acceptable clinical practice? If there is no limit, how should the computer handle this issue? How can a balance be achieved between clinical judgment and automated mechanisms?

Finally, the working group recommended that the ACIP develop a "core parameter" set of data elements that would represent the most salient aspects of ACIP immunization recommendations in a consistent, tabular form. Dr. Kilbourne summarized these possible next steps for the ACIP:

1 Ratify a table-based approach, to the extent possible.
2. Review existing recommendations to formalize a current table.
3. Begin an informatics review of recommendations in development.
4. Write a short statement on the proper choice of time intervals.
5. Decide whether to identify and quantify "lateness."
6. Clarify the role of clinical judgment in the context of computerized decision support.

Discussion

Dr. Guerra complimented Dr. Kilbourne on his cogent framing of the complex issues related to immunization algorithms. Additional sources of complexity include changing schedules, changing technology, the managed care paradigm, and the human element. He felt that ACIP can help

inform this process in a very timely way and suggested that the committee couple their efforts with the evolving informatics work of the All Kids Count process.

Dr. Fleming agreed on the importance of a core set of parameters. The ACIP needs to affirm that there are a core group of parameters that should appear in all recommendations. The committee should move to define these parameters for future recommendations and identify gaps and

inconsistencies retrospectively.

Dr. Schoenbaum remembered a paper that translated an ACIP recommendation into an algorithmic format, documenting inconsistencies and gaps. He did not have the citation but recommended trying to locate it as a starting point. He also noted that trends in performance measurement provide a pragmatic justification for more precision in ACIP statements, even in the absence of a scientific basis for that precision. Dr. Orenstein agreed. He suggested starting to address computerized decision support issues in the development of the rotavirus statement and then retroactively applying these concepts to other statements.

In response to a comment from Dr. Richard Clover about the need for case scenarios to test computer programs, Dr. Larry Blumen acknowledged the need for test cases that are independently validated. A workable process has not yet been developed.

After a brief discussion of what constitutes a late dose, Dr. Davis concluded that the working group on computer algorithms should be a "standing" committee with a rotating membership charged with addressing specific problems as they arise. Dr. Kilbourne said that he would bring more specificity for the members' consideration at the next meeting. Dr. Davis adjourned the meeting for the day at 5:45 p.m.

VFC DISCUSSION

Operational Considerations in the Implementation of VFC Resolutions

The meeting was reconvened at 8:40 a.m. on October 23, 1997. Mr. Dean Mason, NIP, provided the background for a discussion of programmatic issues pertaining to ACIP resolutions and coverage through the VFC program. He made these points:

> The VFC program is a vaccine purchase program enacted with the 1993 Omnibus Budget Reconciliation Act and implemented by the states as required by law in October 1994. By December 1996, 41,845 provider sites (about 75% in the private sector) were enrolled.
>
> The VFC program has increased by more than $100 million yearly, with the exception of 1995. In that year, the cost increase was almost $200 million as states added thousands of providers and made significant vaccine purchases for inventory. The cumulative grant awards for 1994-1997 topped $1 billion in 1997. About 90% of VFC funds awarded have been expended on vaccine purchases. The projected VFC award for 1998 is above $437 million.
>
> In contrast to VFC funding increases, "317" immunization grant funds for vaccine purchases have remained level since 1996. These funds are used to purchase vaccines for children who are not VFC-eligible.

Vaccine supply policies vary among the states. The 15 "universal" states provide public purchased vaccines to all providers for all children that they serve, including those who are fully insured. In 15 other states and the Commonwealth of Puerto Rico, public-purchased vaccines are supplied to providers for both VFC-eligible and underinsured children. In 20 states, public purchased vaccines are supplied to private providers only for VFC-eligible children. State policies for vaccine distribution have remained fairly consistent since the onset of the VFC program, without the massive shift to universal supply that was predicted by early critics of the program.

Mr. Mason then reviewed the process for determining vaccine coverage through the VFC:

The ACIP evaluates the applicability of new vaccines or new vaccine combinations after licensure by FDA. ACIP also considers expanding coverage to new age or target groups as appropriate. ACIP coordinates decisions with the AAP Redbook Committee.

In an action separate from the ACIP's general immunization recommendations, the ACIP adopts a separate resolution for coverage through the VFC program.

The ACIP determines the effective date for the resolution.

Next, Mr. Mason covered issues that affect the implementation of ACIP actions at the state level:

Notification of ACIP actions -- Increasingly, health-care providers are contacting states to request additional vaccine supplies based on new ACIP actions or resolutions. However, the providers are learning about ACIP recommendations before the state health departments are formally informed.

Differences between general immunization recommendations and VFC coverage Although recent ACIP actions, such as expanding VFC coverage for MMR vaccine, address this issue, discrepancies in coverage between general recommendations and VFC resolutions still exist. For example, the ACIP voted in June 1997 to expand varicella vaccine coverage through the VFC program, but that coverage is still more conservative than the general recommendation.

Uncertainties about the adequacy of CDC's contracts -- States cannot make public-purchased vaccines available to health-care providers until CDC has negotiated vaccine contracts and ensured that the contracts are sufficient to cover the states vaccine needs. ACIP resolutions can increase the public need for vaccines by thousands of dollars. Consideration should be given to ensuring the adequacy of current vaccine contracts or to allowing time for CDC to negotiate new contracts before resolutions take effect. Legally, an ACIP resolution cannot take effect until CDC's vaccine contracts, with assurances for sufficient dose amounts, are in place.

HCFA advisories to state Medicaid programs -- HCFA also has time frames for communicating new coverage requirements to state Medicaid programs. Medicaid programs

are allowed up to 90 days after being informed of new ACIP coverage guidelines to implement these new requirements.

State budget constraints -- Because VFC vaccine purchases are limited only to VFC-eligible children and 317 grant funds are not increasing, state budgets are straining to cover more vaccines and more children. Consideration should be given to the impact of ACIP resolutions on state budgets. States consider it important to provide the same coverage to non-VFC-eligible children that VFC provides to eligible children.

Speaking on behalf of NIP, Mr. Mason asked the committee to consider the impact on program operations as decisions are made about the effective date of VFC resolutions. He asked that resolutions not take effect until or before:

State health departments have formally received written communication on ACIP actions
A CDC vaccine contract is established that is sufficient to cover the new or expanded ACIP resolution
The 90-day allowance for state Medicaid programs is recognized
The impact on state budgets is discussed

Discussion

Dr. Davis commended Mr. Mason on his timely and relevant presentation. Dr. DeBuono appreciated the acknowledgement of state issues but was uncomfortable about the suggestion to hold up ACIP recommendations while state budget discussions and negotiations are underway. These can be long, drawn-out processes in many states. She also noted that, with the balanced budget act of 1997 and the expansion of child health insurance programs to include all immunizations, a large number of VFC-eligible children will no longer need to be in the program. She urged members to consider issuing a statement that advocates full coverage of immunizations through child health insurance and that urges states to leave VFC funds for children who are not eligible for the health insurance expansion. Mr. Mason said that there was no intention to suggest that VFC votes would await all state funding decisions; this was a discussion point only. Dr. Guerra added that private insurers should also be encouraged to cover childhood immunizations.

Dr. Fleming also commended Mr. Mason on the presentation and suggested that an update on VFC should become a regular part of the ACIP meeting agenda. He also seconded Dr. DeBuono's suggestion for an ACIP action to encourage immunization coverage under the child health insurance program. Finally, he thanked Mr. Mason for consideration of state issues.

ACIP Adolescent Hepatitis B Recommendations

Dr. Halsey introduced the session on VFC eligibility for hepatitis B vaccination. He explained that VFC eligibility includes all age cohorts except: 1) children ages 7-10 years, and 2) adolescents ages 16-18 years of age who do not report high-risk behaviors. These groups are, however, included in current ACIP and AAP recommendations.

Dr. Halsey advocated eliminating these gaps and expanding VFC eligibility to all children ages 0-18. He maintained that the current eligibility restrictions are confusing to providers and are resulting in increased missed opportunities for vaccination. Physicians are frustrated about the inability to obtain hepatitis B vaccine through the VFC program for children outside the age cohorts and about providing vaccine to some children in a family but being unable to vaccinate siblings who do not fit the age criteria.

The National Task Force on Hepatitis B Immunization: Focus on Asian Pacific Islanders, the Greater Kansas City Pediatric Society, the Immunization Action Coalition, and AAP have all submitted letters asking the ACIP to consider expanding the age cohorts eligible for hepatitis B vaccine in the VFC program.

Dr. Francisco Averhoff, NIP, presented the issue for ACIP consideration: Should VFC eligibility for hepatitis B vaccine be expanded to include 1) adolescents 16-18 years of age, or 2) all children and adolescents 0-18 years of age? To help in the decision, he offered a rationale for expanding eligibility, presented estimates of the impact on coverage and cost, and summarized the views of state program managers.

Rationale for expanding the age cohorts for hepatitis B vaccination

The gap between VFC eligibility requirements and ACIP recommendations for hepatitis B vaccination has resulted in confusion among providers about: 1) eligible and ineligible ages for VFC coverage, 2) vaccination of siblings, 3) determination of adolescent high-risk status, and 4) Asian-Pacific Islander catch-up strategies. Currently, ACIP recommends vaccination of 1) all 11- to 12-year-old children who have not received hepatitis B vaccine, and 2) unvaccinated high-risk older adolescents. AAP recommends that hepatitis B vaccine should be given by or before age 11-12 and that special efforts should be made to vaccinate all adolescents, not only those at high risk. AAFP and AMA recommendations generally follow those of the ACIP.

The VFC program covers children born on or after January 1, 1991, and those born on or after January 1, 1982, who are at least 11 years of age. The gaps in VFC eligibility are in children ages 7-10 years and adolescents ages 16-18 years. Because these gaps narrow each year by one age cohort, all children and adolescents ages 0-18 years will be VFC eligible in 4 years. If the VFC eligibility requirements are not changed, currently ineligible 7- to 10-year-olds will pass through the 11- to 12-year recommendation and will have the opportunity to be vaccinated under existing VFC eligibility criteria. However, 16- to 18-year-olds who are not at high risk will miss the opportunity for vaccination.

Options for expanding VFC eligibility

Dr. Averhoff presented two options for expanding VFC eligibility for hepatitis B vaccine:

Option 1: Include all previously unvaccinated VFC-eligible adolescents age 11-12 years or older

Option 2: Include all previously unvaccinated VFC-eligible children and adolescents 0-18 years

of age

Both options would require modification of existing ACIP recommendations.

Potential impact of expanding VFC eligibility

Dr. Averhoff provided estimates of the potential impact of both options on vaccination coverage levels and expenditures. The estimates were derived from a model for projecting changes in coverage and costs for 1998-2001, the time during which all children 0-18 years will become eligible under existing VFC program requirements. The model was based on these assumptions:

1. The cohort size is 4 million per year for each age group.
2. Cohorts currently not covered are: children 7, 8, 9, and 10 years of age; adolescents 16, 17, and 18 years of age.
3. Current third-dose coverage is 8% for 7-10 year olds and 12% for 16-18 year olds. First- and second-dose coverage levels are 2.5 and 1.75 times the third-dose coverage, respectively.
4. Expansion of VFC eligibility will result in equal expansion of 317, state/local, and private vaccine availability and utilization.
5. Vaccination coverage will increase every year. Third-dose coverage is projected at 8% for 1998, 16% for 1999, 34% for 2000, and 50% for 2001.
6. Vaccine contract prices are $8.17 to $9.91 for 7- to 10-year-olds, and $9.45 for 16- to 18-year-olds.
7. The proportion of vaccines supplied by VFC funds is 42% of the total; 317 funds supply 15%, state/local funds supply 9%, and the private sector supplies 34%.

Dr. Averhoff then summarized the estimates of annual cumulative vaccination coverage attained for each cohort attributable to expanding VFC eligibility. Only 7-year-olds would be affected by the expansion for 4 years; 10- and 18-year-olds would be affected for only 1 year. For 10- and 18-year olds, projected vaccination coverage attributable to the expansion is only 8%. For the cohort of 7-year-olds, the cumulative coverage is projected to reach 74%.

If expansion is limited to only 16- to 18-year-olds, the number eligible for vaccine would decrease annually due to aging out of the VFC-eligible cohorts. The total number of doses and the VFC doses peak in the second year of the expansion:

Year	No. eligible (millions)	Total doses (millions)	No. VFC doses (millions)
1998	10.6	3.3	1.4
1999	6.5	3.9	1.6
2000	2.7	3.1	1.3
2001	0	0	0

If the expansion includes children 7-10 years of age in addition to adolescents 16-18 years of age,

the total number of attributable doses peaks again in the second year of the expansion, this time at a projected 10.3 million doses:

Year	No. eligible (millions)	Total doses (millions)	No. VFC doses (millions)
1998	25.3	8.2	3.4
1999	16.6	10.3	4.3
2000	8.4	9.9	4.1
2001	1.9	2.3	1.0

Annual estimated public sector vaccine costs attributable to expanding VFC eligibility by the two options were calculated by multiplying the estimated number of doses supplied by the applicable price per dose. The first year (1998) costs range from $20 million, if the expansion includes 16- to 18-year-olds only, to $50 million if the expansion includes both groups. The costs increase marginally in the second year, then decrease annually. In the fourth, there would be vaccine costs only for the cohort of current 7-year-olds.

A sensitivity analysis was conducted to assess the robustness of the estimates. A low-cost scenario assumed a higher initial coverage and lower annual coverage than the base-case scenario, resulting in a lower vaccine utilization and lower cost than the base case. A high-cost scenario assumed a lower initial coverage and higher annual coverage attained. When the analysis included only the first year, it showed relatively little variation in cost (because of the modest first-year coverage estimates used): approximately $20 million if the expansion includes only 16- to 18-year-olds, and $50 million if it includes 7- to 10-year-olds and 16- to 18-year-olds. When the analysis included the cumulative costs of all four years of the expansion, the range widened. If expansion was limited to 16- to 18-year-olds, the estimate was $25 million to $100 million. If expansion included both age groups, the cost was $100 million to $250 million.

Issues for consideration

The positive effects of a change in eligibility include: 1) consistency with ACIP recommendations, 2) simplicity, 3) decreased missed opportunities for vaccination, 4) increased opportunities to promote immunization in high-risk adolescents, 5) increased opportunities to promote the A/PI program, and 6) elimination of administrative nightmares for insurers. Negative effects are primarily financial: the VFC program would incur additional vaccine costs, and private insurers, 317 programs, and state/local programs would incur additional vaccine costs plus program implementation costs.

The change would have an unknown impact on school-entry requirements, school-based vaccination programs, the 11- to 12-year immunization visit , and programs targeting high-risk adolescents and adults. The cost-effectiveness of the expansion was not considered.

Poll of program managers

In a poll of immunization program managers, the majority (21/27) of respondents preferred the expansion to include all children and adolescents.

Discussion

Dr. Zimmerman clarified that AAFP's current recommendations go through age 18. Dr. David Fedson pointed out that the approach shifts costs from the future to the present. Dr. Averhoff agreed that this is the case for 7- to 10-year-olds.

Dr. Fleming favored the overall expansion. States are putting a high priority on ensuring coverage for 7- to 10-year-olds. In one sense, this is a cost-saving measure: as state implement middle-school requirements for hepatitis B, immunizing children now as part of routine care will save costs in the long run.

Dr. Halsey presented the results of a study looking at the possibility of expanding the interval between the second and third dose from 6 months to 1 year. The investigators randomized children to receive vaccine at 0, 1, and 6 months or 0, 12, 24 months and studied their antibody responses before and after the third dose. Results showed that children can be immunized at regularly scheduled visits, without the need for extra visits or an extra program.

Proposed VFC resolution

Dr. Harold Margolis presented the proposed VFC resolution. He reminded the committee that any VFC resolution will require a change in the ACIP recommendation. He suggested addressing the VFC wording first and working from there, and the committee concurred. He also suggested starting with Option 1, which was the program managers' preferred approach. The proposed resolution reads as follows:

Resolution No. 10/97

Vaccines to prevent hepatitis B virus infection -- Expansion of eligible age groups

"The ACIP has previously approved resolutions recommending hepatitis B vaccine be included in the Vaccines for Children Program for vaccination of: 1) all infants beginning at birth or by 2 months of age (Resolution 6/94-17), 2) for children 10 years of age or younger in populations at high risk of hepatitis B virus infection (Resolution 5/95-2), 3) for all previously unvaccinated children at age 11-12 years (Resolution 2/95-3), and 4) for older adolescents at high risk of hepatitis B virus infection (Resolution 4/94-A1); and clarified previous resolutions to include all children born on or after January 1, 1991, and all unvaccinated persons born or after January 1, 1982, who are at least 11 years of age (Resolution 6/97-2).

Simplifying the means to assess eligibility for vaccination would eliminate a potential

barrier to achieving high levels of hepatitis B vaccination in those groups of highest priority and would be achieved by expanding the age of eligibility to include those remaining cohorts of children and adolescents not covered by previous Vaccines for Children Program resolutions.

The ACIP affirms the following:

> That the primary priorities for routine hepatitis B vaccination are: 1) infants, 2) children in populations at high risk of hepatitis B virus infection, 3) adolescents at 11-12 years of age, and 4) older adolescents in defined risk groups.
>
> That to facilitate hepatitis B vaccination coverage, the age eligibility should be expanded to include those cohorts of children and adolescents not currently included in the Vaccines for Children Program.

Therefore, the ACIP recommends that hepatitis B vaccine be included in the Vaccines for Children Program for the following age groups:

> All unvaccinated children 18 and under, with vaccination programs prioritized for: 1) all infants beginning at birth or by 2 months of age, 2) all children in populations at high risk of hepatitis B virus infection, 3) children at 11-12 years of age, and 4) adolescents in groups at high risk of hepatitis B virus infection.

This resolution becomes effective following the publication of the revised ACIP statement on hepatitis B vaccination in 1998.

The number of doses, schedules, contraindications, and other groups eligible for hepatitis B vaccine are those defined in previous VFC resolutions (Resolutions 2/94-14, 6/94-A1, 6/94-9, 6/94-17, 2/95-2, 2/95-3, and 6/95-1)."

Discussion

Drs. Le and Guerra supported the resolution but questioned the need to retain the reference to high-risk groups. Dr. Margolis felt that their inclusion reiterated prevention priorities.

Dr. Schoenbaum wondered why the effective date should be tied to the issuing of an ACIP statement with an uncertain publication date. Although Dr. Margolis thought that VFC resolutions cannot become effective without an ACIP statement, Mr. Kevin Malone, Office of the General Counsel, advised that no requirement links the two. Dr. Zimmerman favored specifying a date. Dr. Livengood pointed out that VFC resolutions usually do not go beyond ACIP statements. He also confirmed that current contracts are adequate to support this resolution.

Dr. Glode advocated simplicity. She recommended limited the wording to "all unvaccinated children 18 and under." Dr. Fleming proposed a January 1, 1998, effective date. Drs. Clover,

Graydon, and Gilmet supported the simplified proposal. After some discussion of the January 1 date, a motion was made and seconded to consider the simplified eligibility wording first.

> "... Therefore, the ACIP recommends that hepatitis B vaccine be included in the Vaccines for Children Program for the following age groups:
>
> All unvaccinated children 18 and under."

VOTE. Drs. DeBuono, Schoenbaum, Sherrod, Griffin, Fleming, and Glode voted in favor of the amended resolution. No one voted against the resolution. Drs. Modlin, Guerra, Le, and Davis abstained. The motion carried.

The members then discussed the effective date. Dr. Davis said that, given the adequate vaccine supply, the resolution could be implemented rapidly. Dr. DeBuono asked for more time to bring programs up to speed. Mr. Gary Schatz supported the "sooner the better" stance. After some discussion, a motion was made and seconded to change the effective date to March 1, 1998:

> "Therefore, the ACIP recommends that hepatitis B vaccine be included in the Vaccines for Children Program for the following age groups:
>
> All unvaccinated children 18 and under.
>
> This resolution becomes effective on March 1, 1998."

VOTE. Drs. DeBuono, Schoenbaum, Sherrod, Griffin, Fleming, and Glode voted in favor of the motion; no one was opposed. Drs. Guerra, Le, and Davis abstained. Dr. Modlin was absent for the vote.

<u>Footnote to the harmonized immunization schedule</u>

Dr. Livengood revisited the proposed change in the harmonized immunization schedule for hepatitis B vaccine, which was tabled from Day 1. The proposal was to make a minor change in the footnote to emphasize the intent to vaccinate children whenever they are seen during the health-care process. The amended footnote would read:

> "Children and adolescents who have not been vaccinated against hepatitis B in infancy may begin the series during any visit. Those who have not previously received three doses of hepatitis B vaccine should initiate or complete the series during the 11-12 year visit, but unvaccinated older adolescents should be vaccinated whenever possible."

VOTE: Eight members voted in favor of the change. Dr. Modlin was absent for the vote.

Dr. Le suggested the following change in the explanatory language accompanying the harmonized schedule:

"Vaccines are listed under the routinely recommended ages. Bars indicate the range of acceptable ages for routine vaccination. Catch-up immunization is encouraged whenever possible. [Or, catch-up immunization should be done at any visit when feasible.] Shaded bars indicate vaccines to be assessed and given if necessary at the pre-adolescent visit. (Varicella vaccine should be administered to children not previously vaccinated who lack a reliable history of chickenpox.)"

Dr. Halsey agreed that this change clarifies the intent of the shaded bars. Dr. Davis said that the committee would provide the amended language to the NIP staff.

INFLUENZA DISCUSSION

Dr. Nancy Cox, NCID, introduced the two sessions on influenza, which were for information and discussion only. The first was a description of a joint CDC/Hong Kong Department of Health investigation of the isolation of an avian influenza A(H5N1) virus from a child who died in Hong Kong; the publicity surrounding this incident has increased global awareness of the need for pandemic preparedness. The second presentation was an update on the national influenza pandemic preparedness plan.

Isolation of Influenza Type A (H5N1) in Hong Kong

Dr. Keiji Fukuda, NCID, reported on the isolation of the influenza A(H5N1) virus, the epidemiologic investigation, and the implications of the findings. On August 10, 1997, the National Influenza Center in Rotterdam notified the Hong Kong Department of Health that an influenza A(H5N1) virus had been identified from a human tracheal aspirate specimen obtained in Hong Kong; the report was independently confirmed by CDC a few days later. The Hong Kong Department of Health began an intensive investigation, and CDC joined the effort on August 20.

Avian influenza A(H5) viruses were first identified in terns in South Africa in 1961. The virus was isolated from geese in Guondong province in South China in 1996, and outbreaks of influenza A(H5N1) occurred in March-May 1997 on poultry farms in the New Territories area of Hong Kong. The virus is highly pathogenic in chickens.

The Hong Kong index case occurred in a normal, previously healthy, 3-year-old boy who developed fever, sore throat, and cough on May 9, 1997. He subsequently was seen by his physician, who prescribed antibiotics and aspirin. When the child's condition worsened, he was admitted to the hospital, where he developed respiratory distress. He was intubated, and a tracheal aspirate was obtained. The child died on May 21. The cause of death was respiratory failure. Complications included Reye syndrome and renal failure.

The case investigation centered on these questions:

1. What are the characteristics of the virus?

Virus analysis showed that all eight genes were of avian origin. The hemagglutinin (HA) and neuraminidase (NA) sequences were similar to those from the viruses isolated in the poultry outbreaks in Hong Kong. The H5 HA was similar to the Eurasian lineage of H5 strains. The HA cleavage site motif was also characteristic of other highly pathogenic avian influenza A viruses. Testing showed that the virus retained pathogenicity in chickens.

2. Was there any evidence that it was a laboratory contaminant?

No. First, no other influenza viruses were isolated from other patients in the intensive care unit where the child was hospitalized. Of 85 viral tissue cultures performed on the same day at the laboratory, 27 were specific for influenza. Of these, only one grew influenza A(H5N1). Since January 1997, the laboratory has performed more than 600 tests, with no additional H5N1-positive cultures. Second, H5N1 virus was re-isolated from the original specimen, both in Hong Kong and at CDC. Third, an IFA of tracheal aspirate specificity, performed in Hong Kong, was positive for influenza A. A PCR test of tracheal aspirate specificity, performed at CDC, was positive only for H5N1 genes.

3. Was this a true infection or an incidental finding?

It seems to be a true infection. The child had no history of chronic illnesses. His 11-day illness was consistent with an influenza-like illness complicated by viral pneumonia, Reye syndrome, and other conditions. Evidence for other pathogens was sought and none found.

4. What was the source of the virus and its route of transmission?

These remain unknown. The investigators were unable to establish a direct link with the Hong Kong poultry outbreaks or to establish the presence of influenza A(H5N1) virus in poultry in South China.

5. Was there evidence of other human infections or disease cases?

To date, no new isolates have been identified. Surveillance was increased in Hong Kong and South China, and no unusual increases in influenza-like illnesses have been reported. Approximately 2,000 human serum samples were obtained from this investigation. CDC is working on an ELISA to test serum samples from family members, schoolmates, neighbors, health-care workers, poultry workers, and controls.

Continuing actions include increased human influenza surveillance, testing of a variety of poultry and swine specimens, and ongoing evaluation of the incident and response as a pandemic "dress rehearsal" for CDC.

In conclusion, Dr. Fukuda stated that:

An avian influenza virus caused fatal illness in a child.
This is the first known human influenza A(H5N1) virus infection.
The incident will probably remain an isolated event.
The virus appears to have little pandemic potential.

Lessons learned had both positive and negative components. On the positive side, the incident demonstrated the usefulness of WHO's global surveillance network. It also showed that it is possible to rapidly and cooperatively mount an international investigation that had the required level of laboratory and field support. On the negative side, the incident demonstrated: 1) a long delay between virus isolation and identification (May 21-August 11), 2) a lack of serologic and molecular reagents in some parts of the world, 3) the need for additional training, 4) the need for improved disease surveillance in China and the Pacific basin, and 5) problems in the coordination

of international communication and response. The incident also underscored the need to include more details in the U.S. pandemic plan and to speed the development of the plan.

Discussion

In response to a question from Dr. Schoenbaum about the estimated development time for the new ELISA, Dr. Cox noted that the process has been more difficult than anticipated and has been complicated by the need for strict biosafety precautions.

When asked about his certainty in linking the fatal outcome to influenza, Dr. Fukuda acknowledged that it was clinically difficult to link an agent to an illness in a single case. However, the child's illness and clinical course were consistent with influenza complicated by Reye syndrome. Dr. Glezen asked about the certainty that the virus was a new arrival in Hong Kong. Dr. Fukuda could not be certain due to gaps in surveillance. Dr. Glezen was also concerned about the possibility of an intermediate host.

Dr. Guerra asked about surveillance procedures for tracking international travelers. Dr. Fukuda said there was no system for travelers per se, although surveillance systems are in place in different parts of the world.

Update on the Influenza Pandemic Preparedness Plan

Dr. Raymond Strikas, NIP, provided information on the *Influenza Pandemic Preparedness Plan for the United States* (Draft: August 1997). He outlined a rationale for pandemic planning, reviewed elements of the current plan, and considered the role of ACIP in implementation of a pandemic response. He informed the committee that the current draft of the plan is being reviewed at DHHS; he anticipates that it will be approved soon as a Department-wide plan. Any additional comments from ACIP members are therefore due within 3 weeks.

Influenza pandemics have occurred at unpredictable intervals throughout history, every 10 to 100 years. They are caused by shifts in the major antigenic determinants of the virus. Disease can

spread globally and cause universal infection and potentially high mortality rates. A 3- to 6-month warning period can be expected. In the case of the H5N1 case, the virus was a novel strain, and antigenic shift was noted. Most of the population was probably susceptible to this novel strain, but, fortunately, the virus did not demonstrate the ability to spread geographically. Still, CDC is operating under the assumption that a pandemic will occur in the future. It is a question of "when," not "if."

Since 1993, there has been a joint public- and private-sector effort, currently led by CDC and FDA, to develop a pandemic preparedness plan for the United States. The approach has been to assume a worst-case scenario, i.e., that everyone in the United States is susceptible and that everyone will need to be protected. The objectives are to decrease morbidity, mortality, community disruption, and economic loss. The focus is not only on preparing for a pandemic but also on improving influenza control in inter-pandemic periods (e.g., surveillance, vaccine production and delivery, communication coordination, and emergency response). The plan is designed to be action oriented, user friendly, and dynamic.

The plan focuses on eight areas:

1. Improvements in ongoing virologic and disease-based surveillance systems for influenza
2. Special studies to facilitate early detection and recognition of novel influenza viruses
3. Aggressive annual vaccination programs for high-priority target groups during the current inter-pandemic period and mass vaccination programs in the event of a pandemic
4. Liability coverage for vaccine manufacturers and health-care providers for vaccine produced and administered in response to a pandemic
5. Research and development programs to accelerate the availability and enhance the effectiveness of existing and novel vaccines and antiviral agents against influenza
6. Integrated, multi-component communication systems for rapid information dissemination and exchange
7. Emergency preparedness plans to ensure adequate medical care and maintenance of essential community services
8. Improved national and international collaboration, coordination, and communication

Implementation and management activities center on: CDC/FDA leadership, working group involvement, a formal process for declaring and managing a pandemic, a "mission control" unit (likely at CDC), and designation of legislative authorities to authorize funds and other resources. The plan also calls for additional actions related to pandemic preparedness: further studies of animal subtypes, contingency plans for field studies, vaccine purchase programs, liability protection, vaccine allocation, cost-effectiveness models, disaster planning, pilot testing of state and local guidelines, military planning, international cooperation, and communication systems.

Globally, efforts of several countries to develop their own plans have accelerated since 1992. WHO has also formed a Global Task Force on Pandemic Planning, with CDC representation.

The decision model for declaring a pandemic is as follows:

Antigenic shift is identified.
CDC and FDA inform working group members.
A pandemic alert is declared.
CDC and FDA convene an emergency meeting of advisory groups.
Advisory groups provide information and recommendations to the DHHS Secretary.
The Secretary informs/consults with the White House.
The White House declares a pandemic and activates the pandemic plan.

Discussion

Dr. Le asked how priorities will be determined for distributing vaccines. Dr. Strikas acknowledged that this is still an unknown. Given the objectives of controlling morbidity and mortality, the working group looked first at traditional high-risk groups. Other issues are the need to preserve essential services, to address variations in susceptibility, and to identify those most at risk. The working group will be developing models to study this issue.

Dr. Plotkin asked for reassurances about international preparations and coordination. He was aware of no plan for Europe and wondered how a demand in Europe might affect vaccine availability in the United States, and vice versa. Dr. Cox acknowledged the need for interaction. WHO has formed a task force and is also compiling a worldwide inventory of vaccine companies that details current production capacity and scale-up capacity. Still, much more needs to be done in terms of national, regional, and global planning.

Dr. Bob Chen emphasized that a key bottleneck is vaccine delivery capability. Jet injections are no longer an acceptable option, and nothing is in the pipeline. He was concerned that the plan does not address how to get people vaccinated. The plan needs this emphasis to stimulate the market. Dr. Strikas agreed. Another question is who is going to deliver the vaccines.

Dr. Glezen voiced concerns about current influenza control efforts. If high-risk patients cannot be identified and vaccinated more efficiently than is being done now, he questions the ability of states to respond to a pandemic. In his view, the urgency of the situation has not been recognized. Another issue is diminishing virus surveillance capability as the resources of state public health laboratories continue to be cut. He wondered about the likelihood that funds will be invested to address these deficiencies. Will the plan generate that kind of will? Dr. Strikas said that the interest at DHHS and the progress on the Adult Immunization Action Plan make him cautiously optimistic.

MENINGOCOCCAL VACCINE AMONG COLLEGE STUDENTS

Dr. Nancy Rosenstein, NCID, presented on meningococcal vaccine among college students. She informed the group that, on September 30, 1997, the American College Health Association (ACHA) issued a statement recommending that students consider vaccination to reduce their risk for potentially fatal meningococcal disease and that college health providers take a more proactive role in providing information on and access to the meningococcal vaccine. She then

reviewed six sources of data on the risk of meningococcal disease in college students and discussed plans for further study.

Military data -- The situations of college students and military recruits, who both come from diverse geographic backgrounds to live in crowded and stressful situations, are similar. In World War I and World War II, the U.S. Army experienced epidemics of meningococcal disease after large-scale mobilizations. Recruits were found to be at higher risk than regular troops, and the epidemics were coincident with civilian epidemics. Since 1971, all new recruits have therefore been immunized with meningococcal vaccine. Currently, military recruits are vaccinated with the polysaccharide quadrivalent vaccine, which provides protection against serogroups A, C, Y, and W135. Only rare cases of meningococcal disease due to those serogroups are now reported in the U.S. military.

Descriptive epidemiology -- Active population-based surveillance shows that, although the highest rates of disease in the United States are still among children, the risk is increasing in 15- to 24-year-olds. The rate in 15- to 19-year-olds is about double the U.S. endemic rate of 1/100,000. Data by serogroup suggest that the currently available vaccine would provide protection for about 60% of cases in the 15-24 age group.

Risk factor study -- In a study of risk factors for meningococcal disease (Fischer at al), cases were identified by population-based surveillance, and controls were matched by age. Among adults ages 18 and over, 18% of cases (16/91) and 16% of controls (33/202) attended college. The univariate point estimate for college attendance as a risk factor was 1.2, with a confidence interval of 0.5-2.6.

College survey -- In a survey by Froeschle et al (Connaught Laboratories), a questionnaire was sent to 1,900 universities. Among the 722 respondees, 43 cases of culture-confirmed meningococcal disease were detected; 33 of the 43 cases were in students living in dormitories. The relative risk for dormitory living was 10.7.

U.S. cluster surveillance -- U.S. surveillance systems for meningococcal disease do not provide a reliable determination of whether cases are sporadic or are part of a cluster. CDC has therefore been gathering data from multiple sources to define the epidemiology of clusters of meningococcal disease in the United States for 1994-1996. Six clusters were detected in 2,300 U.S. colleges (Woods et al, preliminary data); four of the clusters were due to serogroup C meningococcal disease; in three cases, the universities instituted vaccination campaigns. During the same time period, 10 clusters were detected in primary and secondary schools and 35 clusters in communities.

Cost-benefit analysis -- Jackson et al (*Am J Public Health* 1995) conducted a cost-benefit analysis of meningococcal vaccination in college students from a societal perspective. Starting with a disease rate of 1/100,000, they modeled vaccinating 2.3 million freshman and found that vaccination would prevent 58 cases and 9 deaths, with a net cost of $46.9 million. If the attack rate was 7.5/100,000, the total net cost would be zero.

Conclusions from these studies are mixed. The military studies suggest that college students may

be at increased risk for meningococcal disease. The descriptive epidemiology suggests that young adults may be at higher risk. However, because the surveillance data do not separate out college students, there is no way to reliably predict the rate of meningococcal disease in this group. The risk factor study did not show that college attendance was a risk factor, but the study was not designed to address that question. The college survey found that dormitory living was a risk factor, but data were insufficient for a multivariate analysis. U.S. cluster surveillance data are difficult to interpret. Further efforts are needed to look at denominators and rates among different colleges and schools. The cost-benefit analysis suggested that from a societal prespective, meningococcal vaccine is not warranted for college students.

Dr. Rosenstein suggested that the lack of sufficient information precludes changing the current ACIP guidelines for control of meningococcal disease. However, CDC hopes to have additional data within the next year. In collaboration with CSTE and ACHA, CDC is planning to do enhanced surveillance for meningococcal disease on college campuses. Cases identified will be used in a case-control study to identify groups of college students who may be at increased risk and could possibly benefit from meningococcal vaccination.

Discussion

Dr. Katz asked about the current status of meningococcal disease in military recruits. Dr. David Trump, Department of Defense, maintained that this is not an issue; vaccines are used almost universally in recruits. In response to another question, Dr. Trump said that he has not looked at the data on Group B disease. Dr. Perkins said that there is no evidence of an increase in Group B disease as a result of vaccination with the quadrivalent vaccine.

Responding to a question from Dr. Fedson about outbreaks in jails, Dr. Rosenstein said that one outbreak was detected in 1989-1992 and one in 1993-1996. Dr. Glode asked if the proposed study could be expanded to determine if college is a risk factor. Dr. Rosenstein replied that enhanced surveillance will likely answer that question.

Dr. Gardner wondered if the ACHA recommends hepatitis and influenza vaccinations for college students. He also asked if ACHA issues separate recommendations for students involved in the health-care professions. Dr. M. Collins, ACHA, said that the organization recommends that college students have evidence of hepatitis B, polio, MMR, DT, and varicella vaccination within the past 10 years. Influenza vaccination is encouraged via educational outreach.

Dr. Plotkin noted that other countries have expanded the use of meningococcal vaccine in response to outbreaks and are looking for ways to increase use and prevent epidemics. Also, several companies are developing conjugate vaccines that ultimately might be used in pediatrics.

In response to a question from Dr. Peter, Dr. Rosenstein said that the U.S. mortality rate from meningococcal disease is 13%. She had no reason to suspect that the rate differs in outbreaks versus endemic disease, but that the data on clusters that we are collecting should better answer

those questions. Dr. Peter also wondered to what degree ACHA recommendations are followed. Dr. Strikas said that about 28 states have pre-matriculation requirements by law (all colleges) or public policy (public colleges).

Dr. Le wondered about the medical-legal implications of the ACHA statement. Dr. Collins has failed to see any legal implications for non-compliance. The ACHA goal is to assuage fear by encouraging informed actions.

SWEDISH ACELLULAR PERTUSSIS MASS VACCINATION PROJECT

Dr. John Taranger, North American Vaccine, spoke as co-principal investigator on a series of clinical trials of a new acellular monocomponent pertussis vaccine. He reported on results from an ongoing mass vaccination project that used the vaccine in the Goteborg area of Sweden.

He first reviewed the history of pertussis vaccination in Sweden. A Swedish-made whole-cell pertussis vaccine was introduced in the 1950s and recommended for general vaccination of infants. During the 1960s, pertussis seemed to disappear, but in 1970 it began to recur at high incidence levels despite a continued vaccination rate of more than 90%. It was later shown that changes in vaccine production during the late 1960s had made the vaccine ineffective. The vaccine was

withdrawn from the market in 1979, and from 1979 to 1996 there was no licensed pertussis vaccine in Sweden.

In 1996, new acellular vaccines were licensed in Sweden. Among them was the monocomponent pertussis vaccine, which was licensed as a three-valent combined product (DTaP). In Denmark, a four-valent vaccine, DTaP-IPV, was also licensed in 1996. In 1997, pertussis toxoid alone was licensed in Sweden for children and young adolescents still at risk for pertussis. The most important supporting data for the licensure of the monocomponent vaccine came from a large-scale Phase III trial (*NEJM* 1995;333:1045-50).

Soon after the successful completion of the trial, which demonstrated safety and efficacy, the Mass Vaccination Project was initiated among the 700,000 inhabitants of the Goteborg area. The project was designed to: 1) examine the ability of the vaccine to break the transmission of pertussis and to induce herd immunity, and 2) examine the safety of the vaccine when used in large numbers. The large population involved in the project allowed for the examination of the risk of rare adverse events (e.g., hypotonic hyporesponsive episodes [HHEs]) as described for whole-cell pertussis vaccines and multi-component acellular pertussis vaccines.

As part of the project protocol, infants are vaccinated three times at ages 3, 5, and 12 months. Children 1 year and older who have already been vaccinated against diphtheria and tetanus receive three doses of the pertussis toxoid alone at the same intervals. Infants have received the DTaP vaccine since September 1995 at community-run child health centers. From the beginning, the enrollment rate has been about 95% (>700 infants/month). The enrollment rate for aP vaccinations of older children increased sharply in the first year of the project and is now

leveling off. The total enrollment is at about 35,000 children, more than 95% of whom were born during the 1990s.

Adverse events among recipients of the vaccine are monitored through monthly reports of deaths, quarterly reports from hospitals, and reports from parents, nurses, and physicians. No serious vaccine-associated adverse events, other contraindicating events, or deaths have been reported.

The 4-valent monocomponent aP vaccine (DTaP-IPV) has also been used in Denmark since the beginning of 1997 for general vaccination of infants. More than 25,000 infants have received their first vaccination, and there are no reports of serious vaccine-associated adverse events.

Epidemiologic surveillance for pertussis in the project area is conducted in several ways. Data on hospitalizations due to pertussis for a 10-year period before the mass vaccination project show an average of 18 hospitalizations per year for infants <6 months of age. According to a statistical model, transmission will be broken if the incidence of hospitalizations in that age group decreases by at least 50%.

Data on positive cultures since 1976 show a marked decrease in culture-verified *B. pertussis* infections after one year of mass vaccination of infants and children. During 1986-1995, in the 10-year period before the mass vaccination project, an annual average of approximately 1,000 positive cultures for pertussis were recorded in Goteborg, with a significant number of children being hospitalized with pertussis complications. During 1996, the number of positive cultures dropped to less than one quarter of the previously reported annual average. The decrease has continued during 1997, and it is expected that the number of positive cultures will drop by more than 95% from the previously reported annual average.

Annual figures show that there is still pertussis in other parts of Sweden. However, pertussis hospitalizations have decreased since 1996, and, so far in 1997, there have been only two hospitalizations due to pertussis in infants <6 months. This is an indication that herd immunity is developing in the project area. The dramatic decrease in pertussis transmission after the initiation of the mass vaccination project has occurred while at least 15% of children in the area were still susceptible. Since continued vaccination of birth cohorts will take place, Dr. Tanager anticipates that stable herd immunity will be established in Goteborg in the near future.

In conclusion, the mass vaccination project has shown that the monocomponent acellular pertussis vaccine is a very safe and effective vaccine. No HHEs or any other contraindicating events have been reported after about 225,000 injections in Sweden and Denmark. A dramatic decrease in transmission of pertussis has been observed in the project area, where there are also indications of herd immunity. Since safety has been a recurring issue for whole-cell pertussis vaccine, the monocomponent vaccine may offer an answer to the public health demand for a safe and effective vaccine against pertussis.

Discussion

Dr. Peter wondered if surveillance included adolescents and young adults and if there was

evidence of disease in that age group. Dr. Tanager reported that, between June 1995 and March 1997, there were 83 pertussis hospitalizations in older children.

In response to a question from Dr. Plotkin about the possible cause of HHE, Dr. Tanager could not speculate but noted that all vaccine components have different biologic activities.

Dr. Orenstein was pleased to see data for a single product and noted that acellular vaccines have been shown to have a major community impact in Japan. He asked about seasonality in the occurrence of pertussis in Sweden. Dr. Tanager said that the numbers are small but that no seasonal patterns in hospitalizations have been discerned. There are seasonal variations in pertussis at the population level.

Dr. Scheifele wondered if the disease control experiences in Sweden and Denmark were similar enough to conclude that the addition of IPV had no impact on efficacy. Dr. Taranger said that no reports have been issued from Denmark. This is a tricky issue, and data are difficult to obtain.

Dr. Glode asked for a comment on the news report that European public health officials are preparing for a continent-wide epidemic of pertussis following an outbreak in the Netherlands of a pertussis strain that is resistant to a leading vaccine. Dr. Taranger said that there has been a tenfold increase in pertussis in the Netherlands during the last 2 years and that 90% of circulating pertussis strains have a mutation for pertactin. If this is an indication that pertactin is important for protection against pertussis, it is too early to form an opinion. However, monitoring of pertussis strains remains important. Melinda Wharton said that the actual finding consists of three amino acid changes near a binding region of pertactin. This represents a change from decades ago, but officials in the Netherlands are circumspect about the implications. There is no evidence that these changes are either functionally important or have resulted in decreased vaccine efficacy. Many questions must be answered before the current outbreaks can be linked to a mutant strain.

SAFETY AND EFFICACY RESULTS FROM PHASE III PIVOTAL TRIAL ON LYME DISEASE

Dr. David Dennis, NCID, reported on progress on a Lyme disease vaccine. Two manufacturers, SmithKline Beecham and Connaught, have used single-protein recombinant outer-surface protein A (OspA) lipidated vaccines in field trials, and both vaccines have been shown to be immunogenic and safe. Phase III studies have been completed, and results were presented at the IDSA meeting in San Francisco in September. Dr. Dennis introduced representatives from the manufacturers, who provided details on their trials.

Dr. Dennis Parenti, SmithKline Beecham, reported on the pivotal efficacy trial for the SmithKline Lyme vaccine, a recombinant DNA-expressed lipoprotein OspA product. The multicenter, randomized, double-blind, placebo-controlled trial was conducted in 31 sites in endemic areas in New England, the mid-Atlantic, and the Midwest. A total of 10,936 subjects were enrolled, and vaccine was administered on a 0, 1, 12 month schedule. Those eligible for inclusion were healthy persons, ages 15-70 years, who were at risk for acquiring Lyme disease;

persons with prior Lyme disease were not excluded.

Serum samples were drawn at baseline, and subjects were administered two doses of vaccine in early 1995. Postcard surveillance was conducted for Lyme disease symptoms and vaccine safety throughout the transmission season. If symptoms suggestive of Lyme disease developed, acute and convalescent serum samples were drawn for Western blot testing. The protocol also included specific procedures based on symptoms. In early 1996, at month 12, subjects had blood drawn and were administered a third vaccine dose, with postcard surveillance again conducted during the transmission season. The study was completed in mid-November 1996, after 20 months and two tick transmission seasons; 95% of subjects made the final visit. The vaccinees continue to be followed for long-term safety monitoring, and the placebo group is currently receiving open-label vaccine.

In year 1, 10% of the study population (1,043) were evaluated for suspected Lyme disease, and 11% (113) met one of the case definitions for Lyme disease. In year 2, 6% (about 700) were evaluated for suspected Lyme disease, and 18% (129) met one of the case definitions. The case definition required that subjects have one clinical manifestation and at least one positive laboratory test for confirmation.

Efficacy results were as follows. In year 1, there were 20 cases in the vaccine group (all with erythema migrans) and 40 cases in the placebo group (39 with erythema migrans; 1 with neurologic disease), for a vaccine efficacy of 50%. In year 2, there were 13 cases in the vaccine group (12 with erythema migrans; 1 with Lyme arthritis) and 61 cases in the placebo group (60 with erythema migrans; 1 with neurologic disease), for a vaccine efficacy of 79%. Approximately 75% of the confirmed cases in year 1 and year 2 were confirmed by culture.

Given concern that vaccination might alter the clinical appearance of disease, attenuate disease, or induce asymptomatic seroconversion, the investigators assessed serum samples obtained at months 12 and 20 for IgG seroconversion. In year 1, 2 vaccinees and 12 placebo subjects seroconverted, for a vaccine efficacy of 83%. In year 2, there were 13 cases of asymptomatic seroconversion, all in the placebo group, for a vaccine efficacy of 100%.
When confounding factors for efficacy were analyzed, a probable age effect was identified. Efficacy was low in the older age group (>65 years). When the analysis was limited to persons ages 15-65 with definite or asymptomatic Lyme disease, year 1 efficacy was 60% (19 cases in the vaccine group versus 48 in the placebo group), and year 2 efficacy was 90% (7 cases in the vaccine group versus 70 in the placebo group).

A total of 192 cases of Lyme disease were documented by seroconversion. Thirteen cases were documented solely by culture information and 11 cases solely by PCR testing; 27 cases of asymptomatic infection were also identified. These 50 cases represent 25% of cases identified and represent a population that would not have been identified by serologic testing alone.

Dr. Parenti felt that the data are very robust. Efficacy could be confirmed by culture data alone or PCR data alone. The data suggest that vaccination does not interfere with laboratory confirmation; does not mask, attenuate, or alter clinical presentation; and does not affect the

duration of symptoms once patients begin therapy.

Animal models suggest that the vaccine's mechanism of action may be unique in that it affords protection by killing the spirochete while it is still inside the tick. Animal data also suggest that protection results from high-titered antibodies to a portion of OspA that has been identified as LA-2; this may be the protective epitope.

With regard to adverse events, the vaccine group had a higher incidence of soreness, redness, and swelling, as well as myalgia, achiness, fever, and chills, compared to the placebo group. Most of these events started either the day of vaccination or a day or two later; most were of mild to moderate severity. The two groups had no differences in the incidence or nature of late adverse events or serious adverse events. There were no episodes of immediate hypersensitivity in the vaccine group and no unusual patterns of adverse events. There was also no evidence that subjects with a previous history of Lyme disease were at higher risk of adverse events.

Dr. Parenti concluded that vaccine efficacy against definite Lyme disease or asymptomatic infection in subjects ages 15-65 years was 90% after three doses. A comprehensive study design led to 26% more cases documented as a result of additional laboratory testing. The vaccine has an acceptable reactogenicity profile and provides an important new public health approach to the prevention of Lyme disease, including asymptomatic infection.

In response to questions, Dr. Parenti added that there were no differences geographically, that 2.3% of subjects were seropositive at baseline, and that 10% or 12% had a history of previous Lyme disease. The issue of age was difficult to address statistically because of the small number of cases. Among the vast majority of older subjects who were vaccine failures, most were not responders after the first two doses.

Next, Dr. John Zahradnik described a similar study of an OspA Lyme disease vaccine manufactured by Pasteur-Merrieux Connaught; the vaccine differs from the SmithKline product only in the lack of an adjuvant. The study was a randomized, double-blind, placebo-controlled 2-year trial conducted in 14 sites in the Northeast and Midwest beginning in Spring 1994. A total of 10,305 subjects (healthy, at risk for Lyme disease, age 18 or older) were enrolled, and vaccine was administered on a 0, 1, 12 month schedule. The study population was observed over two Lyme disease seasons.

Cases were defined by the appearance of erythema migrans or neurologic/cardiac disease for early disease or arthritis for late disease. Efficacy was computed as the excess number of cases in the placebo group versus the vaccine group divided by the number of cases in the placebo group.

In 1994, there were 38 cases in the control group and 13 in the vaccine group, for an efficacy of 68%. In 1995, among those who received the third booster dose, there were 26 cases in the placebo group and 2 in the vaccine group, for an efficacy of 92%. Seven cases (2 in the placebo group and 5 in the vaccine group) occurred in persons who did not receive a booster in 1995.

Efficacy results demonstrate that, in the first year of the trial, 89% of the male participants less than 60 years old were protected after three doses, but that males 60 years or older were provided with little protection (2%). In females, efficacy was 67% in those less than 60 years old and 47% in those over 60 years of age. In the second year, the vaccine provided 100% protection in both males and females under age 60 years. In persons over age 60, there was 67% protection in males and 100% in females. These data suggest that the third dose provided persons age 60 years and older with significant benefit during the Lyme disease season.

In the first year, the vaccine provided 86% protection in persons with a prior history of Lyme disease versus 68% in those with no prior history. In the second year, after the booster dose, protection was increased to 100% in those who had a history of Lyme disease and 87% in those who did not. These data suggest that persons with prior Lyme disease are protected as well, if not better, than persons with no history of disease.

For all three doses, local injection-site reactions occurred more frequently in the vaccine recipients. Most differences in the two groups occurred within 3 days after vaccination. Results showed no evidence that the vaccine increased the risk of Lyme arthritis.

In summary, the vaccine was well tolerated, and most reactions occurred within the first 72 hours after vaccination. The vaccine appears to be capable of significantly decreasing the incidence of Lyme disease, and it does not appear to induce Lyme arthritis.

Discussion

Dr. Modlin asked about plans for studies of children in endemic areas. Drs. Zahradnik and Parenti noted the great interest in Lyme disease in children and thought that future deliberations with the FDA will likely involve studies in children.

PUBLIC COMMENT

Ms. Karen Vanderhoof-Forschner, Chair of the Board of Directors, Lyme Disease Foundation (LDF) addressed the committee.

She said that the LDF was established in 1988 and is the first and largest scientific nonprofit organization dedicated to Lyme disease and other tickborne disorders. The LDF was established at the request of researchers looking for a home organization dedicated to the then "mystery disease." The LDF was established to have the four cornerstone partners of progress -- scientists, government, business, and the public (including patients) -- working together to find long-term solutions. The Board of Directors includes Dr. Willy Burgdorfer (Scientist Emeritus of the National Institutes of Health [NIH]), discoverer of the causative agent of Lyme disease, which was subsequently named *Borrelia burgdorferi* in his honor. This year the LDF received an award from NIH for Outstanding Educational Achievements.

LDF activities cover education, research, and advocacy. The core education program is a yearly,

medically accredited scientific conference that brings together researchers and clinicians from around the world to present the latest discoveries and debate new controversies. Last year's scientific conference, concentrating on chronic Lyme disease, was summarized in the July issue of *Clinical Infectious Diseases*. LDF also publishes a peer-reviewed scientific journal. The scientific advisory committee includes world-renowned experts.

Public education programs include producing an award-winning children's half-hour television special that was nationally broadcast on PBS stations. LDF has distributed children's educational programs to more than 12,000 schools, directly educating about 4 million children. LDF has been the primary source of Lyme disease information for media across the world. A 24-hour hotline handles 60,000 calls per year. Printed materials reach 500,000 people every year, and media information reaches about 50 million people per year. A newly established Web page is already well used. The latest effort has been to mail educational materials, including public service announcements, tabletop display boards, posters, educational videos, and booklets, to the health departments responsible for the 100 counties with the highest reported case counts of Lyme disease.

LDF has funded research at many major institutions, including NIH. The organization helps support groups and patients across the United States. Members also educate Congress.

Despite all of these efforts, however, cases of Lyme disease continue to rise; 1996 had the highest number of reported cases ever. As of last week, approximately 108,000 cases of confirmed Lyme disease data had been reported from 49 states. Although there will be yearly fluctuations in the number of cases -- since there is no way to control ticks -- cases will continue to climb. A safe and effective vaccine is a logical step in the prevention of this disease.

Ms. Vanderhoof-Foschner then cited results from an actuarial study that looked at the societal costs of Lyme disease. The study was conducted by Dr. Irwin Vanderhoof, Professor of Economics, New York University Stern School of Business, in conjunction with the Society of Actuaries and the LDF. This study population included 1,000 physician-diagnosed cases of Lyme disease. The best actuarial estimates have this disease affecting 2 million people with a total cost to society of $18 billion. The 1996 cases cost about $2.5 billion.

Diagnosis is not always easy. Patients saw an average of five physicians before being diagnosed. The majority of patients (55%) had no known rash. The Lyme disease rash is the most important diagnostic sign for the practitioner. There is no test to prove that all of the bacteria are dead and the infection is eradicated. Declaration of a cure is scientifically incorrect. The current diagnosis and treatment protocols inadequately address the real situation of persistent infection. Chronic persisting infection, despite treatment, is a reality.

The disease is a multi-systemic problem. The majority of patients had four to six major categories of problems occurring at the same time: musculoskeletal conditions, neurologic problems, profound fatigue, ophthalmologic conditions, cardiac problems, and gastrointestinal involvement. On two rating scales of frequency and severity, patients indicated they had a high level of frequent and severe pain during the disease.

Lyme disease causes serious problems to society. It takes a person with disseminated Lyme disease an average of 6 months to get diagnosed and start treatment. The total cost averages $68,000. If the case lingers to 12 months before treatment starts, the cost increases to $91,000. If the case is diagnosed and treated in less than 6 months, the cost is reduced to $34,000. Less than half of this cost is for Lyme disease treatment; 23% is in lost wages, and 24% is in medical bills incurred before diagnosis.

Non-cash losses are also important. Approximately 63% of patients in the study experienced mental anguish. This includes the stigma of having the disease and the resulting ridicule. Thirty-five percent had permanent physical damage; 17% lost time at work; and 17% lost time from school, which meant that a family member was at home, too.

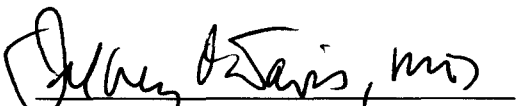
Ms. Vanderhoof-Forschner cautioned that, when a vaccine is judged safe and effective, a tick-bite prevention "Protect and Check" message should be included as part of the overall prevention program. Ehrlichiosis and babesiosis can be transmitted by the same tick and have no known minimum transmission time. People should never be lulled into a false sense of security that a Lyme disease vaccine will take away their worries about all tick-transmitted infections.

The Lyme Disease Foundation is interested in being included in any working group established on the Lyme disease vaccine. Ms. Vanderhoof-Forschner would welcome the opportunity to be included in a future meeting to formally present this and additional independent cost data.

ADJOURN

Dr. Davis thanked all of the presenters for the information provided to the Committee. With no further discussion, the meeting was adjourned at 2:45 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

2/26/98

Date