ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

MEETING

FEBRUARY 16-17, 2000

ATLANTA MARRIOT NORTH CENTRAL
ATLANTA, GEORGIA

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GEORGIA
February 16-17, 2000
Atlanta Marriott North Central

Agenda Item	Purpose/Action	Presider/Presenter(s)
February 16, 2000		
8:30 Welcome		Dr. J. Modlin (Chair, ACIP) Dr. D. Snider (CDC, OD)
9:00 ACIP Policies and Procedures Review section C	Discussion	Dr. J. Modlin (Dartmouth) Dr. D. Snider (ADS,CDC)
9:15 ACIP recommendations for the Pneumococcal conjugate vaccine How should we revise the ACIP recommendations based on FDA licensure? Cost benefit analysis	Discussion Decision	Dr. D. Johnson (Mich. Dept. of Hlth.) Mr. T. Ray (Kaiser Permanente) Dr. C. Van Beneden (NCID, BMD)
11:15 BREAK		
15 Update on the revision of the general recommendations	Information Draft Statement Decision	Dr. W. Atkinson (NIP, ISD) Dr. C. Le (Kaiser Permanente)
12:45 LUNCH		
1:45 Adult Immunization Recommendations Update on standing orders for immunization Pneumococcal disease and vaccination in persons 50-64 years of age Adverse events after yellow fever vaccine Revision of ACIP adult immunization recommendation	Information Discussion	Dr. M. Cetron (NCID, QD) Dr. R. Clover (Univ. of Louisville) Dr. L. McKibben (EPO,OHCP) Dr. J. Silber (Merck) Dr. R. Strikas (NIP,ESD) Dr. C. Whitney (NCID,DBMD)
3:45 BREAK		
4:15 Use of DTaP as the fifth dose following four doses of DTaP Can any licensed DTaP vaccine be administered as the fifth dose following four doses of DTaP? Epidemiology of pertussis in the U.S.	Discussion Decision	Dr. P. Rennels (Univ. Maryland) Dr. M. Wharton (NIP,ESD) Dr. L. Zanardi (NIP, ESD)
6:15 ADJOURN		

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Agenda Item February 17, 2000		Purpose/Action	Presider/Presenter(s)
8:00	Unfinished Business from Previous Day		Dr. J. Modlin (Chair, ACIP)
8:30	Influenza 2000-2001 Control and Prevention of Influenza Recommendations Update of 1999-2000 influenza season and Vaccine strain selection process	Information Discussion Decision	Dr. C. Bridges (NCID,DVRD) Dr. K. Fukuda (NCID, VRD)
10:00	Lyme disease vaccine update: trials in children, alternate dosing, boosters, VAERS data Should recommendations be revised based on presented information	Information	Dr. N. Hayes (NCID,DVD) Dr. D. Parenti (SmithKline Beecham)
10:30	BREAK		
11:00	2-dose adolescent hepatitis B vaccination Can comparable immunogenicity data between the two licensed hepatitis B vaccines be used to make an ACIP recommendation?	Discussion Decision	Dr. S. Finestone (FDA) Dr. H. Margolis (NCID, DVRD)
11:30	Vaccines for Children Program 2-dose adolescent hepatitis B vaccination vote on FDA approved dosage schedule IPV Pneumococcal Rotavirus	VFC Vote	Dr. J. Livengood (NIP,ESD)
12:30	LUNCH		
1:30	Bioterrorism and Anthrax	Information	Dr. D. Ashford(NCID,BMD) Dr. J. Grabenstein (DOD) Dr. C. Helms (Univ. of Iowa)
2:00	Updates National Center for Infectious Diseases National Immunization Program Food and Drug Administration Vaccine Injury Compensation Program National Vaccine Program	Information	 Dr. A. Mawle (NCID, OD) Dr. W. Orenstein (NIP, OD) Dr. W. Egan (FDA, CBER) Dr. G. Evans (HRSA) Dr. M. Myers (NVPO)
3:00	Combination DTPa/HepB/IPV vaccine	Information	Dr. B. Howe (SmithKlein Beecham)
	Public Comment		
3:30	ADJOURN		

ACIP February 16-17, 2000

ATTENDEES:

Committee Members
Dr. John Modlin (Chair)
Dr. Dennis Brooks
Dr. Richard Clover
Dr. David Fleming
Dr. Charles Helms
Dr. David Johnson
Dr. Chinh Le
Dr. Paul Offit
Dr. Margaret Rennels
Dr. Lucy Tompkins

Ex Officio Members
Dr. William Egan (FDA)
Dr. Geoffrey Evans (HRSA)
Dr. Michael Gerber (NIH)
Dr. Randolph Graydon (HCFA)
Dr. Martin Myers (NVPO)
Dr. Kristin Nichol (VA)
Dr. Douglas Thoroughman (IHS)
Dr. David Trump (DOD)

Liaison Representatives
Dr. Jon Abramson (AAP)
Dr. Eric France (AAHP)
Dr. Stanley Gall (ACOG)
Dr. Pierce Gardner (ACP)
Dr. Barbara Howe (PRMA)
Dr. Randolph Jackson (NMA)
Dr. Samuel Katz (IDSA)
Dr. Victor Marchessault (NACI)
Dr. Yvonne McHugh (BIO)
Dr. Paul McKinney (ATPM)
Dr. Georges Peter (NVAC)
Dr. Larry Pickering (AAP)
Dr. Jose Santos (HICPAC)
Dr. Bill Schaffner (AHA)
Dr. David Wilson (AMA)
Dr. Richard Zimmerman (AAFP)

Executive Secretary
Dr. Dixie Snider

Office of the General Counsel
Mr. Kevin Malone

Office of Public Affairs
Charlis Thompson

EPO
Dr. Linda McKibben

National Center for Infectious Diseases
Gregory Armstrong
David Ashford
Richard Besser
Lynnette Brammer
Carolyn Bridges
Martin Cetron
Suzanne Cotter
Nancy Cox
Scott Dowell
Keiji Fukuda
Susan Gorman
Ned Hayes
Peggy Honey
Nina Marano
Harold Margolis
Kathryn Mosher
Kathryn Orr
Erin Murray
Gary Sanden
Stephanie Schray
Ann Schuchat
Fangjun Shore
Jordan Tappero
Bill Thompson
Chris Van Beneden
Cyndi Whitney
Andrea Winguist
Mira Zader
Elizabeth Zell

National Immunization Program

Curtin Allen
William Atkinson
F. Averhoff
Sharon Balter
Joe Beaver
Roger Bernier
S. Scott Brown
Bob Chen
Susan Chu
Gary Coil
Gary Euler
Elizabeth Fair
Bill Gallo
Idalia Gonzalez
Pina Haber
Beth Hibbs
S.G. Humiston
Sonja Hutchins
Alan Janssen
Suzanne Johnson-DeLeon
Duane Kilgus
Mary Lambert
Charles LeBaron
Tasneem Malik
Dean Mason
Mary McCauley
Gina Mootrey
William Nichols
Jessica Nyich
Walter Orenstein
Mark Papania
Bette Pollard
Vitalli Pool
Pam Protzel-Berman
Dianne Quarterman-Ochee
Susan Reef
Lance Rodewald
Raula Rosenberg
Ben Schwartz
Stephanie Sevanson
Sonita Singh
Jim Singleton
Nichol Smith
Bob Snyder
Shannon Stokley
Ray Strikas
Vishnu-Priya Sueller
Craig Swilkins
Kathy A. Towers
Fran Walker
Bruce Weniger
Melinda Wharton
Lynn Zanardi
Laura Zimmerman

NCEH

Russ Havlak

NVPO

Alicia Pastema

Other Government Attendees

Karen Farize, FDA
LTC John Grabenstein,US Army SGO
Dr. Karen Goldenthal, FDA
Douglas Pratt, FDA

Others Present

Betsy Abraham, SmithKline Beecham
Murray Abramson, Merck Company
Betsy Alnaham, SmithKline Beecham
Mekibib Altaye, Norfolk, VA
E. McKee Anderson, Wyeth Lederle
B.F. Anthony, BCG
Lynn Bahta, Immun. Action Coalition
Sharraine Barks, Washington, D.C.
Don Beeman, , Merck Company
Sharon Bell, Decatur, Georgia
Werten Bellamy, Wyeth Company
Brannt Brehn, Merck
Dennis Brodes, Johnson Medical Center
John W. Bosleyo, Merck Company
Sean Campbell, Aventis Pasteur
Dan Casto, San Antonio, Texas
Jill Chamberlain, Vaccine Bulletin
Hillel Cohen, Merck Company
Tim Cook, Merck
Lisa Courtade, Swiftwater, PA
Pat Cota, AAP
Glenna Cwolis, Ft. Washington, PA
Dack Dalrymple, Bailey & Dalrymple
Natalie Devare, Wyeth Company
Frank Dzvonik, SmithKline Beecham
Craig Engesser, Wyeth Lederle
Michele Erstein, Cohne & Wolfe
Nolan Feintuch, Atlanta, Georgia
Nancy Fix- Bloeser, Wyeth Company
Mary Gadek, Lebanon, New Jersey
Eugene Gangarosa, Private
Joe Gangi, OSI
Bruce Gellen, Vanderbilt
Maribeth Gidley, Miami, Florida
Alan Gievert, DeKalb Co. Board of Health
Ruth Gilmore, GA Immunization Prog
Cynthia Good, Good For Patents
Lance Gordon, OraVax, Inc.
Alain Goulet, Nortboro, MA
Jesse Greene, SC Department Health
Kenneth P. Guito, Aventis Pasteur
Neal Halsey, John Hopkins University
Ghrdiner Harris, New York, New York
J. Scott Harward, SmithKline Beecham
Philip Hasegaua, Merck
Bill Hausdroff, Wyeth Company
Jeanne Hayward, Merck Company
Jeff Hickman, Swiftwater, PA
Bita Honarvar, Pediatric News
Phil Hosback, Aventis Pasteur
John Jabara, Philadelphia, Pennsylvania
Clare Kahn, SmithKline Beecham
Achim Kaufhrld, SB Biologicals
Stephanie Keith, North American Vac.
Vanda Kelly, Columbia, South Carolina
Alan Kimure, BIO Chem. Pharm.
Michelle Kirsche, Slack, Inc.
Judy Klein, Merck
A.N. Krishnary, Swell, New Jersey
Tom Lake, Hotboro, Pennsylvania
Len Lavenda, Aventis Pasteur
Jonathan Lipton, Philadelphia, PA
Scott Litherland, Parallax Comm.
Harold Lupton, Aventis Pasteur
Chris Malinowski, Lyme Disease Foundation
Frank Malinowski, Latonsville, Maryland
Paul Mendelman, Aviron
Kathryn Metcalfe, New York, New York
Sherri Michelstein, Cooney/ Waters
Peggy Monkus, Altanta, Georgia
Ardythe Morrow, Center for Pediatric Research
Stan Music, Merck Company
Carla Newby, Meningitis Foundation
Peter Paradiso, Wyeth Company
Dennis Parenti, SmithKline Beecham
James Pilcher, AP
Stanley Plotkin, Aventis Pasteur
Alan Pool, Decatur, Georgia
Jean Popirak, GA Immunization Program
Jill Pulley, Mountain View, California
Sara Radcliffe, PhARMA
Scott Ratzan, Washington, D.C.
Kamal Ravikant, Santa Clara, California
G. Tom Ray
Cassandra Richards, Infect. In Children
Beverly Robertson, Columbus, Georgia
Anne Roger, Parallax Communication
Zeil Rosenberg, Becton Dickenson

David Ross, Merck Vaccine Division
Fred Ruben, Aventis Pasteur
Louis Sanquinl, SmithKlein Beecham
Kristine Severyn, Ohio Parents for Vaccine
Lynn Forsyth Shepherd, Washington, DC
Judith Shindam, Aventis Pasteur
Jeffrey Silber, Merck Company
Howard Six
Natalie Smith, Calif. Dept. of Hlth. Services
Anne Marie Spain, Martinez, Georgia
Stacy Stuerle, Merck Company
Charles Swartz, Peachtree City, Georgia
John Talarico, NYS Dept. of Health
Derik Tauven, Aventis Pasteur
Kay M. Tomashek, GA Dept. Human Resources
Karen Townsend, AAP
Miriam Tucker, Pediatric News
Henrietta Ulkini, Merck
Tom Vernon, Merck
Tuoras Verstraeter, Atlanta, Georgia
Dave Webster, Aventis Pasteur
Deborah Wexler, Imm. Action Coalit.
Brian Williams, Atlanta, Georgia
Melanie Willis, AAP
H. David Wilson, Univ. of North Dakota
Elise Wisnewski, West Point, PA
Steven Wriett
Robert Zeldin, Merion, Pennsylvania

Advisory Committee on Immunization Practices
February 16-17, 2000

FEBRUARY 16, 2000

The Centers for Disease Control and Prevention convened a meeting of the Advisory Committee on Immunization Practices (ACIP), February 16-17, 2000 at the Atlanta Marriott North Central Hotel in Atlanta, Georgia. Dr. John Modlin, Chairman of the ACIP, introduced himself and called the meeting to order at 8 30 a.m. He asked each of the voting members of the committee to introduce themselves and divulge any conflict of interest they might have. He reminded the group that voting members are asked to divulge conflicts of interest in writing and recuse themselves from voting on items with which they have a significant conflict of interest. Liaison and ex-officio members are not required to divulge conflicts of interest.

Drs. Lucy Tompkins and Charles M. Helms stated no conflicts of interest. Dr. Dennis Brooks is involved with Wyeth-Lederle. Dr. Richard Clover received honoraria and/or grants from Wyeth, SmithKline Beecham, and Merck. Dr. Margaret Rennels has vaccine contracts with Wyeth-Lederle, Aventis Pasteur, and Merck. Dr. Chinh Le is employed by a company that is conducting a vaccine study with Merck, Wyeth-Lederle, SmithKline Beecham, North American Vaccine, and Aventis Pasteur. Dr. Paul Offit is co-holder of a patent on a rotavirus vaccine and consults with Merck and Company on development of that vaccine.

Ex-officio and liaison members in attendance:

- Dr. George Peter, National Vaccine Advisory Committee (NVAC)
- Dr. Sam Katz, Infectious Disease Society of America (IDSA)
- Dr. Barbara Howe, Pharmaceutical Researach and Manufacturers of America (PhARMA)
- Dr. Larry Pickering, American Academy of Pediatrics (AAP)
- Dr. Jon Abramson, Chair of the Committee on Infectious Disease, American Academy of Pediatrics (AAP)
- Dr. Rudolph Jackson, National Medical Association (NMA)
- Dr. Yvonne McHugh, Biotechnology Industry Organization (BIO)
- Dr. Paul McKinney, Association of Teachers of Preventive Medicine (ATPM)
- Dr. Pierce Gardner, American College of Physicians (ACP)
- Dr. William Schaffner, American Hospital Association (AHA)
- Dr. Victor Marchessault, Canadian National Advisory Committee
- Dr. Stanley Gall, American College of Obstetricians and Gynecologists (ACOG)
- Dr. David Wilson, American Medical Association (AMA)
- Dr. Richard Zimmerman, American Academy of Family Physicians (AAFP)
- Dr. Eric France, American Association of Health Plans (AAHP)
- Dr. Jane Siegel, Healthcare Infection Control Practices Advisory Committee
- Dr. Douglas Thoroughman, Indian Health Service
- Dr. David Trump, Department of Defense (DoD)

- Dr. Martin Myers, National Vaccine Program Office (NVPO)
- Dr. Kristin Nichol, Department of Veterans Affairs
- Mr. Randolph Graydon, Health Care Financing Administration (HCFA)
- Dr. Michael Gerber, National Institutes of Health (NIH)
- Dr. William Egan, Food and Drug Administration (FDA)
- Dr. Geoffrey Evans, National Vaccine Injury Compensation Program

Opening Comments

Dr. Modlin introduced ACIP Executive Secretary, Dr. Dixie Snider, Associate Director for Science, Centers for Disease Control and Prevention (CDC). Dr. Snider referred to the publicity concerning the way CDC has used funds appropriated for chronic fatigue syndrome and hantavirus and reassured attendees of CDC's commitment to take corrective action. Management controls have been established and exercised to ensure that funds designated for specific activities are used for those activities and that Congress is notified whenever funds appropriated for a specific public health issue are used for some other public health purpose. He announced that Dr. Satcher, the Surgeon General and Assistant Secretary for Health, has appointed a committee headed by Dr. Ed Brant, former Assistant Secretary for Health, to investigate events concerning rotavirus vaccine. Several ACIP members have provided this committee with information for its report to the Assistant Secretary for Health. A session will be scheduled for the June meeting that will address issues relating to the use and development of rotavirus vaccines for developing countries, a subject that was discussed at the World Health Organization (WHO) meeting last week.

Dr. Snider welcomed Dr. Michael Gerber who has replaced Dr. Regina Rabinovich as the ex-officio member from the National Institutes of Health (NIH) and Dr. Douglas Thoroughman who is representing the Indian Health Service. The ACIP's new phone, FAX numbers, and e-mail address were presented. The dates for the next ACIP meetings are June 21-22 and October 18-19. As only 10 appointed members will be present today, Dr. Snider explained that ex-officio members can be temporarily designated as voting members when there are less than seven members qualified to vote due to a conflict of interest.

Dr. Modlin announced that the statements on varicella, Lyme disease, Hepatitis A, and combination vaccines have been published. The harmonized schedule, which was voted on at the October meeting, has also been published.

At the last meeting, Dr. Chinh Le of Kaiser Permanente suggested that the ACIP should consider reducing some doses in the childhood vaccine schedule. Several members have expressed an interest in forming a working group to study this possibility. This working group would include representation from the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), CDC, and the Food and Drug Administration (FDA). The following members volunteered for this project: Drs. Offit, Brooks, Clover, Fleming, Evans, Egan, Myers, Gerber, Marchessault, Pickering, Zimmerman, Howe, Mawle, and Rennels.

Modifications to ACIP Policies and Procedures

Problems requiring urgent attention of the ACIP such as recent issues concerning thimerosal and intussusception after rotavirus vaccine administration sometimes arise between scheduled meetings. To address this problem, Drs. Modlin and Peter organized a working group of National Vaccine Advisory Committee and ACIP members. The purpose of this working group was to suggest to CDC ways for ACIP members to consult with CDC as quickly as possible between meetings without violating federal advisory committee regulations. With input from legal counsel, some changes have been made in ACIP's Policies and Procedures statement that satisfy these criteria.

Dr. Snider presented the following changes that have been made to the ACIP Policies and Procedures document. Section C on page 5 has been added.

Paragraph 2, Section C states:

> If there is a need to consult ACIP members on an urgent or emergency basis, the Executive Secretary may request that the Chair establish and convene an "emergency consultation workgroup" consisting of ACIP members, to discuss the nature of the emergency and possible responses to it. The workgroup will report its findings and recommendations to the full committee.

Paragraph 3, Section C states:

> In exceptional circumstances, either in follow-up to the workgroup consultation or as an initial response to the emergency, the Director of CDC may call an emergency meeting of the ACIP without prior notice in the Federal Register or with less than the usual 15 day notice. If the notice cannot be published at least 15 days prior to the meeting, a Federal Register announcement shall include the reasons for providing less than 15 days notice, as provided under GSA regulations at 41 CFR 101-6.1015(b)(2). If exigent circumstances make publication of the Federal Register notice prior to the meeting impossible, the notice shall be published in the Federal Register as soon as possible after the meeting. In addition, under such circumstances, the agency shall utilize other appropriate mechanisms for providing notice of the meeting prior to its occurrence.
>
> The work group also addressed past difficulties with issues regarding conflicts of interest among ACIP members. The work group intends to add the following new language to the Policies and Procedures document. The major purpose of this language is to retain the expertise of the current panel while alerting people who are nominating prospective members that during their term of service, members will:
> - not hold stock in vaccine companies
> - not serve on the Board of Directors of vaccine companies
> - not be in positions that require them to be active solicitors of funds from vaccine companies

Dr. Le requested clarification regarding honoraria paid to ACIP members. Although drug companies often sponsor speaking engagements, the speaker may be paid with a check that has been issued by a hospital or some other organization. Dr. Modlin said that such honoraria should be declared because the underlying support is viewed as coming from the manufacturer.

Review of Pneumococcal Conjugate Vaccine Statement

Dr. Modlin stated that the ACIP voted at the October meeting on the indications for administration of 7-valent pneumococcal conjugate vaccine (Prevnar ® - PCV7). However, as some ACIP members expressed concerns regarding the indications agreed upon, the Chair requested the work group to reexamine the recommended indications and present their review today.

Dr. David Johnson, Michigan Department of Health, presented the status of FDA licensure. When PCV7 is licensed, the product insert will probably state that the vaccine is indicated for prevention of invasive disease in infants and toddlers and the insert will likely include a schedule, immunogenicity data, and safety data for children up to 9 years of age. Licensure of the vaccine is expected very soon.

New Safety Data

Dr. Chris Van Beneden, National Center for Infectious Diseases (NCID), presented new information regarding the safety data for catch up for children beyond infancy and toddlerhood. She offered combination data from 4 different studies in tabular form, courtesy of Wyeth. No control vaccines were used.

The percentage of children with local reactions such as erythema, induration, and tenderness that occur within 3 days of PCV7 immunization is similar to that for children in the Northern California Kaiser Study for Infant Immunization. However, in one study, the rates for erythema and induration were higher (48%); tenderness was also higher in that study. For catch up vaccination, the number of children experiencing systemic reactions such as fever $\geq$38°C or 39°C was also similar to the Kaiser study. No deaths were attributed to the conjugate vaccine.

Study Among Children in Day Care in Israel

A double-blind, randomized trial was conducted among healthy toddlers attending day care centers in Israel. One of two vaccines was given to these children: either a control vaccine or a 9-valent CRM vaccine, which is the same protein carrier used in the conjugate vaccine. The vaccine used in the Israel study has two extra serotypes.

According to Active Bacterial Core Surveillance (ABCs) data, for children under the age of 2 years, serotype coverage is almost exactly the same for the 7-valent and the 9-valent

vaccines. For children between 2 and 4 years of age, the coverage for the 7-valent vaccine is about 2.4% lower. For older children and young adults, the coverage is markedly different. Therefore, the serotype coverage data can be compared if restricted to children under the age of 5.

Children between the ages of 12 and 35 months were immunized. Those 12-17 months received two doses of the conjugate vaccine; children 18-35 months received one dose, which differs slightly from the U.S. schedule (one dose at 24 months).The primary and secondary study objectives were the effect on carriage of *Streptococcus pneumoniae* and the effects on morbidity indicators and antibiotic use, respectively.

The 131 children in the study received the conjugate vaccine and 130 received the control vaccine. The children were followed up month to month during the first year and every 2-3 months the second year for an average follow-up of 21 child-months. Overall beginning one month after vaccination, carriage among children receiving the conjugate vaccine was 20% and 33% for children receiving control vaccine. Children who had received the conjugate vaccine were less likely to carry vaccine-type *S. pneumoniae* 1 month and longer after immunization.

A statistically significant decrease in carriage of penicillin non-susceptible *S. pneumoniae* as well as a decrease in morbidity occurred among children who received the conjugate vaccine. Evidence exists of herd immunity among the younger siblings of children immunized with either vaccine. Upper and lower respiratory infections and the amount of time children required antibiotics decreased among those receiving the conjugate vaccine.

Discussion

New FDA data on pneumococcal vaccine indicate that the incidence of febrile seizures was increased among the pneumococcal group versus the meningococcal group, when the former vaccine was administered with whole cell pertussis vaccine. Dr. Pratt, FDA, responded that a greater number of febrile seizures occurred within 3 days of vaccination with pneumococcal vaccine. Because the majority of children experiencing seizure had received concomitant whole cell pertussis vaccine, the use of acellular pertussis vaccine is now recommended. Fever over 39° C occurs in about 2-3% of children.

Cost and Cost-Effectiveness of the Pneumococcal Vaccine

The list price for a single dose of this vaccine is $58.00. Contract negotiations are currently taking place, but the federal contract price of the vaccine is not known at present.

Dr.Tom Ray, Kaiser Permanente, presented an analysis of the cost-effectiveness of the conjugate vaccine for healthy infants who had received 4 doses of the vaccine and for toddlers who had received a single dose of catch-up vaccine. The break-even costs for healthy infants receiving 4 doses are $46.00 per dose from the societal perspective and $18.00 per dose from the health care payer perspective. Given the proposed $58.00 charge, there would be net costs from the societal perspective. For toddlers receiving a single catch-up dose, the break-even cost of the vaccine depends on the incidence of pneumococcal disease. For toddler catch-up vaccination,

$58.00 represents a cost saving from the societal perspective for children in day care. This saving does not apply to children not attending day care. Other measures of cost-effectiveness such as cost of life-years-saved are considered crude measures because pneumococcal vaccine also prevents many cases of acute otitis media (AOM) and nonfatal invasive disease.

The cost analysis shows a greater benefit of this vaccine from the societal perspective than the health care payer perspective, which may present the biggest challenge in funding this and other vaccines that will be considered in the future. No evidence exists for quality adjusted life years for episodes of AOM, pneumonia, and nonfatal disease. No additional adverse events were assumed in the cost analysis.

Discussion

Data show that children attending day care have a greater risk (2.4 times higher) for having pneumococcal disease compared with those not attending day care. As efficacy data do not exist for toddlers and these estimates were extrapolated from the rates observed in infants, Dr. Le advised the ACIP to wait to make a statement about cost-effectiveness until more information is available. He cited the Hepatitis A vaccine as a case in point.

Dr. Kristine Severyn, Vaccine Policy Institute, requested that the cost analysis slides shown today be made available to the public later today or tomorrow. Dr. Modlin responded that this information would not be distributed at this time because it has not been published.

Dr. France, American Association of Health Plans, commented that because managed care groups and others have a fixed pot of money, they must prioritize information on prevention services to determine how that money is spent. Dr. Blake Caldwell and Dr. Jeffrey Harris have instituted efforts to prioritize the recommendations that exist in preventive services in terms of their importance. They examined the preventable burden, often described as quality adjusted life-years saved, and cost-effectiveness. Scores are assigned on the basis of quality adjusted life-years-saved and the ability to save cost. Childhood immunization, tobacco efforts, and adult pneumococcal vaccine have received top scores. He advised ACIP to be careful about prioritizing because all of these groups look to ACIP for advice. He proposed that whenever ACIP makes a recommendation on a vaccine, that a table of quality adjusted life-years saved data be attached and that manufacturers provide cost data at the outset of deliberations.

Draft Recommendations for Children

Dr. Johnson continued with his presentation of the modifications suggested by the work group to the tentative recommendations formulated by ACIP at the October meeting. The work group requested that ACIP recommendations be made available when the vaccine becomes available; that the recommendations be as simple as possible; and that there be concurrence between ACIP, CDC, AAP, and AAFP.

The following draft recommendations were agreed on, pending further information, at the October meeting. The recommendations for immunization with pneumococcal vaccine were for all children up through 59 months of age with the following three priorities.

Priority 1:
- All children ≤23 months of age

- Children with very high rates of pneumococcal disease (children with sickle cell disease, functional or anatomic asplenia, HIV infection; children who are immunocompromised or have chronic disease; Alaskan Natives or American Indians)

Priority 2:
- All children 24 to 35 months of age

- Children age 36 to 59 months at increased risk for pneumococcal disease (children who attend group day care, are socioeconomically disadvantaged, or who had frequent or complicated episodes of AOM)

Priority 3:
- All other children 36 to 59 months of age not covered in the other recommendations

The work group suggests the pneumococcal vaccine be recommended for use among the birth cohort for infant immunization and for catch-up vaccination in children through 23 months of age. A second recommendation is that this vaccine be used in children 24 to 59 months of age who have very high rates of invasive disease. Vaccination should be considered for all children 24 to 59 months of age with particular priority given to children in this age range who attend group child care, those who are socioeconomically disadvantaged, and those with frequent or complicated AOM in the previous year. The latest/best information about invasive disease was projected.

Dr. Modlin indicated that the ACIP voted on the draft of the recommendations for the pneumococcal vaccine at the October meeting with the stipulation that if new information became available before licensure, the committee could revisit the recommendations. Dr. Modlin called on Ms. Carla Newby who had asked to make a brief comment before discussion of the recommendations began.

Comment

Carla Newby, General Manager of the Meningitis Foundation of America, whose son died of pneumococcal meningitis, read her letter regarding the ACIP recommendations made at the October meeting that all children up to the age of 5 years be given the new pneumococcal vaccine. She urged ACIP to give strong, clear recommendations that all children be given this vaccine regardless of their age, health status, income level, and ethnic background. She emphasized that the cost of not protecting every child particularly those between 2 and 5 years of age should be the main issue for consideration, not the cost of the vaccine.

Discussion

Dr. Abramson began the discussion stating that the AAP has not taken an official position regarding which groups of children should be administered the vaccine because the AAP is struggling with the need to provide a life-saving vaccine versus its cost-effectiveness. He expressed two primary concerns: where the money will come from to cover a broader range of children and the possibility that physicians might have to choose one vaccine over another. He stated that a two-tiered recommendation might be acceptable to the AAP, but specific wording had not been determined.

Dr. Fleming added that for many states, the cost of the vaccine would be a major factor in determining who would receive it. He favored the new recommendations that have been proposed by the work group today. Dr. Offit emphasized that the benefits of this vaccine clearly outweigh its risks for anyone under the age of 5, but real world issues suggest that determining "the most bang for the buck" is very important. He and Dr. Le discussed the type of language that should be used to avoid misinterpretation of the recommendations.

Because vaccine efficacy begins to diminish at age 4 and continues to drop with increasing age, the ACIP was asked whether it had considered recommending conjugate vaccine for children up to age 3 and switching to the polysaccharide vaccine for those 4. This strategy would cut cost and improve the percentage of coverage. Although the work group has discussed this option, its members chose not to recommend it according to Dr. Johnson. He stated that the recommendations regarding the polysaccharide vaccine may be modified in the future, but the work group chose not to address them at this time, as the polysaccharide vaccine efficacy data for children between 2 and 5 years of age is not impressive.

Dr. Brooks suggested adding the group of children identified as socioeconomically disadvantaged to **Priority 1** after Alaskan natives. Dr. Rennels noted that the markedly higher incidence rate of pneumococcal disease among African-American children 24-35 months of age cannot be ignored and the rational approach would be to include African-American children along with Alaskan Eskimos and Native Americans. She asked for a clearer definition of the term socioeconomically disadvantaged.

Precedent exists for making recommendations for specific racial at-risk groups and CDC policy does not preclude this practice. Dr. Orenstein mentioned the feeling of distrust that many African Americans exhibit regarding immunization. They are concerned they have been targeted for certain vaccines that might have substantial side effects. Some members believed a race-based inclusion might make the recommendations easier to implement, whereas others favored age-based recommendations. Dr. Rennels argued that disease incidence should have the most impact on whether this inclusion should be made. Dr. Jackson noted that the incidence of pneumococcal disease among other minorities such as Latinos has not been addressed.

According to Dr. Van Beneden, little data exist for other ethnic minorities, which would make it difficult to reliably estimate their incidence of pneumococcal disease. Dr. Schwartz stated that data involving small numbers of the Northern California Latino population in the

Kaiser Infant Study clearly indicated no increased risk of pneumococcal disease among this ethnic group. Dr. Peter suggested that if a racial group is identified, the recommendations should state that socioeconomic status is not a factor. He stated further that it is most important to agree on recommendations that can be reconsidered and revised on a yearly basis if necessary as more information is learned about the vaccine after licensure takes place.

Dr. Abramson suggested adding a fourth category to include "anyone else for whom the vaccine is requested" so that the recommendations confer to health care providers the ability to give the vaccine to anyone requesting it. Dr. Le noted that the data representing African Americans is inflated because it does not exclude children with sickle cell disease and HIV. On the basis of his calculations regarding this overlap of the two groups, Dr. Schwartz indicated that about 10% of the increased risk among African-American populations is related to sickle cell disease.

Concern was expressed regarding implementation of the vaccination program for all children following licensure because of the limit to the amount of vaccine that can be distributed. Dr. Modlin explained that no cohort has ever been totally vaccinated within 3 months of licensure with the possible exception of the polio vaccine; it has taken years for complete vaccination to be accomplished in the past. Dr. Tomkins agreed that all children up through 23 months of age and those in the highest-risk groups should be vaccinated first, a choice that is now identified as the new Option B.

Public Comment

Dean Mason, a representative of the National Immunization Program (NIP), stated that health care providers have certain sensitivities and hesitate to ask patients about their racial identity. If ACIP votes into the recommendations that children 24-59 months of age can be considered for vaccination, then the Vaccination for Children (VFC) program will cover the cost of the vaccine for anyone who wants it. Many states require health insurance plans to cover vaccinations if they are recommended by ACIP.

Peter Paradiso, representing Wyeth, mentioned the short–term cost burden of this vaccine relative to the benefit from a public health perspective and his view of this chance to immunize children on a broad scale as an opportunity. The children who will derive the most cost-effective benefit are 24-36 months of age because they receive a single dose and that group has a considerable disease burden up to age 5.

Dr. Merelman suggested that reductions in illness similar to those that occurred with the *Haemophilus influenzae* type B (Hib) conjugate vaccine could occur with PCV7 provided the ACIP takes action to recommend vaccination for children under 5 years of age. Dr. Le responded that the colonization data is insufficient to support the idea that disease will decrease as a result of immunizing more toddlers. He favors incorporating a statement that permits parents and providers who request the vaccine to receive it.

Regarding the magnitude and severity of pneumococcal disease, Dr. Schwartz contrasted it with *H. influenzae* type b infection, which is much more severe. He stated that invasive pneumococcal disease is most often an outpatient disease characterized by fever. The data from the Kaiser efficacy study indicate that 16 of 17 patients were managed as outpatients; only one patient required hospitalization. Adverse event data demonstrate that the attributable rate of excess fever is up to 10%. For children 24-59 months of age, about 2% will have fever higher than 39° C. The Kaiser study data also indicate that 10 to 30/100,000 children will develop febrile seizures attributable to the vaccine. Douglas Pratt, FDA, stated that the seizure rate for this vaccine is low compared with historical data for the pertussis vaccine. Anne Schuchat of the Respiratory Diseases Branch, CDC, noted that 50% of children having invasive disease are hospitalized, so the data from the Kaiser study may not be representative. Dr. Le disagreed that the mortality rate for children with pneumococcal meningitis is 30%; Dr. Modlin agreed, stating that 5-18% is the rate most often quoted.

The issue before the committee, according to Dr. Modlin, is whether to include all children under 36 months of age in the first priority group as an age-based recommendation or whether to include African-American children in the high-risk groups under 35 months of age. Dr. Johnson reviewed the two options for the committee's consideration:

Option 2B:
Recommended vaccine use:

- all children ≤23 months of age
- children 24-59 months of age, including African-American children, those with sickle cell disease and HIV, Native Americans, Alaskan Native Americans

The vaccine should be considered for:

- children 24-59 months of age (with priorities for children in day care, socioeconomically disadvantaged children, children with frequent/complicated acute otitis media (AOM))

Option 2C:
Recommended vaccine use:

- all children ≤35 months of age
- children at high risk 36-59 months of age, not including African-Americans

The vaccine should be considered for:

- children 36-59 months of age

The voting members discussed the options in detail and stated their preference. As a result of this discussion, a third option, **Option 2D**, was added.

Option 2D:

Recommended vaccine use:

- all children ≤23 months of age
- high risk children 24-59 months of age, not including African-Americans
- African-American children 24-35 months of age

The vaccine should be considered for:

- children 24-59 months of age (with higher priority given to those in day care, socioeconomically disadvantaged and those with recurrent acute otitis in the previous year)

Dr. Helms made a motion to adopt Option 2B, which was seconded by Dr. Tompkins. Representatives from the AAP and the AAFP were asked for their input regarding Option 2B. The AAP would support 2B provided the statement "and anyone else who requests this vaccine" was added. Dr. Modlin requested that members vote only on the option on the table, and the addition of the statement suggested by the AAP can be discussed at a later time. The AAFP would support either option.

Dr. Modlin asked for a VOTE to adopt Option 2B:

- all children ≤23 months of age
- children 24-59 months of age, including African-American children, those with sickle cell disease and HIV, Native Americans, Alaskan Native Americans

The vaccine should be considered for:

- children 24-59 months of age (with priorities for children in day care, socioeconomically disadvantaged children, children with frequent/complicated acute otitis media (AOM))

Potential financial conflicts of interest required the Executive Secretary to designate the ex-officio members as voting members.

In Favor:	Johnson, Helms, Tomkins, Evans, Gerber, Myers
Opposed:	Offit, Modlin, Fleming, Graydon
Abstain:	Le, Clover, Brooks, Rennels, Nichol, Trump, Egan
Absent:	Guerra, Word
Outcome:	Passed

Update on Revision of the General Recommendations

Dr. Le thanked members of the work group who are working to finalize a Draft Statement of the general recommendations, which should be ready to present at the June ACIP meeting. The revised general recommendations will focus on technical considerations regarding vaccine safety. Clear policy statements need to be made on the following issues:

- violations of the minimum age and/or the minimum interval between doses of a multidose vaccine and the appropriate language to describe the grace period

- appropriate management of persons who receive two or more parentally-administered live attenuated viral vaccines less than 28 days apart

- the ACIP policy on accepting vaccinations administered outside the United States

Roger Bernier presented data regarding the progress made thus far. The work of the subgroup on Decision Rules has been integrated into the general recommendations, and the work group has attempted to produce a proposal that reflects the concerns of constituents and Program Managers. The current proposal creates a grace period around each of the recommended ages for vaccinations and around each of the recommended intervals between doses. The changes in the new proposal are ones of implementation and in the way the information within it is communicated.

Issues for Discussion and Decision

Dr. William Atkinson, NIP, Information Services Division (ISD) presented the issues before ACIP:

1. **Violations of the youngest recommended age and/or shortest recommended interval between doses of a multidose vaccine.**

First introduced in 1983 as part of the *General Recommendations on Immunization*, the concept of a minimum interval is frequently faced by state immunization programs. Data indicate that violations are common. According to the 1997 National Immunization Survey, 23% of children had one or more vaccine violations.

The current recommendation states that doses of vaccine administered "at less than the recommended intervals may decrease the antibody response and therefore should be avoided. Doses administered at less than the recommended minimum interval should not be considered as part of the primary series." This statement has been interpreted as meaning that anything less than the minimum interval or age should be repeated; intervals and ages are illustrated in a widely distributed table of information, Table 10.

The concept of defining and incorporating a "grace period" into the *General Recommendations on Immunization* was introduced to and endorsed by ACIP at the October 1999 meeting. The actual length of the grace period needs to be defined in order to create an algorithm for computerization of immunization recommendations. For reasons of practicality, the ACIP Workgroup on the Standardization of Decision Rules proposed that the length of the grace period be four days.

Little immunogenicity data exist regarding intervals of less than one month. Dr. Atkinson stated by way of clarification that the grace period should be considered a retrospective assessment of a dose that should/should not be excluded from the schedule; it is an enforcement issue. Dr. Atkinson advocates simplicity in this matter, requesting that the same grace period be applied to all antigens and all doses, unless ACIP determines a need for exceptions.

Discussion

Dr. Weniger from the audience advised the ACIP be very precise when defining the grace period. In response, Dr. Atkinson referred to "Table X," the revision of Table 10, which uses weeks rather than days for calculating the validity of a dose.

Because of the obvious general agreement (indicated by nodding heads) among the voting members to define the grace period as 4 days, Dr. Modlin stated there would be no need to take a formal vote on this issue.

Discussion ensued concerning Part B of this question: whether the 4-day grace period should be applied to all antigens or whether live attenuated vaccines specifically Measles, Mumps, and Rubella (MMR) and varicella should be excluded. The simplest choice that would avoid legislative confusion or changes in state regulations regarding school entry is to make this grace period apply to all antigens. Dr. Zimmerman suggested adding a compromise clause that a grace period applies unless state laws override. Dr. Orenstein pointed out that MMR is administered "on or after the first birthday" in many states. Bob Snider, NIP, said that more than three fourths of the states selected the first birthday as the cutoff point for MMR. Dr. Peter explained that in many states, it is the Board of Health that makes these regulations, not the state legislature.

Dr. Modlin asked the voting members their opinion about excluding MMR. Dr. Fleming remembered that ACIP voted to exclude MMR in a previous ACIP meeting. Dr. Snider stated that since the initial vote occurred in an earlier meeting, the issue can be reconsidered today.

Dr. Tompkins made a motion to adopt the recommendation for a grace period to apply to the MMR and varicella vaccines, which Dr. Offit seconded.

Dr. Modlin asked for a **VOTE to adopt the recommendation for a grace period to apply to the MMR and varicella vaccines.**

In Favor:	Offit, Le, Rennels, Clover, Brooks, Tompkins, Modlin
Opposed:	Johnson, Fleming, Helms
Abstain:	None
Outcome:	Passed

Dr. Atkinson presented the following recommendation, which had been accepted by ACIP in 1996 and was again accepted today:

The fourth dose of DTP/DTaP should be administered to children 12-15 months of age and at least 6 months after the third dose. However, ACIP recommends that the fourth dose of DTP/DTaP not be repeated unless it has been administered less than 4 months after the third dose.

2. The next issue concerns the need for a clear statement regarding nonsimultaneous administration of live attenuated vaccines.

The following wording is found in the *General Recommendations on Immunization*: "when feasible, live virus vaccines not administered on the same day should be given at least one month apart." Guidance from ACIP is needed regarding violation of this recommendation.

No additional studies have addressed this issue specifically since the work in 1965 of Petralli et al. in which the authors postulated that the decreased response to smallpox vaccine was caused by interferon production induced by the measles vaccine. The decision posed to ACIP is as follows:

What should be ACIP's recommendation for the management of persons who have received parenteral live virus vaccines less than 30 days apart (or 28 days/4 weeks for consistency with other interval formats)?

Two options were proposed:
Option 1:
A parenteral live virus vaccine not administered on the same day but separated by fewer than 4 weeks following another live virus vaccine should be repeated at an interval no less than 4 weeks after the invalid dose (the vaccine given second).

Option 2: Two or more parenteral live virus vaccines may be administered on the same day. Administration of two or more parenteral live virus vaccines within a 4-week period (i.e., separated by 1-28 days) should be avoided because of theoretical concerns about interference with the immune response by different vaccines. However, if two or more parenteral live virus vaccines are administered fewer than 4 weeks apart, neither vaccine dose need be repeated.

Discussion
An audience member urged caution because of the lack of data regarding the measles and varicella vaccines. Tom Vernon stated that the product label for MMR indicates a 3-month interval. No interference was noted between measles vaccine and yellow fever vaccine with very short intervals. Dr. Orenstein is concerned about the lack of data and feels that this is not the right time to make a change in the recommendations.

Dr. Modlin noted the informal agreement among ACIP members to accept Option 1: a 4-week interval with a 4-day grace period. Violations of the grace period will require

reimmunization; however, if a titer documents an adequate response, the dose would not need to be repeated. Dr. Modlin stated there was no need for a formal vote on this issue because Option 1 is so strongly favored by ACIP.

3. The acceptability of vaccines administered outside the United States.

The 1994 *General Recommendations on Immunizations* states:

> "the acceptability of vaccinations received outside the United States depends primarily on whether receipt of the vaccine was adequately documented and whether the immunization schedule (i.e., age at vaccination and spacing of vaccine doses) was comparable with that recommended in the United States. Any dose [with written documentation] administered at the recommended minimum interval [and ages] can be considered valid."

New information gathered by Dr. Peggy Hostetter of Yale University suggests that this recommendation needs revision. Of 55 adoptees from Eastern Europe, China, and Russia, only 38% had adequate antitoxin titers for DTP. The disparity is greatest among children adopted from orphanages. She and other physicians in the adoption community recommend repeating all doses for children who have received three or fewer doses of DTP in their home country and checking titers in children receiving more than three doses. However, limited data exist regarding children from countries other than Eastern Europe, China, and Russia.

The decision before the committee is should ACIP modify its position for acceptability of vaccinations received outside the United States in light of the paucity of data that exists. Three options are offered for ACIP's consideration:

Option 1: **No change in the current recommendation**. Accept doses if supported by written documentation, and if supported by written documentation, comply with current recommended ages and intervals for a *compressed* vaccination schedule. All written vaccination records should be examined carefully to ensure compliance with U.S. ages and intervals.

Option 2: Accept documented doses that comply with U.S. recommended ages and intervals **except for children adopted from orphanages in Eastern Europe, China, and Russia**. For these children, vaccines should be repeated or repeat vaccination on the basis of serologic testing.

Option 3: **Add to Option 2 the recommendation to evaluate certain subgroups based on the number of documented doses** as recommended by Dr. Hostetter and others. For example, repeat all doses of MMR and Hib, repeat all doses of DTaP if three doses or fewer of DTP are documented. For children with more than three documented doses, consider serologic testing for diphtheria and/or tetanus antitoxin to determine the need to repeat some or all doses.

Discussion

Dr. Modlin suggested tabling this issue until the June meeting because of the complexity of the topic. The ACIP would like to examine Dr. Hostetter's data more closely, perhaps by inviting her to make a presentation to ACIP at the June meeting, in order to make an informed decision. No one objected to his proposal, and the topic was tabled.

Decision: Tabled

Update on Adult Immunization Recommendations

Dr. Richard Clover introduced several topics reviewed by the Adult Working Group: acellular pertussis vaccine for adolescents and young adults, pneumococcal disease in persons 50-64 years of age, adverse events following immunization with yellow fever vaccine, and revision of the ACIP recommendations for adult immunization. Not all of these issues will be addressed in this session of the ACIP; those not addressed will be covered in detail in subsequent meetings.

Update on Standing Orders for Immunization

Dr. Linda McKibben, Epidemiology Program Office (EPO), stated that the Adult Immunization Working Group suggests the following revisions in the recommendations for settings and target populations.

- Add "workplace and employees" to the list of settings and target populations.
- Delete "65 and older" as part of the wording
- Delete a condition for vaccinations other than pneumococcal vaccine. (Last sentence of earlier version: "If state or local public health surveillance data show significant vaccine-preventable disease burden, SOPs are also recommended for other vaccines, such as Hepatitis B vaccine in correctional facilities or tetanus or diphtheria toxoids for the elderly.")
- Changes were made to the final paragraph of the Recommendations section regarding program or vaccine safety to improve scientific accuracy. Some references were moved as well.

Discussion

Although hospital vaccination has been warmly accepted in certain institutions, the terminology "standing orders" has been rejected by some physicians because they feel they are losing autonomy. Although alternative wording may be considered more palatable, ACIP chose to retain the present wording.

Dr. Clover made a motion to accept these modifications to the Recommendations, which was seconded by Dr. Fleming.

Dr. Modlin asked for a **VOTE to accept these modifications to the Recommendations**:

- Add "workplace and employees" to the list of settings and target populations.
- Delete "65 and older" as part of the wording
- Delete a condition for vaccinations other than pneumococcal vaccine. (Last sentence of earlier version: "If state or local public health surveillance data show significant vaccine-preventable disease burden, SOPs are also recommended for other vaccines, such as Hepatitis B vaccine in correctional facilities or tetanus or diphtheria toxoids for the elderly.")
- Changes were made to the final paragraph of the Recommendations section regarding program or vaccine safety to improve scientific accuracy. Some references were moved as well.

In Favor:	Offit, Le, Johnson, Brooks, Fleming, Clover, Helms, Tomkins, Modlin
Opposed:	None
Abstain:	Rennels
Outcome:	Passed

Update of Adverse Events Associated with Yellow Fever Vaccine

Dr. Cetron, National Center for Infectious Diseases, presented new activity concerning yellow fever vaccination. A 56-year-old healthy physician concurrently vaccinated for yellow fever and typhus developed high fevers 4 days after vaccination. Within a short time, he developed what was originally thought to be encephalitis and died. Autopsy results revealed a large, necrotic liver and central herniation of the brain. Other laboratory findings were negative or inconclusive.

Discussion

In the case of yellow fever presented at the last meeting, the virus was isolated and cultured from CSF and serum and was sequenced using RT-PCR. As the etiology of the case presented today has not been determined, the role of vaccination is unclear. Dr. Cetron stated that he has an opportunity to examine other data sets of adverse events from Britain and Brazil.

This case presentation highlights weaknesses in the vaccine safety surveillance network; with additional funding, it is hoped that vaccine safety assessment centers will be instituted to establish protocols and provide clinical data. Because of the inconclusive nature of this case the work group has opted to leave the wording of the recommendations as it stands.

Review of Current Recommendations for Pneumococcal Vaccine

Dr. Clover presented the work group's interest in new data about smoking and its association with increased risk of pneumococcal disease;its concern regarding whether at-risk adults, particularly African-Americans, are being adequately covered by current ACIP recommendations for immunization; and whether the polysaccharide vaccine should be recommended for all persons 50 to 64 years of age.

Dr. Cynthia Whitney, NCID, presented recent data indicating that smoking and having young children in day care are significant risk factors for adult invasive pneumococcal disease (IPD). Racial disparity in disease incidence is evident, according to the emerging infections program, Active Bacterial Core Surveillance (ABCs), with African Americans younger than 65 having much higher rates than whites ≥65 years of age. Some of the disparity can be attributed to the higher prevalence of HIV/AIDS among younger age groups, which is a strong risk factor for IPD. The majority of deaths due to IPD occur among adults age 65 and older.

James A. Singleton, NIP, presented current vaccination coverage data elicited through the National Health Interview Survey (NHIS). NHIS is an annual national household survey conducted among the civilian, non-institutionalized U.S. population that monitors progress for Healthy People objectives. African-Americans over age 65 have the highest incidence of high-risk conditions that indicate a need for the pneumococcal vaccine. Those with an identified risk have a higher vaccine coverage rate. Adding smoking as a risk factor increases the estimates of the prevalence of persons with high risk conditions. The rates of vaccination for influenza are higher than for pneumococcal vaccine. Vaccination rates increase with an increase in the number of physician contacts that occur in a 12-month period. At-risk adults age 50-64 years are more likely to get a flu shot than the pneumococcal vaccine. Barriers to vaccination delivery include those that affect both patients and physicians.

Discussion

For adults, self-reporting of pneumococcal vaccination is a sensitive but not very specific (~70%) measure. Studies show that a significant number of people who stated that they had not received pneumococcal vaccine had actually received it. The burden of invasive disease is likely underestimated as well. Dr. Jackson noted the low rate of immunization for influenza among health care workers; in fact only about one third of health care workers receive annual influenza vaccination.

Overview of Pneumococcal Vaccine Effectiveness

Dr. Strikas indicated that two published studies best address the issue of pneumococcal polysaccharide vaccine (PPV) effectiveness in persons 50-64 years of age. Shapiro et al. published a case-control study in 1991 that suggested the effectiveness of PPV declined over time and with increasing age. A 1993 study published by Butler et al. employed the indirect cohort method; it demonstrated no difference in effectiveness for the age groups studied and no change in protection over time. Neither study clarifies the actual duration of protection.

The cost of a one-time PPV vaccination without revaccination is modest for persons 50-64 years of age (as determined by Whang and Sisk, unpublished data). The cost-effectiveness of PPV vaccination compares well with other preventive measures for this age group such as colorectal cancer screening and annual mammograms. The vaccine is considered very safe. According to Vaccine Adverse Event Reporting System (VAERS) data for 1991-1999, the most frequently reported adverse outcomes were local in nature. Not much difference was found between the first and second doses. Outcomes temporally associated with vaccination included edema, pain, pneumonia, and fever.

Pneumococcal Revaccination

Dr. Cynthia Whitney, NCID, reviewed the current ACIP recommendations concerning revaccination with pneumococcal vaccine. Persons immunized for the first time at age 65 or older should receive only one dose. Persons who are not immunocompromised but who have heart or lung disease or other chronic conditions or live in special environments or settings should be vaccinated when their situation is first diagnosed; they should be revaccinated at age ≥65 years, if at least 5 years have passed since the first dose. Immunocompromised persons should be revaccinated 5 years after the first dose. No efficacy or cost-effectiveness data exist for revaccination with PPV.

Preliminary Safety and Immune Response Data

Dr. Jeff Silber of Merck Research Laboratories presented data concerning local reactions and immunogenicity associated with PNEUMOVAX® 23 vaccination in adults who had been immunized 5 years previously. A secondary goal was to determine systemic safety for those over 65 and in a younger cohort aged 50 to 64 years who had been immunized at least 3 years before. Although immunocompromised patients were excluded from this study, those with chronic diseases were not.

The safety analysis showed no serious adverse events associated with vaccination. The younger age group (50-64) reported more local and systemic adverse events than did the older group (>65), but this finding was also evident among those receiving placebo. Symptoms such as headaches, chills, and body aches were reported most often. The rates of adverse events for the group receiving revaccination were higher than for primary vaccination.

Local reactions whether mild or severe peaked on day 1 and were gone by day 3. Analgesic use was low although it was higher among those undergoing revaccination than primary vaccination. Compared with initial vaccination, revaccination induced significantly lower antibody titers for 4 of 8 serotypes tested among persons 65 years of age, and significantly lower titers for 6 of 8 serotypes for persons ages 50-64.

Dr. Whitney reviewed a study conducted by Jackson et al. of patients 50-74 years of age who had never been immunized or who had been immunized at least 5 years earlier. Side effects were measured after administration of 23-valent polysaccharide vaccine. Immune response was measured in a subset of this group.

No serious adverse events occurred among these patients. Local side effects occurred most often among revaccination patients; this group was also more likely to have a local reaction >4 inches compared with those undergoing primary vaccination. No increased risk of large local reactions occurred in immunocompromised persons. The risk of local reaction correlated with prevaccination type-specific antibody level. Two other small studies indicate a higher frequency of adverse events when healthy adults are revaccinated within 2 years of the first dose; some uncontrolled or small studies indicate no difference if the second dose is given 5 years or more after the first dose.

Opsonophagocytic titers (Jackson et al., unpublished data) rise following both first vaccination and revaccination, although the rise is not as high for the latter. Therefore, the immune response may not be as great following revaccination. In closing her presentation, Dr. Whitney stated that several issues concerning PPV are unknown at this time:

- the duration of protection following vaccination
- frequency and severity of adverse events after a third dose, particularly in those who had a local reaction to the second dose
- vaccine efficacy among African-Americans, smokers, and following revaccination
- cost-effectiveness of vaccination at age 50 if revaccination at 65 is considered
- whether the immune responses observed with revaccination correlate with clinical protection

Discussion

Physicians are receptive to immunizing their patients because of the increase in the proportion of strains of pneumococci that are resistant to currently available antimicrobial agents. According to Dr. Ruben, when compared with subcutaneous (SQ) administration, intramuscular injection (IM) of a polysaccharide meningococcal vaccine reduces local reactions by more than half. This effect probably carries over to other vaccines as well.

Dr. Gardner suggested that smoking should be considered an indication for pneumococcal immunization because thousands of cases of pneumococcal disease could be prevented. High-risk groups such as African Americans should also be considered for immunization. Dr. Schwartz stated that a universal recommendation beginning at age 50 might be risky because healthy adults 50 years of age would require revaccination when they are older and the efficacy of revaccination is unknown. More information is needed about the level of

compliance with revaccination recommendations already established; about the acceptability of adverse events; and about how well people respond to revaccination. He advised addressing the needs of high-risk groups first.

Regarding local reactions, Dr. Silber reiterated that they were all self-limited and not serious. To establish whether the supply of the vaccine is sufficient to cover a broader cohort of vaccinees, a Wyeth representative stated that additional information would be required from ACIP as to the number of serotypes and the level of efficacy needed from such a vaccine. Education of health care providers is necessary to reinforce the need, and raise the rates, for immunization. The National Medical Association has recommended that those age 65 and older be vaccinated.

Dr. Modlin stated that because availability of a conjugate vaccine for adults is unlikely in the near future, the ACIP will ultimately have to make decisions regarding expanding the indications for polysaccharide vaccine. He suggested developing some specific options for the June agenda, perhaps revisiting the data presented today, and making some decisions regarding this issue at the June meeting.

Decision: Tabled

Use of DTaP as the Fifth Dose of the DTaP Series

Dr. Melinda Wharton, NIP, reported that only one of the currently available acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DTaP) is licensed for use as the fifth dose of 5-dose series (ACEL-IMUNE®, Wyeth-Lederle Vaccines and Pediatrics). A second vaccine, Tripedia® (Aventis Pasteur, Inc.) is currently under consideration for licensure for use as the fifth dose following four previous doses of Tripedia®. Mixed sequences are not licensed for any of the vaccines. In the United States, there are four DTaP vaccines currently licensed for use in infants. These vaccines differ in several ways: the number of pertussis antigens included, the methods of preparation of those antigens, the diphtheria toxoid content, the tetanus toxoid content, the aluminum content, and the preservatives used.

Safety Issues

Safety data were gleaned from several studies. Local reactions such as erythema and induration were lower among those who had previously received 3 does of whole cell vaccine than among recipients of four doses of acellular pertussis vaccine. Following administration of acellular vaccine, the reactions were often large sometimes involving swelling of the thigh and an increase in thigh circumference. An increase in the reactogenicity of dose 4 was demonstrated for all four of the currently licensed products.

Dr. Margaret Rennels presented data from the NIH-supported multicenter trials of the safety and immunogenicity of fourth and fifth consecutive doses of various DTaP vaccines.

After dose 4, 2% (n=20) of children given the same DTaP for all four doses had swelling of the entire thigh, and 6.3% (n=1) of children receiving whole cell vaccine had swelling of the entire thigh. Boosting with DTaP after priming with whole cell vaccine did not produce the same effect. Increased rates of irritability, erythema, and early mild pain were reported among those with thigh swelling, but severe pain was uncommon.

Entire thigh swelling was reported after dose 4 with 9 of 12 vaccines tested. A trend toward increasing rate of swelling was noted with the concentration of all vaccine contents, especially the diphtheria toxoid content, which was statistically significant. Dr. Rennels advocated standardization of methods of data collection and reporting in the future to make the decision-making process easier on advising committees.

Dr. Wharton reported that the frequency of significant reactions following the fifth dose in a 5-dose series of Lederle DTaP was about 20% for redness and 13% for swelling. Unpublished data regarding the frequency of redness and swelling >50 mm was substantial for the Aventis Pasteur DTaP as well. A follow-up study of the SmithKline Beecham DTaP vaccine administered to children as a 5-dose series indicated similar findings. With increasing dose number of the DTaP vaccine, the frequency and severity of local reactions increases. No data were available for the fifth dose of the other U.S. licensed acellular pertussis vaccine.

Discussion

The AAP advocates education of parents regarding the significant number of local reactions observed with all of the vaccines and is concerned about the need to administer this vaccine in five rather than four doses. Dr. Karen Farizo, FDA Medical Reviewer, explained that extensive areas of redness and swelling were not recognized as a problem with U.S.-licensed whole cell pertussis vaccine, but these reactions have been a problem associated with Canadian vaccines. Dr. Marchessault, Canadian National Advisory Committee on Immunization, replied that more reactions occurred after the fifth dose when absorbed DTP was used. However, he added that these reactions may have occurred because the vaccine was administered SQ rather than IM. Reactions after the fourth dose do not preclude a fifth dose.

Licensure and Mixed Sequence Vaccines

Three vaccine manufacturers are currently seeking licensure from the FDA for their vaccines to be used for the 5-dose series according to Dr. Wharton. None of the DTaP vaccines are licensed for use as a mixed sequence.

Although data regarding efficacy and safety are sparse, interchangeability has not been demonstrated to raise rates of adverse events. The frequency of mixed sequence vaccination is unknown, and it is unclear whether this practice of nonstandard immunization has resulted in the recent increase of pertussis.

Update of Pertussis in the United States

Dr. Linda Zanardi, NIP, reported that following the introduction of the DTP vaccine in the late 1940s, a dramatic decrease occurred in the number of pertussis cases reported in the United States. Since 1980, that trend has changed. In the late 1990s about 6700 cases/year were reported. Infants have the highest incidence rate particulary those $\leq$3 months of age; however, the incidence rate is rising in other age groups as well, especially among persons 10 to 19 years of age. Polymerase chain reaction (PCR) may be replacing culture as the primary diagnostic method.

Discussion

Data regarding pertussis among persons $\geq$10 years of age shows that many cases were confirmed by epidemiologic linkage instead of laboratory testing, which may be associated with school outbreaks. About 0.2% of reported cases for 1998 were imported cases.

Language of the Pertussis Vaccine Statement

Dr. Wharton read the following from the previously published pertussis vaccine statement:

> Whenever feasible, the same brand of DTaP vaccine should be used for all doses in the vaccination series. Data do not exist regarding safety, immunogenicity, and efficacy of using DTaP vaccines from different manufacturers for successive doses of the primary booster vaccination series. However, the vaccine provider may not know or may not have available the type of DTaP vaccine previously administered to a child. Neither circumstance should present a barrier to administration of the vaccine and any of the licensed DTaP vaccines may be used to complete the vaccination series.

This statement does not cover the possibility that a vaccine given in four doses may not be licensed for the fifth dose. Dr. Wharton proposed the following addition to the recommendation for the committee's consideration:

In circumstances in which the provider does not know which DTaP vaccine a child received or knows but does not have that vaccine available, the ACIP recommends that the provider use whatever DTaP vaccine he or she has available even if that would result in administering a mixed sequence of DTaP vaccine or using a vaccine that is not currently licensed for use as a fifth dose following four doses of that vaccine.

Discussion

The FDA has addressed the issue of mixing and matching of vaccines and whether it is advisable to follow four doses of an unlicensed vaccine with a licensed vaccine for the fifth dose. Dr. Egan suggested that this DTaP recommendation be considered an interim recommendation until other vaccines become licensed. In "the real world" mixing and matching of vaccines is commonplace. Physicians use whatever vaccine is on hand and rarely ask the patient to recall the

name of the manufacturer of vaccines previously administered in the series. Reality and practicality should drive the form of the recommendation that is adopted. The problematic language of the last sentence in the draft statement was discussed:

> If the DTaP vaccine previously given is not known, is not available, or has not yet been approved for the entire 5 dose series, the vaccine provider should administer any licensed DTaP as the fifth dose when age-appropriate.

Continuation of protection from disease is the most important issue when considering vaccines containing differing concentrations of components such as toxoid. A more liberal policy would prevent states from violating the standard of care. Although all the vaccine manufacturers intend to seek licensure of the fifth dose, there is concern that they now have the opportunity to have their vaccine used for the fifth dose without doing the necessary studies to achieve licensure. Dr. Egan stressed that a qualification stating the temporary nature of this recommendation would help prevent such an unfavorable event from occurring.

Public Comment

A spokesperson from Aventis Pasteur stated that Tripedia® should be licensed for the fifth dose relatively soon. Reported reactions of swelling of the entire or upper arm following administration of Tripedia® is about 3% in clinical trials, a fact that needs to be communicated to physicians and parents. In the future, more widespread reporting of reaction rates to clinical centers for evaluation will be encouraged.

Voting members were polled concerning their views regarding the two questions requiring the attention of ACIP. Those issues are whether ACIP should encourage use of any licensed DTaP vaccine for the fifth dose and the extent to which ACIP should encourage that the fifth dose be from the same manufacturer as previous doses.

A difficult problem for the interim is the use of drugs for an unlicensed or off-label indication. ACEL-IMUNE® is the only vaccine currently licensed for five doses. By way of clarification, Dr. Karen Farizo, FDA, explained that acellular pertussis vaccines that are licensed for the first four doses are licensed for a fourth or fifth booster dose following a primary series with whole-cell pertussis vaccine. Forty-three states offer provider choice at some level for any of the vaccine products. Access to these vaccines is not a factor.

Dr.Wharton presented the draft that has been circulated to the membership:

Although administering a single DTaP vaccine for the entire series is preferred, using a different DTaP vaccine from that previously received is preferable to deferring vaccination. If the DTaP vaccine previously given is not known, not available, or has not yet been approved for the entire 5 dose series, the vaccine provider should administer any licensed DTaP as the fifth dose when age-appropriate.

Several suggestions were made regarding changes in the wording so it would reflect the preference of ACIP for use of a licensed product from the same manufacturer for a given vaccine series. Dr.Wharton indicated the intent was to state a preference for using a single product with the understanding that this may not happen in practice.

As the term "licensed" was deemed ambiguous in this context, either "current" or "available" were suggested as a replacement. The final wording that was agreed upon follows:

> Data do not exist regarding the safety, immunogenicity, and efficacy of using DTaP vaccines from different manufacturers in a mixed sequence.
>
> Although administering a single DTaP vaccine for the entire series is preferred, using a different DTaP vaccine from that previously received is preferable to deferring vaccination. If the DTaP vaccine previously given is not known, not available, or has not yet been approved for the entire 5-dose series, the vaccine provider should administer any available DTaP as the fifth dose when age-appropriate.

Dr. Helms made a motion to include this new wording in the draft statement, which was seconded by Dr. Fleming.

Dr. Modlin asked for a **VOTE to include this new wording in the draft statement:**
Data do not exist regarding the safety, immunogenicity, and efficacy of using DTaP vaccines from different manufacturers in a mixed sequence.
Although administering a single DTaP vaccine for the entire series is preferred, using a different DTaP vaccine from that previously received is preferable to deferring vaccination. If the DTaP vaccine previously given is not known, not available, or has not yet been approved for the entire 5-dose series, the vaccine provider should administer any available DTaP as the fifth dose when age-appropriate.

In Favor:	Offit, Le, Johnson,Clover, Helms, Brooks, Tomkins, Modlin, Fleming, Helms, Rennels
Opposed:	None
Abstain:	None
Outcome:	Passed

The vote on this issue concluded the day's business. The meeting was adjourned at 6:30p.m

February 17, 2000

Dr. Modlin convened the meeting at 8.30 a.m. and announced that a quorum was present. Dr. Walter Orenstein will replace Dr. Snider as the acting Executive Secretary today.

Update of 1999-2000 Influenza Season

Dr. K. Fukuda, NCID, reported statistics relating to the current flu season in the U.S. He named the vaccine strain selections for the prevailing and upcoming flu seasons, which have just been announced by WHO.

According to vaccine surveillance data, the onset of this year's flu season took place 4 to 6 weeks earlier than the previous two years. Although the clinical and virological parameters have been similar to those of the past two years, mortality has been higher this season. Media interest has been higher as well. Almost all isolates this season have been Influenza A, subtype H3N2 Sydney virus.

The number of cases peaked during 1999 week 51 - 2000 week 2, with the highest number of physician visits reported in the west south central region of the country followed by the Pacific region. The excess pneumonia and influenza (P & I) mortality rate is clearly higher this season than for the last several seasons and was: 8.4% for week 52 of 1999 and 11.2% and 9.9% for weeks 3 and 6, respectively, of 2000. Factors affecting mortality include infectious agents (incidence/virulence); population factors (levels of immunity, vaccine coverage and effectiveness); changing behaviors (international travel); population characteristics (number of elderly with chronic conditions); and measurement issues.

Since their first appearance in 1968, H3N2 viruses have caused more illness and death than H1N1 and B viruses. The vaccine match appears to be good this season; approximately 90 million doses of flu vaccine were produced and distributed in the U.S.

Older age is a significant risk factor for P & I mortality. More than 90% of influenza-related deaths occur among the elderly, and the number of elderly persons is increasing. Implementation of new ICD-10 coding for pneumonia decreased P & I death statistics dramatically (~60%). In fact, the coding for pneumonia may be modified by WHO because of the worldwide impact of this change.

The mortality reporting system (MRS) surveillance case definition of P & I death was expanded, in part, to counter the effect of the ICD-10 coding change. The MRS case definition now describes a P & I death as "influenza anywhere on the death certificate" or "pneumonia anywhere on the death certificate." This methodological change to a multiple cause case definition does not totally account for the increase in P & I deaths seen this season.

In the future, earlier access to NCHS data will promote earlier determination of final P & I estimates. Vaccine effectiveness data will be available later this year. Analysis of virus isolates is ongoing.

Discussion

Although close correlation exists for the circulation of RSV and influenza viruses, the impact of RSV is not as significant among the elderly as in younger populations. Dr. Fukuda stated that it would be difficult to determine the incidence among the elderly of misdiagnosis of influenza-like illnesses that are actually due to RSV. Dr. Modlin commented that new data suggest RSV does contribute to some morbidity and mortality among the elderly in adult intensive care units.

Vaccine effectiveness is determined using a variety of methods. One technique compares the rates of hospitalization for vaccinated and nonvaccinated adults. As most people were vaccinated between the middle of October and the middle of November, it is unclear why the current flu season began early. Dr. Kristine Severyn, Vaccine Policy Institute, referred to a published report that the increased media attention given to this year's flu season was fueled by drug company ad campaigns for their new influenza drugs.

Changes to the Influenza Vaccine Recommendations

Dr. Carolyn Bridges, NCID, stated that new references and additional resources regarding outbreak infection control issues have been added to the ACIP recommendations regarding influenza vaccination. Several changes have been made to the ACIP recommendations for the control and prevention of influenza:

1. A statement adding persons aged 50-64 to other groups targeted for annual influenza vaccination was accompanied by an explanation of the reasoning for this recommendation (voted on October, 1999).

Comments:

Dr. Orenstein asked for a clarification of the benefits of widespread immunization of healthy people aged 50-64 years. Dr. Bridges explained that the rationale for this change is based upon evidence that many at-risk individuals in this age group do not get vaccinated and the increased prevalence of high-risk conditions in this age group. In addition, other preventive measures begin at the age of 50.

Immunization of healthy working adults is cost-effective and reduces lost work time. This addition to the recommendations should be advertised to the news media because communication via the media educates consumers, caregivers, and health care providers. Even though this change is an age-based strategy, it is important to use new technology to continue to identify at-risk populations. Increasing the rates of influenza immunization is expected to decrease antibiotic use.

Additional changes made to the ACIP recommendations:

2. Information on health care worker vaccination rates was added.

Comments:

The wording of this change should emphasize that it is imperative for health care workers to undergo immunization. Coverage for this benefit was urged.

3. Information on other vaccine components such as thimerosal was added. The new wording indicates that manufacturers may/may not have thimerosal-free vaccine available for 2000-2001.

4. A modification was added to the recommended timing for organized vaccination programs in response to disruptions caused by the late delivery of vaccine that occurred this season. Scheduling of these events after mid-October is advised.

Comments:

Vaccine availability may not correspond to the optimal time for administration. Practitioners may require sufficient latitude in the recommendations in order to administer the vaccine earlier than recommended, if necessary. No vaccine shortage occurred this season. Considering the vagaries involved in making and distributing vaccine, it is best to be a little less specific and build in a "cushion" of time in the statement.

5. The wording in the vaccine for travelers section was clarified and now states that the benefit of revaccinating in the spring for summer travel is unknown.

6. The section stating a preference for the use of DTaP over DTP when administered with influenza vaccine was removed because ACIP now recommends exclusive use of acellular pertussis vaccine.

Comments:

As smoking is a significant risk factor relative to the severity of influenza, smoking risk should be addressed in both the influenza and pneumococcal recommendations.

7. A statement about standing orders for vaccination of nursing home residents was added; other locations/environments will be added as well.

8. The section that addresses addition of person aged 50-64 years to the group recommended for vaccination was updated.

9. The section regarding recommendation of vaccination of young children was rearranged; a statement that the ACIP work group will consider safety issues and other consequences of recommending this vaccine for young children was included.

10. A statement was added regarding laboratory diagnosis.

11. Statements on the use of antiviral medication were added.

12. Information was added regarding neuraminidase inhibitors.

13. A statement was added on the use of antiviral agents in pregnancy.

Discussion

The suggestion was made to add the statement "standing orders should be considered" in acute care hospitals. Immunization of pregnant women will result in passive immunization of children less than 6 months of age; eventually the recommendation for immunization of children may be extended to include children under 3 years.

Despite the focus of recent media attention on antiviral drugs rather than the availability of the influenza vaccine, ACIP still recognizes the value of using the media to educate the general public about this vaccine. Although the NIP has addressed various ways to promote the message about adult immunization, this effort has been limited because funding has been limited. Dr. Orenstein stated that the 317 Grant Program does allow states to use funds for implementation of adult immunization service delivery. The funding of this program is currently under review.

Dr. Modlin requested that the committee vote on the changes and additions to this recommendation today because publication of this statement is scheduled for April 14. After some discussion regarding conflict of interest, Dr. Modlin determined that all the voting members would be eligible to vote on this issue. Dr. Helms made a motion to adopt the changes to the Influenza Recommendations, which was seconded by Dr. Tomkins.

Dr. Modlin asked for a **VOTE to adopt the changes to the Influenza Recommendations:**

1. A statement adding persons aged 50-64 to other groups targeted for annual influenza vaccination was accompanied by an explanation of the reasoning for this recommendation (voted on October, 1999).

2. Information on health care worker vaccination rates was added.

3. Information on other vaccine components such as thimerosal was added. The new wording indicates that manufacturers may/may not have thimerosal-free vaccine available for 2000-2001.

4. A modification was added to the recommended timing for organized vaccination programs in response to disruptions caused by the late delivery of vaccine that occurred this season. Scheduling of these events after mid-October is advised.

5. The wording in the vaccine for travelers section was clarified and now states that the benefit of revaccinating in the spring for summer travel is unknown.

6. The section stating a preference for the use of DTaP over DTP when administered with influenza vaccine was removed because ACIP now recommends exclusive use of acellular pertussis vaccine.

7. A statement about standing orders for vaccination of nursing home residents was added; other locations/environments will be added as well.

8. The section that addresses addition of person aged 50-64 years to the group recommended for vaccination was updated.

9. The section regarding recommendation of vaccination of young children was rearranged; a statement that the ACIP work group will consider safety issues and other consequences of recommending this vaccine for young children was included.

10. A statement was added regarding laboratory diagnosis.

11. Statements on the use of antiviral medication were added.

12. Information was added regarding neuraminidase inhibitors.

13. A statement was added on the use of antiviral agents in pregnancy.

In Favor: Offit, Le, Rennels, Johnson, Fleming, Clover, Helms, Brooks, Tompkins, Modlin
Opposed: None
Abstain: None
Outcome: Passed

Update on Lyme Vaccine

Dr. Ned Hayes, NCID, presented vaccine safety information gleaned from VAERS data. VAERS is a passive surveillance system for monitoring adverse events and is a collaborative effort between CDC, NIP, and FDA. LYMErix™ is the Lyme Disease vaccine manufactured by SmithKline Beecham that was licensed by the FDA on December 21, 1998. More than one million doses were distributed in the first year after licensure. Approximately 500,000 individuals have received the vaccine.

In its first year, 386 adverse events associated with LYMErix™ were reported to VAERS. More adverse events were reported in women and in states having endemic Lyme disease. The median age of recipients was 50 years (range, 15-82 years). The adverse events

were severe enough to require hospitalization in about 5% of cases. Two deaths were reported. Autopsies performed on the two men who died 1 and 3 days after vaccination demonstrated that both had hypertensive cardiovascular disease.

Adverse events including myalgia, injection site reactions, arthralgia, headache, fever, chills and fever, tremor, pain, asthenia, flu-like syndrome, and chills. Most of these occurred within 1 day of vaccination, a few appeared up to 30 days after vaccination. Twelve cases of arthritis and eight cases of facial paralysis were reported. Adverse events, particularly cases of arthritis and facial paralysis, will be monitored as data accumulates regarding the Lyme vaccine.

Discussion

The majority of adverse events occurred after the first dose of LYMErix™. Four patients suffered permanent disabilities: 1) rheumatoid arthritis and peripheral edema; 2) deafness; 3) osteoporosis, pain, joint disease, and necrotic bone; 4) myasthenia neuritis and paresthesias. None of the adverse events of facial paralysis occurred in individuals younger than 15 years of age.

Safety of LYMErix™

Dr. Dennis Parenti, SmithKline Beecham, addressed the existing long-term safety data collected for LYMErix™.

Follow-up data, 21-36 months after vaccination, indicate 11 cases of arthritis among original vaccinees. However, none of the cases of arthritis were considered related to the vaccine. Five cases of paresthesia had other etiologies as well.

One source of booster data, study Lyme 017, indicated no serious adverse events and two cases of noninflammatory arthritis. For Lyme 016, two adverse events occurred; however, both complications were related to the primary series. No late-onset vaccine-related events occurred. Another ongoing study of booster safety, conducted among patients receiving booster vaccine 12 months previously, demonstrates no vaccine-related arthropathy and no unusual pattern of adverse events to date.

Of the ten subjects in the database who met the criteria for the definition of inflammatory arthritis (joint swelling), six cases appear to be new. One case of facial palsy was due to Lyme disease itself and was not vaccine-related. This situation highlights the difficulty that sometimes occurs in determining whether an adverse event is related to vaccination or to some other cause.

Alternate Dosing Schedules

Dr. Parenti stated that alternate dose schedules are needed for this vaccine to provide maximum protection in a shorter period of time. The goal is to administer the first two doses at any time and the third dose just prior to the season of exposure. Two studies (schedule: 0,1,6 or

0,1,2) demonstrate no increased risk associated with administering three doses of vaccine over a shorter period of time.

A serum level of 1400 ELISA units of total IgG correlates with a high probability of protection in the ensuing year. The post-dose 3 data from the efficacy trials demonstrate Geometric Mean Titers (GMT) from all three dosing schedules that would confer protective ability one month after vaccination. The FDA is currently reviewing the alternate dose schedule data.

Pediatric Trials

A double-blind, randomized, open-label dose selection pilot study was done among children 5-15 years of age in Europe. They received a 3-dose regimen (schedule: 0,1,2). No adverse events occurred with subsequent doses. The vaccine was well tolerated and was more immunogenic in children than adult subjects. This information was recently published in the *Journal of Pediatrics*.

A double-blind, placebo-controlled trial in the U.S. was performed in ~4,000 subjects between 4 and 18 years of age. This group received the vaccine on a 0, 1, 12 schedule. Safety data for these children were similar to that for adults. For solicited adverse events, there was a higher incidence of local injection site reactions and self-limited flu-like illness. After two doses, IgG titers rose to seroprotective levels that are similar to those in adults after three doses.

Sales of the vaccine are highest in highly endemic areas, especially the northeast region of the U.S. The vaccine coverage rate in highly endemic areas is less than 3%.

Discussion

Dr. Parenti stated that the episodes of afebrile chills and tremors are reportedly uncomfortable, but are short-lived, usually appearing immediately after vaccination takes place. He outlined an ongoing Phase-4 case cohort study at Harvard Pilgrim Health Plan designed to evaluate adverse events, particularly inflammatory arthritis. A large number of patients will be followed for ~4 years and ICD-9 codes will be recorded. An interim report of the findings of this study is likely in mid-summer.

In response to Dr. Abramson's question about side effects, Dr. Parenti stated that it does not appear that side effects increase with increasing doses. The possibility that two doses may be sufficient for children is being considered. It is unlikely that a pediatric vaccine will contain an antigen concentration lower than 15 micrograms (mcg).

Two dosing schedules (0,1,12 and 0,1,6) have comparable rates regarding persistence of antibodies. According to new data before the FDA, a booster may be indicated 12 months after the third dose.

Two-Dose Adolescent Hepatitis B Vaccine

Dr. Modlin pointed out that only one Hepatitis B vaccine is now licensed for the 2-dose adolescent dose schedule. The ACIP has been asked to make a recommendation stating whether either or both of the two Hepatitis B vaccines can be used for this indication. The public health benefits associated with passing this recommendation include simplifying the schedules and purchase of vaccine for the Vaccines for Children (VFC) program. The purpose of today's discussion will be to determine if sufficient data exist to decide whether the two vaccines are equivalent.

Dr. Hal Margolis, NCID, began the presentation by pointing out articles relevant to Hepatitis B vaccination that have appeared recently in the medical literature. He stated that past ACIP recommendations regarding Hepatitis B vaccine have not been totally "in sync" with the package insert, illustrated by the following historical experience with this vaccine.

The active prophylaxis recommendations that ACIP introduced in 1987 were based on data from trials done in China. These studies did not employ vaccines licensed in the U.S. at that time. Data from a subsequent off-shore trial was never presented to the FDA. Another example concerns data from a clinical trial presented to ACIP that were never published; these data promoted a change in the dosing schedule (from 0,1,6 to 0,1-6), which made a big difference in implementation. The third example relates to use of the combination vaccine (COMVAX – combined Hib and Hepatitis B) to complete the postexposure regimen.

Trials Outside the United States

Dr. Betsy Abraham, SmithKline Beecham, reminded ACIP that at the last meeting, Merck and Company announced that the FDA has approved use of two doses of their hepatitis vaccine at the adult dosage (10 mcg) for adolescents 11-15 years of age on a schedule of 0, 4 - 6 months. She presented the case for approving identical use of Engerix-B (20 mcg), produced by SmithKline Beecham.

Engerix-B is currently licensed for adolescent use (schedule: 0, 12, 24 months in adolescents 15-16 years of age) and for adolescents at the adult dosage on a 3-dose regimen. Two dosage strengths of Engerix-B are printed on the package insert: the usual adolescent dosage, 10 mcg, and an alternate dosage of 20 mcg. Both dosages are currently licensed on a 0,1,6-month schedule.

The data from three non-U.S. studies illustrate the immunogenicity of the two-dose regimen of Engerix-B among children 11-18 years of age. The study design of a study conducted in Canada was single-blind randomized in three groups; in Taiwan, open randomized in two groups; and in Belgium, single-blind, randomized in three groups. The seroprotection rate at months 7 after vaccination ranged from ~92 to 95% for 11-15 year olds on a 2-dose schedule based on the studies done in Canada and Taiwan. The Belgium study demonstrated much lower GMTs among older adolescents (16-18 years) compared with younger adolescents (11-15 years) at month 7; all subjects were on a 3-dose schedule.

Discussion

According to Dr. Abramson, the AAP is concerned that the 2-dose regimen costs more than the 3-dose schedule. The Chief of Marketing for SmithKline Beecham responded that the cost of these vaccines is comparable. As this vaccine is recommended for a limited age range (11-15 years), confusion regarding its implementation may result in the market. Vaccination schedules should be flexible enough to capture adolescents adequately. The simplest schedule will gain the most compliance.

Dr. Egan stated that the FDA does not consider these vaccines generically equivalent. The 10 mcg Merck product was licensed for a 2-dose regimen in October, 1999 for adolescents 11-15 years old (schedule: 0,4 - 6) after FDA review. He suggested submitting the SmithKline data to the FDA for review, a point that prompted discussion whether it is appropriate for ACIP to make a decision on this issue or whether it should be turned over to the FDA. Dr. Snider stated that such issues have been decided on a case-by-case basis and that there is flexibility within both the FDA and ACIP. As FDA has expressed a preference to examine the data, Dr. Snider stated that it would be best to not take any action today that would preclude further discussion with FDA concerning this issue. Dr.Orenstein stated that as ACIP has an obligation to sometimes make decisions in the interest of public health when data are not available there is likely to be some tension between ACIP recommendations and the information on the package insert approved by the FDA. Since the committee had not received the information presented today in written form before the meeting, it may be difficult to make an informed decision without having sufficient time to review all the data.

Dr. Modlin asked the voting members how they felt about making a decision today versus having additional time to request more data and think over their decision. Dr. Offit stated that if Dr. Egan is uncomfortable, he would be as well.

Dr. Rennels requested reactogenicity data, which Dr. Abraham provided in tabular form. Redness, swelling, and soreness all occurred at low rates for both the 20 mcg 2-dose and 10 mcg 3-dose schedule; more reactogenicity occurred with three doses. No grade 3 (serious) symptoms occurred although headache, fever, and malaise were reported.

Dr. Fleming requested that ACIP not defer this issue as many states are in the process of trying to implement adolescent school-based entry requirements for Hepatitis B. The current untenable situation is that the school must know the manufacturer of the product to determine whether a student is adequately covered.

Dr. Brooks stated that he would prefer a simpler regimen. Dr. Offit cautioned that, despite the FDA issue, ACIP should not exclude a vaccine that is probably going to work as a 2-dose schedule. Dr. Howe added that the data presented today is all that is available from the manufacturer and by the time more data were generated, it would be irrelevant to the target population.

Public Comment

Dr. Brolin, Merck Vaccine Division, emphasized that the data show these vaccines are not identical; he has data showing that the first dose response is strikingly different. He commented that the respective roles of ACIP and FDA and the process used to make a determination of equivalence should be reevaluated.

Dr. Modlin asked for a show of hands of voting members who have a conflict of interest with either Merck or SmithKline. Six members indicated no conflict; however, this is not enough for a quorum. It would be necessary to deputize the ex-officio members to have a vote today. Dr. Modlin polled the members regarding their desire to vote today on the issue of a 2-dose regimen for the Hepatitis B vaccine:

In Favor:	Johnson, Fleming, Tompkins
Opposed:	Helms, Brooks, Modlin, Myers, Evans, Gerber

Dr Modlin stated that as the majority of members oppose voting, an official vote would not be taken today and ACIP will issue no recommendation regarding this regimen at this meeting. Dr. Snider suggested that discussions take place between CDC, FDA, and the manufacturer about the adequacy of the data and what can be inferred from the data. Dr. Fleming said he would like to have results of those discussions for the next meeting. Dr. Orenstein suggested that additional published information should be included as well.

Vaccines for Children (VFC)

Rotavirus: Dr. Ben Schwartz, NIP, presented the draft VFC resolution for rotavirus. Before the last ACIP meeting, the manufacturer withdrew the vaccine from the market and ACIP voted at that same meeting to withdraw its recommendation for use of this vaccine. Today's resolution would repeal the earlier VFC resolution for rotavirus vaccination.

Dr. Johnson made a motion to accept the draft resolution for rotavirus, which was seconded. Dr. Modlin asked how many members have a conflict of interest with Wyeth. Ex-officio members were deputized in order to have a quorum.

Dr. Modlin asked for a **VOTE to accept the draft resolution for rotavirus**.

In Favor:	Offit, Johnson, Fleming, Helms, Tompkins, Evans, Modlin, Gerber, Graydon, Trump
Opposed:	None
Abstain:	Le, Brooks, Rennels
Outcome:	Passed

Polio: The second VFC resolution for consideration would replace the previous resolution regarding polio vaccine. The new resolution recommends replacing the sequential schedule of administering inactivated polio vaccine (IPV) and oral polio vaccine (OPV) with a regimen in which all four doses are IPV, reserving OPV for specific groups of children. Eligible groups include all children 6 weeks of age to 18 years of age. Recommended dosage intervals, contraindications, and precautions for administration, approved previously, have not been altered.

Dr. Johnson made a motion to accept the draft resolution for polio vaccine, which was seconded by Dr. Rennels.

Dr. Modlin asked for a **VOTE to accept the draft resolution for polio vaccine:** The new resolution recommends replacing the sequential schedule of administering inactivated polio vaccine (IPV) and oral polio vaccine (OPV) with a regimen in which all four doses are IPV, reserving OPV for specific groups of children. Eligible groups include all children 6 weeks of age to 18 years of age. Recommended dosage intervals, contraindications, and precautions for administration, approved previously, have not been altered.

Potential financial conflicts of interest required the Executive Secretary to designate the ex-officio members as voting members.

In Favor:	Offit, Johnson, Fleming, Helms, Tompkins, Evans, Modlin, Gerber, Graydon, Trump
Opposed:	None
Abstain:	Le, Brooks, Egan, Rennels
Outcome:	Passed

Dr. Atkinson suggested that the wording of the first two sentences of this resolution be modified to "the recommended interval of 8 weeks" from "the recommended minimum interval of 8 weeks," to reflect the previous day's discussion about intervals. Since there were no objections to this suggestion, Dr. Snider indicated the committee's acceptance of this change.

Hepatitis B: Dr. Schwartz introduced the new resolution for the Hepatitis B vaccine, which incorporates the use of a 2-dose vaccine (Merck) schedule for children 11-15 years of age. Eligible groups remain the same: unvaccinated children and adolescents from birth to 18 years of age. This resolution includes specific dosages for the groups identified as eligible for post-exposure immunoprophylaxis. Other changes include the 2-dose catch-up vaccination schedule for adolescents and specifics regarding the minimum dose interval for the 2- and 3-dose schedule.

The suggestion was made to substitute the word "licensed" to "recommended" in the footnote regarding the 2-dose catch-up vaccination. The committee agreed to this change.

Dr. Johnson made a motion to accept the draft resolution for the Hepatitis B vaccine, which was seconded by Dr. Tompkins.

Dr. Modlin asked for a **VOTE to accept the draft resolution for the Hepatitis B vaccine**: The new resolution for the Hepatitis B vaccine incorporates the use of a 2-dose vaccine (Merck) schedule for children 11-15 years of age. Eligible groups remain the same: unvaccinated children and adolescents from birth to 18 years of age. This resolution includes specific dosages for the groups identified as eligible for post-exposure immunoprophylaxis. Other changes include the 2-dose catch-up vaccination schedule for adolescents and specifics regarding the minimum dose interval for the 2- and 3-dose schedule. Substitute the word "licensed" to "recommended" in the footnote regarding the 2-dose catch-up vaccination.

Potential financial conflicts of interest required the Executive Secretary to designate the ex-officio members as voting members.

In Favor:	Johnson, Fleming, Helms, Tompkins, Evans, Modlin, Gerber, Graydon, Trump, Brooks
Opposed:	None
Abstain:	Offit, Le, Rennels, Egan
Outcome:	Passed

Pneumococcal Conjugate Vaccine: Dr. Modlin announced that the pneumococcal conjugate vaccine was licensed today. Dr. Schwartz reviewed the recommendations the ACIP agreed to yesterday.

The ACIP recommends the pneumococcal conjugate vaccine for:

- All infants at least 6 weeks of age and for catch-up immunization of children ≤23 months of age

- Children between 24 and 59 months in high risk groups (sickle cell disease, HIV, specific immunocompromising illness, specific chronic conditions), African-American, Native American, and Alaskan Native American children

Pneumococcal conjugate vaccine should be considered for:

- All children 24-59 months of age with priorities for children in day care, socioeconomically disadvantaged children, and those with frequent/complicated AOM during the previous year

The purpose of this resolution is to add pneumococcal conjugate vaccine to the VFC program and to consolidate the previous resolution pertaining to pneumococcal polysaccharide vaccine into this resolution. It clarifies when each vaccine should be used and specifies the chronic illnesses that indicate use of the polysaccharide vaccine.

Pneumococcal Conjugate Vaccine: All children between 6 weeks and 59 months of age are considered eligible for pneumococcal conjugate vaccine. The recommended schedule includes a primary series and booster dosing based on the age immunization was first begun. Children with immunocompromising or chronic conditions would receive 2 doses and healthy children one dose if vaccination is initiated at >23 months of age. Children who have specified chronic illnesses should receive a single dose of polysaccharide vaccine after conjugate vaccine at a minimal interval of 2 months. American Indian and Native Alaskan children should only receive either vaccine, but should not receive the vaccines sequentially. The recommended interval in the primary series is 2 months with a minimum interval of 6 weeks. Contraindications and precautions for vaccination include allergy to vaccine components and acute, moderate, or severe illness with or without fever.

Pneumococcal Polysaccharide Vaccine: Children and adolescents between 2 and 18 years of age with functional or anatomical asplenia, immunocompromising illness, a specified chronic illness, a bone marrow transplant, or who are Alaskan Native or American Indian are eligible for pneumococcal polysaccharide vaccine. There is no change to the recommended vaccine schedule or dosage intervals. Contraindications and precautions for vaccination include allergy to vaccine components and acute, moderate, or severe illness with or without fever, and pregnancy.

Discussion

As pneumococcal disease occurs with greater frequency among those with immunocompromising and chronic illnesses, the recommendation to follow conjugate vaccine with polysaccharide will broaden the scope of protection in these children. This practice does not increase the rate of adverse events in those with sickle cell disease. Conjugate vaccine alone was not recommended for American Indian and Alaskan Native populations because it would cover only 50-60% of the serotypes distributed within their communities.

The ACIP discussed the broad language Dr. Schwartz chose to describe the groups eligible for the conjugate vaccine. He offered an alternative for the ACIP to consider. Dr. Orenstein proposed the following modification to the original definition to maintain the tenor of the recommendation: vaccination may be considered for all other healthy children 24-59 months of age.

Dr. Johnson suggested that several members prefer Dr. Schwartz's second option regarding eligible groups with the following modifications:

Conjugate Vaccine to Prevent Pneumococcal Disease Eligible Groups

All infants and children at least 6 weeks of age through 23 months of age

All children in the following groups who are between 24 and 59 months of age with particular consideration for

• Children with functional or anatomic asplenia including those with sickle cell disease;

• Children with immunocompromising illness (i.e., HIV infection or AIDS, malignancies, chronic renal failure, nephrotic syndrome, organ or bone marrow transplant) or who are receiving immunocompromising medications;

• Children with chronic conditions that increase the risk of pneumococcal infections or their complications (i.e., chronic cardiopulmonary disease excluding asthma, diabetes mellitus, or CSF leak);

• African American, Alaskan Native, and American Indian children;

• Children who attend out of home day care and who have recently experienced frequent or complicated episodes of AOM

Dr. Abramson reiterated his earlier concern that the recommendations be structured to allow parents who request the vaccine to have it. Dr. Fleming stated his concern that these changes imply fiscal obligations that may be considerable As ACIP acts as a "payroller for the taxpayer," Dr. Fleming stated a need for fiscal information regarding the cost of the proposed changes to the resolution. An audience member stated that the commercial price of the conjugate vaccine is $58.00, but negotiations are under way to lower that price if possible. Dr. Fleming calculated that the vaccine eligibility described here would cost the taxpayers about $1 billion, a figure that greatly exceeds the cost of other public health programs.

After the lunch break, discussion resumed regarding the VFC resolution on pneumococcal conjugate vaccine. Dr. Fleming proposed delaying a vote today and suggested an open conference call meeting among ACIP members as soon as possible to discuss complex issues such as the cost burden attendant to this resolution. He made a motion to table the issue to vote on the VFC resolution on pneumococcal conjugate vaccine, which was seconded by Dr. Offit.

Dr. Modlin asked for a **VOTE to table the issue regarding the VFC resolution on pneumococcal conjugate vaccine.**

In Favor:	Offit, Rennels, Johnson, Fleming, Helms, Tompkins, Modlin, Brooks
Opposed:	None
Abstain:	Le
Outcome:	Passed

Dr. Modlin stated that ACIP would organize a conference call to address VFC draft options as soon as possible. He asked Drs. Fleming and Offit to work with Dr. Schwartz in preparing a draft of options of this resolution for distribution to ACIP members in advance of the conference call. Dr. Johnson volunteered as well for this mini-working group.

Review of Bioterrorism and Anthrax

Dr. C. Helms opened the session stating the ACIP/ImVac Joint Bioterrorism Working Group was formed to assist CDC with issues regarding the civilian use of vaccines for prophylaxis and treatment of diseases of highest concern for bioterrorism. The two vaccines under current study are the anthrax vaccine for prevention of anthrax and the vaccinia vaccine for the prevention of smallpox.

This work group has prepared a draft of recommendations addressing the effectiveness and safety of the anthrax vaccine; pre-exposure use of the vaccine in bioterrorism and non-bioterrorism situations; post-exposure use of the vaccine in potential bioterrorism situations; the number and route of vaccinations; and future research. He requested that members review the draft that has been distributed and contribute their input so this issue can be addressed more fully at the next ACIP meeting.

Control and Prevention of Anthrax

Dr. Dave Ashford, NCID, presented the existing draft regarding the control and prevention of anthrax focusing on the use of anthrax vaccine in the U.S. These recommendations concern the use of the aluminum hydroxide adsorbed cell-free Anthrax Vaccine Adsorbed (ADA) for protection against disease caused by *Bacillus anthracis*. Also included is information on the use of chemoprophylaxis against *B. anthracis*. The draft contains scientific data already presented at the October ACIP meeting.

Vaccine Safety: Prelicensure data indicate that local and systemic reactions continue to be low. Postlicensure adverse events surveillance reveals that pregnant women should not be vaccinated unless absolutely necessary and anthrax vaccine is contraindicated for persons having a previous anthrax infection or who have experienced anaphylaxis after vaccination.

Pre-exposure administration of vaccine is recommended for occupational and laboratory exposure, particularly for persons engaged in activities with a high potential for aerosol production, and for bioterrorism preparedness. Regarding bioterrorism preparedness, the work group has determined that:

> *some sense of a calculable risk assessment* should be made but *at present, the target population for a bioterrorist release of B. anthracis cannot be predetermined and the risk of exposure cannot be calculated. In addition, studies suggest an extremely low risk of exposure due to secondary re-aerosolization of previously settled B. anthracis spores. Because of these factors, pre-exposure vaccination for the above groups is not recommended* in bioterrorism planning. Other options such as post-exposure antibiotic prophylaxis can be used in the event of bioterrorism.

Currently, there is no FDA-approved regimen for post-exposure prophylaxis with antibiotics approved for the treatment of anthrax. Little data exist regarding the efficacy of chemoprophylaxis alone and in combination with vaccine following exposure to *B. anthracis* spores.

The work group concluded that:

> *postexposure prophylaxis against B. anthracis is recommended following an aerosol exposure to B. anthracis spores. Such exposure may occur following a laboratory accident or a biological terrorism incident. Prophylaxis may consist of antibiotic therapy alone or the combination of antibiotic therapy and vaccination, if vaccine is available. Because of the potential persistence of spores in vivo, it is recommended that antibiotic therapy be continued for at least 30 days if used alone. And although the supporting data is less definitive, longer antibiotic therapy (up to 42-60 days) may be indicated. If vaccine is available, antibiotics may be discontinued after 3 doses of vaccine have been administered (0, 2, and 4 weeks). Doxycycline or ciprofloxacin may be chosen initially for antibiotic chemoprophylaxis until organism susceptibilities are known; however, neither drug is FDA-approved for this use.*

Research Agenda:

The work group proposed institution of the following research efforts:

- animal immunogenicity studies
- clinical and safety evaluation of the vaccine to include comparison of routes of adminstration and a reduction in the number of inoculations needed
- enhanced surveillance through the VAERS system that would include electronic reporting
- reactogenicity and pre-exposure strategies evaluation
- more research into post-exposure antibiotic therapy, especially in combination with the vaccine

Dr. Ashford explained that Congress has given CDC a mandate to evaluate issues regarding AVA. In 1999, $20 million was transferred to CDC for the collaborative study of the safety and efficacy of this vaccine including determining the risk factors for adverse events, immunological correlates, and optimal vaccination schedules. Agencies cooperating with CDC in this effort, including NIH and the Department of Defense (DoD), have formed an interagency scientific work group on anthrax vaccine research with representatives from NIP, NCID, FDA, the United States Army Medical Institute of Infectious Diseases (USAMRID), and the Anthrax Immunization Program.

Language of the Existing Document: Members of the work group have disagreed about the language regarding unpublished data from a DoD pilot study dealing with a change in the route of administration of the vaccine and a reduction in the number of doses.

The intent of this section, according to Dr. Schwartz, is to provide flexibility to physicians in the DoD who are administering this vaccine to service members. Although the studies are investigational, the data allow clinicians to make adjustments for service members who may have experienced a previous adverse event. Because of the nature of the data, the sentence *"At this time, the ACIP cannot recommend changes in vaccine administration"* has been added to this section of the document.

Dr. J. Grabenstein, DoD, began his presentation by clarifying the work group's recommendation: the anthrax vaccine is not necessary for bioterrorism purposes for the civilian population but is recognized as having value for military personnel in the event of biowarfare.

Dr. Grabenstein presented data from in a USAMRID pilot study of AVA showing a quick rise in IgG concentrations following the first 3 doses of the 6-dose schedule; however, correlation of this finding with immunogenicity has not been established. When dosing intervals between the first two doses were prolonged, the serological response rate and titers increased substantially. ELISA evaluations demonstrated similar, faster serological protection with the different dosing regimens compared.

Women experienced more SQ side effects than men. A change from SQ administration to IM dramatically reduces injection site reactions but has little effect on the rate of systemic reactions.

The ACIP unanimously endorsed inclusion of this data in the document. Dr. Modlin proposed adding the following statement as well: *These regimens are not yet FDA-approved.*

Discussion

Dr. Le suggested that concurrent research be started on chemoprophylaxis as antibiotic research is likely to be less expensive and quicker than vaccine research. Dr. Helms responded that although no MIC data exist regarding antibiotic regimens, Dr. Le's point was well made. Dr. Helms invited ACIP members to express their comments regarding the direction and progress of this work group.

Dr. Gardner suggested that ACIP review other vaccines on a regular basis, particularly when an adverse event is reported such as that associated with the yellow fever vaccine. Dr. Snider responded that CDC was specifically asked to address those agents that have potential for bioterrorism such as anthrax. Dr. Abramson stressed the urgent need for more research into antimicrobial prophylaxis as no data currently exist for protecting or treating children exposed to anthrax.

Agency Updates

National Center for Infectious Diseases (NCID)

Dr. A. Mawle, Office of the Director, stated that a recent DNA sequencing workshop held at CDC resulted in CDC's designation as the strain repository for varicella. This designation

will not only benefit strain surveillance and studies of the impact of the vaccine but future varicella genome research as well.

She documented an outbreak of *H. influenzae* type B that recently occurred in six Pennsylvania Amish children under the age of 3 years, which was investigated by the Division of Bacterial and Mycotic Diseases. As all these children were unvaccinated, this area of the country should be considered underserved. Studies conducted in two different districts revealed low carriage rates of 27% and 3%, and typing studies demonstrated different types. There was no religious objection to vaccination, but the parents did not consider it a priority.

National Immunization Program (NIP)

Dr. Orenstein announced provisional data for 1999 indicating substantial reductions in morbidity for eight vaccine-preventable diseases, especially measles. Indigenous transmission of measles in the U.S. will likely be considered eliminated as all of the 100 cases reported last year are thought to be imported. Immunization coverage levels are at their highest reported levels: for most vaccines coverage is greater than 90%. Combined 4:3:3:1 series data show coverage of 79%; however, significant state-to-state variations are apparent. Decreasing immunization trends are occurring in some cities.

The President has submitted a 1999 budget request to Congress for the 317 Grant Program that includes a $10 million increase for vaccine but does not include a provision for pneumococcal vaccine. No increase was requested for operational funds. Increases were added for vaccine safety activities and global polio eradication.

Additional money has been found to fund several needs. An independent expert group has been contacted to evaluate timely review of new vaccine safety concerns and to guide research priorities. Better collection of VAERS data is another priority. Some studies of adverse events will be started, especially on vaccine-associated autism. Better methods will be established to communicate with parents and providers regarding their concerns about vaccine safety.

Comment

Dr. Le asked whether comprehensive national surveillance of Hepatitis B is expected in the future. Sentinel counties provide most of the current information but no additional funding has been allocated to enhance data reporting. Adverse events will continue to be investigated.

Regarding varicella vaccine coverage, more than 60% of the birth cohort live in states that have school entry requirements for immunization, which should result in vaccination of more than 80% of this group by the end of 2000. The goal is to make varicella a reportable disease.

Food and Drug Administration (FDA)

Dr. Egan reported the FDA's recent approval of licensure of the pneumococcal conjugate vaccine. Two meetings regarding the components of two combination vaccines took place recently. One meeting specifically addressed the Hib vaccine, and the other covered combination vaccines in general. An upcoming advisory meeting will address SmithKline's license application for their DTaP /Hepatitis B/IPV combination vaccine.

Vaccine Injury Compensation Program

Dr. G. Evans, Health Resources and Services Administration, reported that for the year 2000 about 10 cases of vaccine-related injury have been reported thus far. The Hepatitis B, varicella, and Hib vaccines were added to the program in 1997, which accounted for the higher number of claims made last year. More than 200 Hepatitis B claims await adjudication, the most for any vaccine added recently. A little more than $1.1 billion has been spent on awards to date, and $1.4 billion remains in the trust fund for compensation.

Congress passed legislation enacting an excise tax on pneumococcal vaccine, which became effective on December 17, 1999. However, this vaccine is not officially covered under the program until CDC publishes a recommendation for its use in children. "The Vaccinate America's Children Now Act," if passed, will reduce the amount of tax on covered vaccines from $.75 to $.25. In 1996, the Senate passed a bill allowing compensation for vaccine-related injury even when there are no continued effects beyond 6 months. Given the recent cases of intussusception associated with the rotavirus vaccine, Congress added language that would allow claims "which resulted in inpatient hospitalization and surgical intervention."

The General Accounting Office (GAO) was charged with evaluating the amount of time to process a claim, the effect of Table changes on receiving compensation, and the trust fund options. The GAO recognized the need for a consistent methodology for evaluating and reporting on the various factors used to add or remove injuries from the Table. This methodology should include specific scientific and public policy considerations in the decision-making process. The entire GAO report can be downloaded from the Internet (www.gao.gov/new.items/he00008.pdf).

Discussion

Dr. Katz asked whether Congress could release funds from the injury compensation trust fund and use them for vaccine safety research. Although this idea has been discussed formally in Congress and within Advisory Committees, the GAO and the current administration has not taken an official position because no easy mechanism is in place for such a transfer of funds.

Combination DTPa/HepB/IPV Vaccine

Dr. Barbara Howe, SmithKline Beecham, presented safety and immunogenicity data for her company's combination DTPa/HepB/IPV vaccine, which will be known by the trade name Infanrix ® DTPa/HepB-IPV.

The combination vaccine consists of three separate products: the diphthena, tetanus, and acellular pertussis component (Infanrix®) licensed in the U.S. in 1997; the recombinant Hepatitis B vaccine (Engerix-B®) licensed in the U.S. in 1989; and enhanced potency-inactivated IPV vaccine grown in VERO cells. No thimerosal is added as a preservative and the product is adsorbed onto aluminum salts

Twelve trials evaluated this combination vaccine in 10 countries. The indication SmithKline Beecham is seeking is for a 3-dose primary vaccination in infants beginning at 6 weeks of age. The combination would reduce by approximately one-half the number of injections currently recommended for all vaccines in the primary series.

A trial conducted at UCLA, Center for Vaccine Research (Dr. Joel Ward) compared the following regimens:

- One group received three consecutive doses of the combination vaccine coadministered with Hib (at 2, 4, 6 months of age)
- A second group received two doses of the combination vaccine along with Hib (at 2 and 4 months) and at 6 months, a combination DTPa/HepB vaccine coadministered with Hib and oral polio vaccines
- A third group received three doses of DTPa/HepB and IPV and Hib at separate sites (at 2,4, and 6 months)
- The fourth group received separate injections of DTPa, HepB, and Hib with oral polio vaccine given orally

The following discussion focused on the comparison of three consecutive doses of the combined vaccine (first group) to the "standard of one" separate injections with OPV (fourth group). The combined vaccine was at least as immunogenic as separate injections. The seroprotection rates for diphthena (D), tetanus (T) and Hepatitis B (HepB) ranged from 99 to 100% one month after immunization. The D, T, and Hep B GMTs for the combination vaccine were higher than for separate injections. Vaccine response rates for the three pertussis antigens were high (≥91%) regardless of the group and again, the anti-PT and anti-pertactin GMTs for the combination vaccine were higher than for separate injections. The results were comparable for responses to polio and Hib and there was no negative impact of coadministered Hib vaccine.

Adverse events such as pain, redness, or swelling (regardless of the injection site) were reported slightly more often for the combined vaccine. Children receiving three doses of combined vaccine reported a slightly higher, but not statistically significant, rate of solicited mild fever (defined as T≥100.4F) than children getting separate injections. Rates of other solicited general symptoms (fussiness, loss of appetite, more than usual, etc.) were compatible between the two groups.

The benefits of the combination vaccine include a reduction in the number of injections and the number of visits needed to administer the vaccine. This combination vaccine is expected to improve vaccination coverage, especially for vaccines for which coverage has lagged behind such as monovalent Hepatitis B. It is also expected to make room for new injectable vaccines such as the pneumococcal conjugate vaccine.

Discussion
Anti-pyretic use was very high at each dose for both those who received the combination vaccine and those who received separate injections. No data exist regarding use of this vaccine in the setting of post-exposure prophylaxis for Hepatitis B.

Public Comment
Dr. Zimmerman, speaking on behalf of the AAFP, stated that although the meningococcal polysaccharide vaccine is efficacious, offers good protection, and appears to be safe, meningococcemia is not a primary cause of death for college-age adults. At the last meeting, ACIP charged primary care physicians to counsel these patients regarding the meningococcal vaccine. However, as time spent with these patients in the office setting is limited, the AAFP believes that the ACIP recommendations for implementation of vaccination for this disease is impractical.

Dr.Abramson suggested development of educational pamphlets to address this need. Drs. Zimmerman and Le advocate college-based programs to effect large-scale immunization of this age group.

Dr. Scott Ratzan reminded ACIP of the long-term public health objectives as they relate to the rising incidence and prevalence of Lyme disease. He advocated changing the wording of the recommendations about the Lyme vaccine and urged clarity in advancing the goals of the Healthy People 2010 agenda for Lyme disease.

The meeting was adjourned at 3:30 p.m.

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

John F. Modlin, M.D. Date