CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

Minutes of the Meeting Held on

October 20-22, 1999

1600 Clifton Road
Atlanta, Georgia

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GEORGIA
October 20-22, 1999
Auditorium B

Agenda Item	Purpose/Action	Presider/Presenter(s)
October 20, 1999		
8:30 Welcome		Dr. J. Modlin (Chair, ACIP) Dr. D. Snider (CDC, OD)
9:00 Thimerosal and Vaccines - I Background: Mercury Exposure And Human Health Hepatitis B Vaccine Policy	Information Discussion	Dr. L. Ball (FDA, CBER) Dr. R. Bernier (NIP, OD) Dr. C. DeRosa (ATSDR) Dr. E. Mast (NCID, DVRD) Dr. J. Risher (ATSDR)
10:15 BREAK		
10:45 Thimerosal and Vaccines - II Should the ACIP Express a Preference for DTaP and Hib Vaccines that do not Contain Thimerosal as a Preservative?	Discussion Decision	Dr. N. Halsey (Johns Hopkins Univ) Mr. D. Mason (NIP, ISD)
1 Public Comment		
12:15 LUNCH		
1:15 Thimerosal and Vaccines - II	Decision (continued)	
1:45 Bioterrorism Workgroup Update Anthrax Vaccine	Information	Dr. D. Ashford (NCID, DBMD Dr. M. Braun (FDA, DSE) Dr. C. Helms (Univ. of Iowa) Dr. J. Grabenstein (DOD, AVIP)
2:30 Harmonized Schedule	Discussion Decision	Dr. R. Burr (NIP, ESD) Dr. J. Livengood (NIP, ESD)
3:30 BREAK		
4:00 Meningococcal Vaccination of College Students Should college students be vaccinated for meningococcal disease?	Discussion Decision	Dr. D. Fleming (Oregon Health Div) Dr. N. Rosenstein (NCID, DBMD)
5:30 Update: Use of Meningococcal Conjugate Vaccine in the United Kingdom	Information	Dr. D. Salisbury (United Kingdom)
6:00 ADJOURN		

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

Agenda Item	Purpose/Action	Presider/Presenter(s)
October 21, 1999		
8:00 Unfinished Business from Previous Day		Dr. J. Modlin (Chair, ACIP)
8:30 Adult Workgroup	Information	Dr. M. Cetron (NCID, DQ)
Plans to revise Adult Immunization recommendations	Discussion Decision	Dr. R. Clover (Univ. of Louisville) Dr. B. Howe (SmithKline Beecham)
Approval of Standing Orders for Immunization		Dr. L. McKibben (EPO, OHCP) Dr. G. Mootrey (NIP, ESD)
Yellow Fever Vaccine and the Elderly Age-specific risk of adverse events		Dr. R. Strikas (NIP, ESD)
Combination Hepatitis A/B Vaccine		
10:15 BREAK		
10:45 Update from Decision Rules Workgroup	Information	Dr. R. Bernier (NIP, OD) Dr. F. Guerra (San Antonio HD)
11:00 Influenza Vaccine	Discussion	Dr. K. Fukuda (NCID, DVRD)
Neuraminadase inhibitors Use in pregnancy and young Children	Decision	Dr. A. Winquist (NCID, DVRD)
12:30 LUNCH		
1:30 Public Comment		
1:35 Recommendation for use of Pneumococcal Conjugate Vaccine	Discussion Decision	Dr, C. Van Beneden (NCID, DBMD) Dr. D. Johnson (Michigan DOH)
3:15 Vaccines for Children Pneumococcal Vaccine	VFC Discussion	Dr. J. Livengood (NIP, ESD)
3:30 BREAK		
4:00 Prevention of Pneumococcal Disease in adults <65 years old	Information Discussion	Dr. J. Butler (NCID, AIP) Dr. C. Whitney (NCID, DBMD)
4:30 Alternate Hepatitis B Vaccine Schedule for Adolescents	Information	Dr. H. Margolis (NCID, DVRD) Dr. T. Vernon (Merck)
5:00 Updates	Information	
National Center for Infectious Diseases		Dr. A. Mawle (NCID, OD)
National Immunization Program		Dr. W. Orenstein (NIP, OD)
Food and Drug Administration		Dr. W. Egan (FDA, CBER)
Vaccine Injury Compensation Program		Dr. G. Evans (HRSA)
National Vaccine Program		Dr. R. Breiman (NVPO)
6:00 ADJOURN		

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

Agenda Item	Purpose/Action	Presider/Presenter(s)
October 22, 1999		
8:00 Unfinished Business from Previous day		**Dr. J. Modlin (Chair ACIP)**
8:30 Rotavirus Vaccine and Intussusception **Does rotavirus vaccine cause intussusception?**	**Information** **Discussion**	**Dr. A. Jumaan (NIP, ESD)** **Dr. P. Kramarz (NIP, ESD)** **Dr. J. Livengood (NIP, ESD)** **Dr. M. Massoudi (NIP, ISD)** **Dr. T. Murphy (NIP, ESD)**
10:15 BREAK		
10:45 Rotavirus Vaccine Recommendations **Does the ACIP wish to change its Recommendation on use of Rotavirus Vaccine?**	**Discussion** **Decision**	**Mr. R. Deuson (NIP, ISD)** **Dr. R. Glass (NCID, DVRD)** **Dr. B. Ivanoff (WHO)** **Dr. J. Livengood (NIP, ESD)** **Dr. P. Paradiso, (Wyeth/Lederle)**
12:00 Public Comment		
12:15 ADJOURN		

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1600 Clifton Road
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ACIP October 20-22, 1999

ATTENDEES:

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

Ex Officio Members
Dr. Robert Breiman (NVPO)
Dr. William Egan (FDA)
Dr. Geoffrey Evans (HRSA)
Dr. Randolph Graydon (HCFA)
Dr. Gina Rabinovich (NIAID)
Dr. Kristin Nichol (UMVAMC)
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. David Wilson (AMA)
Dr. Richard Zimmerman (AAFP)

Executive Secretary
Dr. Dixie Snider

Office of the General Counsel
Kevin Malone

EPO
Martha Alexander
Jennifer Danielson
Michael Favorov
Linda McKibben
Linda Steiner-Sichel
Christine Zahniser

National Center for Infectious Diseases
Miriam Alter
David Ashford
Beth Bell
David Bell
Richard Besser
Joseph Bresee
Carolyn Bridges
Jay Butler
Martin Cetron
Debline Dalton
Roz Dewart
Clare Dykewicz
Roger Follas
Alicia Fry
Keiji Fukuda
Francisco Gimenez-Sanchez
Rana Hajjeh
Terri Hyde
Kirsten Ivie
Naomi Katz
Amy Khan

National Center for Infectious Disease
Nino Khetsuriani
Jairam Lingappa
Rob Lyerla
Harold Margolis
Michael Martin
Eric Mast
Juliette Morgan
Bradley Perkins
Sarah Reagan
Nancy Rosenstein
Daniel Singer
Kanta Subbarao
Chris VanBenden

National Immunization Program
Melissa Adam
William Atkinson
Sharon Balter
Kris Bisgard
Roger Burr
Bob Chen
Pam Ching
Susan Chu
Angie Cobb
Gary Coil
Maria Danovaro
Gary Euler
Elizabeth Fair
Karin Galil
Paul Gargiullo
John Glasser
Idalia Gonzalez
Rafael Harpaz
Beth Hibbs
Sonja Hutchins
Darlene Johnson
Laurie Johnson
Mary Lambert
John Livengood
Dean Mason

National Immunization Program Cont.
Mary McCauley
Gina Mootrey
Trudy Murphy
Serigne Ndiaye
Walter Orenstein
Robert Pless
Rebecca Prevots
Lance Rodewald
Ben Schwartz
Sabeena Setia
Jim Singleton
Gerlinda Somerville
Cathy Stout
Ray Strikas
Amra Uzicanin
Thomas Verstraeten
Bruce Weniger
Melinda Wharton
Lynn Zanardi
John Zhang

NIOSH
Wendy Heaps

Office of Public Affairs
Charlis Thompson

NCEH
Tom Sinks

ATSDR/OAA
Chris DeRosa

National Immunization Hotline
Michele R. Bailey

ASTHO
Claire Hannan

NVPO
Alicia Pastema

Other Government Attendees

C.D. Atreya, FDA
Leslie Ball, FDA
M. Miles Braun, FDA
Nancy Cherry
Julianne Clifford, FDA
Carl Frasch, FDA
Antonia Geber, FDA
Karen Goldenthal, FDA
Douglas Pratt, FDA
Barbara Styrt, FDA

Others Present

Betsy Abraham, SmithKline Beecham
Murray Abramson, Merck Company
Lock Van Alpehn, RIVM
Kathryn Arnold, GA Immun. Prog.
B.F. Anthony, BCG
Lynn Bahta, Immun. Action Coalition
Devos Beatrice, SmithKlein Beecham
Don Beeman, , Merck Company
Werten Bellamy, Wyeth Company
Karen Biscardo, PMC
Michael Blum, Wyeth Company
John W. Bosleyo, Merck Company
Tina. L. Bryant, ASHMA
Jillian Cameton, Cohne & Wolfe
Sean Campbell, PMC
Hanson Cars, Goleborg Sweden
Lynn Cates, ASPE
Jill Chamberlain, Vaccine Bulletin
Helen Cicirello, NAVA
Hillel Cohen, Merck Company
Lewore Cooney, Cooney & Waters
Mike Cooper, Reuters
Dack Dalrymple, Bailey & Dalrymple
Natalie Devare, Wyeth Company
Philippe DeWals, Univ. of Sherbrooke
Richard C. Dinovitz, Wyeth Company
Laurie Doeple, NIAID/NIH
Gary Dubin, SmithKline Beecham
Matthew Dunne,OED Communication
Frank Dzvonik, SmithKline Beecham
Steve Erickson, Ketchum
Michele Erstein, Cohne & Wolfe
David Fedson, PMC
Pam Fesaon, PMC
Nancy Fix- Bloeser, Wyeth Company
Eugene Gangarosa, Private Consultant
Joe Gaugi, OSI
Ruth Gilmme, GA Immunization Prog
Cynthia Good, Good For Patents
Elizabeth Goss, Bennett & Turner
LTC John Grabenstein,US Army SGO
Jesse Greene, SC Department Health
Henry Grick, PMC
Kenneth P. Guito, PMC
Jill Hackell, Wyeth Company
Neal Halsey, John Hopkins University
Bill Hausdroff, Wyeth Company
Joanne Hayward, Merck Company
Joe Heyse, Merck Company
Lori Hickman, Roche Laboratory
Sandra Holmes, SmithKline Beecham
Bita Honarvar, Pediatric News
Phil Hosback, PMC
Dominick Iacuzioi, Roche Laboratory
Bruce Jelli, IBST
Ling Ju, Merck Company
Claire Kahn, SmithKline Beecham
Albert Z. Kapikian, NIAID/NIH
Browen Kaye, AHP
Stephanie Keith, North American Vac.
Jim Kenimer, BCG
Alan Kimure, BIO Chem. Pharme
R. Kohleral, Wyeth Company
Stephanie Kull, MFA
John LaMontane, NIAID/NIH
Andria Langenberg, Chiron Corp.
Len Lavenra, PMC
Dagna Lawter, Wyeth Company
Scott Litherland, Parallax Comm.
Patricia Luces-Schnerre, Wyeth Co.
Marianne Maw, WAB FM-CBS Radio

Others Present Cont.

Carlton Meschievitz, PMC
Sherri Michelstein, Cooney & Waters
Peggy Monkers, GA Immun. Program
Barbara Mullarkey, IVAC
Stan Music, Merck Company
Andrie Nahmia, Emory University
Maragrita Nava, Conava
Carla Newby, MRA
Gary Noble, Johnson & Johnson
Daniel O'Ray, Hoffman LaRoche
Peter Paradiso, Wyeth Company
John Percy, CNN
Stanley Plotkin, PMC
Jane Quinn, Merck Company
Cassandra Richards, Infect. In Children
Hans Rimble, RIVM
Anne Roger, Parallax Communication
Rhonda Rowland, CNN
Fred Ruben, PMC
Jerald Saddoff, Merck Company
D.D.M. Salibury, London Dept. Health
Jerald Santosham, John Hopkins Univ
Florian Schodel, EVAX Technologies
Michael Severirv, Merck Company
Frederic Shaw, TDH/HCR
Judith Shindam, PMC
Jeffrey Silber, Merck Company
Rhonda Sjoberg, AVIRON
Natalie Smith, CDHS
Virginia Spicher, Ped. Inf. Dis. Emory
Wendy Stephenson, Wyeth Company
Stacy Stuerle, Merck Company
George Thiry, SmithKline Beecham
Al Thompson, SmithKline Beecham
Richard F. Thompson, Medical Group
Peter Tobar, Wyeth Company
M.E. Tucker, Medscape Consumer
Miriam Tucker, Pediatric News
James C. Turner, ACH
Theresa Turski, GA Imm. Program
Ben VandenBroecke, SmithKline Bee.
Kathleen Vandendael, EVM
Peter Vigliarolo, Cooney & Waters
Leslie Wade, CNN
Barbara Watson, Phil Dept. Health
Dave Webster, PMC
Peggy Webster, NCAI
Tina Wenz, Ketchum
Deborah Wexler, Imm. Action Coalit.
Jo White, North American Vaccine

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Advisory Committee on Immunization Practices

Wednesday, October 20, 1999

The Centers for Disease Control and Prevention convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on October 20-22, 1999 at Clifton Road in Atlanta, Georgia. Chair Dr. John Modlin called the meeting to order at 8:35 am. The ACIP members, ex-officio representatives, and liaison members introduced themselves and stated any potential conflicts of interests. This is compulsory for ACIP members and voluntary for others. Voting members may participate in discussions involving products or companies with which they have substantial conflicts, but must recuse themselves from voting on those issues, including VFC votes.

ACIP members:
Bonnie Word, M.D., pediatric infectious disease physician, State University of New York at Stonybrook: no conflicts.
Margaret B. Rennels, M.D., University of Maryland School of Medicine: planning to conduct vaccine evaluations for Wyeth Lederle, Merck, Pasteur-Merrieux Connaught, and SmithKline Beecham. Has consulted for SmithKline Beecham and Wyeth Lederle and given talks sponsored by Wyeth Lederle, on safety monitoring boards for SmithKline Beecham and Pasteur-Merrieux Connaught.
Lucy S. Tomkins, M.D., Professor, Departments of Medicine and Microbiology and Immunology, Stanford University Medical Center. no conflicts.
Dennis A. Brooks, M.D., Site Medical Director, Johnson Medical Center, Johns Hopkins: one consultation for Wyeth Lederle.
Richard D. Clover, M.D., Professor and Chairman, Department of Family and Community Medicine, University of Louisville: received grants and honoraria from SmithKline Beecham, Wyeth Lederle, and Merck.
Charles M. Helms, M.D., Ph.D., Professor of Medicine, University of Iowa: no conflicts.
Paul S. Offit, M.D., Chief, Section of Infectious Diseases, The Children's Hospital of Philadelphia: He co-holds a patent and consults in the development of a rotavirus vaccine by Merck.
David R. Johnson, M.D., M.P.H., Michigan Department of Community Health: no conflicts.
Chinh T. Le, M.D. Staff Physician, Kaiser Permanente Medical Center: Kaiser conducts research with Merck, SmithKline Beecham, North American Vaccine and Pasteur-Merieux Connaught. He owns stock in Merck.
David W. Fleming, M.D.: no conflicts.
Fernando A. Guerra, M.D., Director of Health, San Antonio Metropolitan Health District: His department has done vaccine evaluation studies for SmithKline Beecham, Merck, North American Vaccine, and he served as consultant for Pasteur-Merrieux Connaught.
John F. Modlin, M.D., Professor of Pediatrics and Medicine, Dartmouth Medical School: no conflicts.

Liaison and ex officio members:
Robert F. Breiman, M.D., National Vaccine Program Office, CDC.
William Egan, Ph.D., The Center for Biologics Evaluation and Research, FDA
Geoffrey S. Evans, Division of Vaccine Injury Compensation, HRSA
T. Randolph Graydon, Director of Advocacy and Special Issues, Center for Medicaid and State Operations
Regina Rabinovich, M.D., Division of Microbiology and Infectious Diseases, NIAID/NIH
Kristin Lee Nichol, M.D., Professor of Medicine, University of Minnesota, Chief of Medicine, VA Medical Center
David H. Trump, M.D., M.P.H., Office of the Assistant Secretary of Defense (Health Affairs)
Richard Zimmerman, M.D., American Academy of Family Physicians
Larry Pickering, M.D., American Academy of Pediatrics
Jon Abramson, M.D., American Academy of Pediatrics
Eric K. France, American Association of Health Plans
Stanley A. Gall, M.D., American College of Obstetricians and Gynecologists
Pierce Gardner, M.D., American College of Physicians
William Schaffner, M.D., American Hospital Association
H. David Wilson, M.D., American Medical Association
W. Paul McKinney, M.D., Association of Teachers of Preventive Medicine
Yvonne E. McHugh, Ph.D., Biotechnology Industry Organization
Victor Marchessault, M.D., Canadian National Advisory Committee on Immunization
Jane D. Siegel, M.D., Healthcare Infection Control Practices Advisory Committee
Samuel L. Katz, M.D., Infectious Diseases Society of America
Jose Ignacio Santos-Preciado, National Immunization Council and Child Health Program, Mexico
Rudolph E. Jackson, M.D., National Medical Association
George Peter., M.D., National Vaccine Advisory Committee
Barbara J. Howe, M.D., Pharmaceutical Research and Manufacturers of America

OPENING COMMENTS

ACIP Executive Secretary, Dr. Dixie Snider, welcomed the attendees and explained that John Livengood acts in his place if he is absent. He announced that John Modlin had been appointed for another term as chair of the committee, however this was the last meeting for Regina Rabinovich as an ex-officio member. He reminded members of the new E-mail address: acip@cdc.gov. The next meeting is February 16 and 17, 2000 at the Marriott at Century Center. The following meetings will be June 21 and 22, and October 18 and 19, place to be announced. He noted that the Executive Secretary has the authority to designate ex officio members to vote when regular members have conflicts of interest. The ACIP meeting is an open discussion and there would be a formal public comment period for which individuals should sign up in advance, especially for prepared statements. Members were asked for comments about the immunization section of a document concerning prevention of opportunistic infections in bone marrow transplant patients.

Dr. Modlin announced that one statement on hepatitis had been published since last June.

THIMEROSAL AND VACCINES

Dr. Modlin introduced the topic by explaining that the thimerosal problem surfaced in late June after the ACIP meeting. It developed so quickly that CDC leadership had to make decisions without ACIP input. Since the issue of procedures needs further discussion, Dr. Modlin and Dr. Peter are proposing a joint working group of ACIP members, and NVAC and CDC legal staff to review the current policies and procedures. Dr. Word, Dr. Reynolds, Dr. Clover, Dr. Helms, Dr. Offit, and Dr. Guerra volunteered to be on the committee.

Background: Mercury Exposure and Human Health

Dr. R. Bernier, NIP, OD. Chronology: In 1997 there was legislation calling for a review of Hg in drugs and biologics and in June 1999 it was first recognized that cumulative exposure to thimerosal and mercury may exceed some guidelines for some groups of children. A joint statement was issued by the Public Health Service and AAP with the goal of removing thimerosal-containing vaccines and postponing hepatitis B vaccination. The FDA sent a letter to manufacturers, and CDC and AAP communicated directly to their membership. There was also a public workshop in August. Recently there has been a resumption of hepatitis B vaccination at birth.

Thimerosal is on today's agenda because supply changes can create new options; some aspects of immunization policy were not addressed earlier; and some aspects that were addressed may need adjustments. The three options are: 1) no further changes, 2) change recommendations to prefer vaccines that contain no thimerosal, but to go ahead and vaccinate if the thimerosal-free vaccines are not available, and 3) postpone vaccination until the vaccines are available.

The FDA's Investigation of Thimerosal in Vaccines

Leslie Ball, FDA. Vaccines formulated in multi-dose containers must contain preservatives (with certain exceptions). Preservatives must not be toxic to recipients and not de-nature the product; and preservatives should not be used solely to reduce the viable microbial count as a substitute for good manufacturing practices. There are several places where antimicrobial agents occur in the manufacturing process. They can be an inactivating agent, e.g., whole cell pertussis vaccine, or a bacteriostatic agent in the production process, e.g., influenza vaccine. The preservative can be used in bulk containers or as a diluent.

Thimerosal is the most common preservative. The use of preservatives in multi-dose vials is not always effective. There have been reports of abscesses, especially from group A streptococcus. Preservatives shouldn't be a substitute for proper technique in withdrawing the vaccine from multi-dose vials. Some U.S.-licensed vaccines do not contain preservatives, such as most live attenuated vaccines, most Hib vaccines, Hib-Hepatitis B combination, and some rabies vaccines.

Thimerosal Safety Assessment

Merthiolate, the thimerosal trade name, was first marketed in 1930. It is 49.6% mercury by weight, metabolized to ethylmercury and thiosalicylate. In a 1976 CBER review, its use was evaluated in adults over a lifetime, but researchers did not look at the effects of mercury-containing preservatives in infants. The FDA became involved because of general concern over the health effects of human exposure to mercury from environmental sources, especially mercury intentionally introduced in drugs and foods. With the increase in the number of vaccines recommended for routine use in infants, there is the potential for increased exposure of infants to mercury in the form of ethylmercury.

The FDA concentrated on thimerosal-containing vaccines in the Recommended Childhood Immunization Schedule and focused on infants because developing brains are at greater risk from exposure to mercury. Vaccines containing thimerosal include hepatitis B, DTaP and Hib, so within its first 6 months an infant can be exposed to as many as nine different thimerosal-containing vaccines

There is a paucity of data on thimerosal, so the harmful effects of doses in vaccines is unclear. The FDA adapted the National Research Council's paradigm for risk assessment with regard to hazard identification, dose-response assessment, exposure assessment and risk characterization. They reviewed animal toxicity data and studies on other preservatives used in biologicals and found sensitization reactions (low doses) and evidence of neurotoxicity (high doses), as well as nephrotoxicity (high doses). In case report/case series of acute toxicity, they were on the order of 90 to 330 mg/kg, but there were also certain observed effects, such as local necrosis, acute hemolysis, disseminated intravascular coagulation, and acute renal tubular necrosis. Central nervous system effects included obtundation, coma and death. There were no data on thimerosal toxicity at doses found in vaccines, other than hypersensitivity. When VAERS reports were examined, they found 45 reports from 1990-98 alleging adverse reactions due to thimerosal, but causality could only be inferred. Most involved local hypersensitivity reaction.

Because of the lack of data on low-dose thimerosal toxicity, the FDA decided to do a comparison with methylmercury, even though equating ethylmercury with methylmercury is admittedly controversial. There were two studies regarding infants born to women who ingested high concentrations of methylmercury and exhibited CNS effects, one in Minamata Bay, Japan and the other in Iraq. There were also two population-based studies examining the effects of eating contaminated fish in the Seychelles and Faroe Islands. On basis of these studies, several organizations have suggested limits for safe intake of methylmercury in diet.

The FDA calculated maximum exposure to thimerosal in vaccines in infants 6 months and younger and found they could potentially receive up to 187.5 micrograms. If the six-month dose of flu vaccine was included, the amount could be as high as 200 micrograms. Using EPA/ATSDR suggested limits for safe intake, they calculated the amount of ethylmercury intake

that was potentially "safe" during the first six months, for different weights. EPA guidelines were exceeded, not taking into account additional exposures to mercury from the diet and the environment. In reviewing the literature, only one study was found that looked at whether mercury levels increased after vaccination. Preterm and fullterm infants with birth dose of hepatitis B showed a change in mercury levels identified before and after vaccination.

Conclusions: There was no evidence of harm at doses found in vaccines, and evidence of thimerosal toxicity was found only with respect to hypersensitivity reactions (low dose) and necrotoxicity and neurotoxicity (high dose). Use of thimerosal in vaccines may result in intake of ethylmercury during the first six months that exceeds EPA recommendations for methymercury.

Options to reduce or eliminate thimerosal include using only single-dose vials, using alternative preservatives, reducing the amount of thimerosal in vaccines, or maintaining the current amount of thimerosal in vaccines. Short-term solutions include the use of existing thimerosal-free products, combination vaccines, or single-dose vials. Long-term solutions include development of new preservatives or new technologies decreasing the need for preservatives. Potential roadblocks are the fact that regulatory requirements depend on where thimerosal is used during the manufacturing process, the safety and effectiveness of any replacement, and storage and cost if using single-dose vials.

Actions taken:

- FDA sent a letter to manufacturers on July 1st, requesting plans for removal of thimerosal or rationale for continued use.
- Center for Biologics committed to a rapid review of products not containing thimerosal.
- Thimerosal-free hepatitis B vaccine supplement was approved at the end of August.
- AAP/PHS issued a joint statement.
- PHS workshop
- PHS agencies are collaborating on further research.

ATSDR's Perspectives on Health Guidance for Methylmercury

Christopher De Rosa, Director of Division of Toxicology, ATSDR. ATSDR was mandated to prepare toxicological profiles on each priority substance found at hazardous waste sites, to identify data gaps for each substance and point to research programs to assess hazards. Profiles must be updated at least every three years.

Chronology: The first profile on methymercury was released in 1989 and updated in 1993 using the Iraqi data set. The resulting health guidance value was 1.1 μg/kg/day, the same number currently used by EPA. A series of expert panel meetings were held in 1994 and 1995 to see if there were more robust analytic techniques that could be applied to the Iraqi data set to undergird confidence in the health guidance value, but the advice was to await results of ongoing epi

studies. In 1996, the ATSDR updated the mercury profile based on a review of the Seychelles data set. Since then a number of meetings have been held to discuss implications of findings from three sets of raw data.

Evaluation of three studies:
Iraq: This was a retrospective study based on a poisoning incident in which seed grain fumigated with mercury was used to bake bread. The researchers followed a cohort of 83 mother/infant pairs for two or three years after the incident, and mothers were asked when their children first walked or talked. Data were subject to retrospective recall and there was a high level of exposure to other Hg sources in the Iraqi environment. The level of mercury exposure was high, ten to several hundred ppm, but only a few mother/infant pairs were exposed at levels of concern. The key index of exposure was hair, where each cm corresponds to one month of exposure.

Seychelles: This was a prospective, longitudinal study of 800 mother/infant pairs. The developing foetus was the population followed (most sensitive subgroup in the human population). Fish was the primary medium of exposure through the diet. The environment itself is pristine. The population experiences chronic low level exposure (0.3 ppm), consistent with levels of mercury in the fish supply in the U.S. However the corresponding levels of mercury in the population are 10 times higher than this country, because the Seychelles have the highest level of per capita fish consumption in world. For outcome, they used standardized measures of global cognitive function. The McCarthy subscales were made available to the panel and there was no evidence of any domain-specific effects.

Faroe Islands: This was also a prospective, longitudinal study of 1000 mother/infant pairs. The population was the developing foetus and the outcome was children's cognitive development, using domain-specific effects to assess different areas of the brain. The vehicle of exposure is pilot whale meat consumed once a month or less. The mercury levels are high in whales (3 ppm), similar to fish in the U.S. But since exposure is intermittent, levels in the population are similar to that of the Seychelles. There is concurrent exposure to PCBs at high levels in the whale blubber. Levels of PCBs are three times the FDA tolerable intake. Only 3 of 208 PCB congeners were measured in the Faroes, so even if neurological effects were caused by PCBs, it is possible that mercury would still be more highly correlated with these effects than PCBs.

Current practice in deriving health guidance values: Factors of 10 are protective, which gives a confidence level of 95%. They might be referred to as extrapolation factors to account for missing data sets. If there is no data on a subgroup, a factor of one to 10 is invoked to account for the missing data set. When comparing no adverse effect (NOAEL) to low adverse effect (LOAEL), a factor of 10 is used to extrapolate the NOAEL, and to extrapolate across duration from a sub-chronic to a chronic study. If there are misgivings about the overall data base, the modifying factor is evoked.

MRL derivation considerations: Mercury is ingested by mothers and then paramercury levels are measured by converting hair levels to blood concentrations based on known ratios of hair to blood levels. Most center around 250, which is the value used. Blood concentration then has to be converted to daily intake using a formula worked out by WHO.

A generic approach was used for the Uncertainty Factor and Modifying Factor. They used 1.5 to account for pharmacokinetics, and 1.5 for pharmacodynamics. These two generally account equally for variability in humans. Then they used a Modifying Factor of 1.5 to reflect the fact that the full range of domain-specific endpoints has not yet been assessed in the Seychelles.

In summary: The highest quintile exposure in the Seychelles, which ranged from about 12 to 27 ppm of maternal hair level (mean = 15.3 ppm), was used as the NOAEL. That was equivalent to an intake of 0.061 µg/l, which was converted to an intake rate of 0.0013 mg/kg/day. An overall value of 4.5 was used to divide into intake rate, resulting in MRL of 0.003 mg/kg/day. These values were used to compare with different mercury levels in vaccines.

Dr. John Risher, ATSDR. Methylmercury was used as a surrogate for ethylmercury. The Seychelles study was selected because it was a long-term (multiple generations), prospective, double blind study. It was also a large study with an average of 12 fish meals/week. The average mercury concentration is comparable to upper U.S. levels of exposure. The confounding factors are minimal (smoking low, pristine environment, basic health good, education universal, and low levels of alcohol, lead, and PCBs).

To derive chronic oral MRL for MeHg, they started with the mean hair level of the highest exposed group in the Seychelles and came up with 0.0003 mg/kg/day. Very conservative assumptions were used for converting blood to daily intake. They used 0.5 as the total amount of methylmercury in the overall body burden that is in the blood.

To determine what effect the mercury in the flu vaccine would have on blood levels of a pregnant woman, they took the Seychelles highest quintile of exposure (hair concentration) and back calculated to a blood concentration of 61 micrograms per liter. That was an average methylmercury blood concentration throughout pregnancy, which is relatively high, but still no effects were seen in children. This was compared with the general population in the U.S., whose hair level is about 1 ppm mercury, and came up with a blood concentration of 4 micrograms per liter, one fifteenth of that of Seychelles mothers. In the worst case scenario, if a mother was given a 12.5 µg injection, and all was absorbed into the blood rapidly and not distributed, at some point an additional 3 micrograms per liter would be added to her blood. That's a blood concentration of only 7 micrograms per liter or less, which is well below any known safe level.

Discussion

Dr. Offit asked about the relative risks of ethyl vs methylmercury. Dr. De Rosa replied that the literature on ethylmercury was limited, based on poisoning from attempted suicide. Ethylmercury behaves more like inorganic mercury. It is rapidly broken down, and there is some inorganic toxicity to the kidney, plus neurotoxicity. It is somewhat less toxic than methylmercury because of the breakdown to inorganic form. It is also more soluble.

Dr. Egan asked whether the elimination constant was just for adults, or was it the same for infants. Dr. De Rosa replied that the constant was determined from a study of women of reproductive age. Dr. Risher added that it depends on the age of the infant. Suckling rats do not excrete ethylmercury, but there are no studies in humans. Fred Ferris at Mercer looked at rats and reported that once mercury is in the blood, transfer to all body tissues is very rapid, except for hair and brain tissue.

Dr. Halsey asked if there would be a reassessment of the minimum risk level if evidence of domain-specific adverse effects are found in the follow up of the Seychelles cohort. Dr. De Rosa responded that the health guidance value would be re-evaluated, depending on the outcome of all the studies. Dr. Halsey asked whether they had addressed the issue of the safest maximum exposure for infants at birth or two months of age receiving a single dose. Dr. De Rosa said they had looked at it for flu. Then Dr. Halsey asked whether they had addressed the issue in other settings. Dr. Risher said that none of the levels in Tom Clarkson's data approach the level that was in maternal blood throughout gestation. Dr. Halsey noted that since there is not enough data to say they are different, they must be considered equivalent. Dr. Risher replied that some conclusions can be drawn from chemical observations, but once the methylmercury bond is broken, the mercury becomes inorganic in the tissues or is excreted in the urine.

Dr. France requested clarification of the differences in MRLs between EPA, FDA, ATSDR, and asked which was closer to the truth. Dr. De Rosa explained that the EPA's number was based on their report to Congress in 1995, before the Seychelles data was available. They were working with Iraqi data and applied benchmark dose modeling to identify NOAEL. They applied uncertainty factors to their NOAEL and arrived at value of 0.1 micrograms/kg/day. The FDA value has been in place for 20-30 years and was also based on Iraqi data. The FDA value comports with the current WHO value. Dr. Risher added that Tom Clarkson, one of the principal investigators in Iraq and Seychelles, and others have publicly expressed extreme reservations about the use of Iraqi data because of limitations presented earlier.

Dr. Katz asked about hair studies in infants and children receiving vaccines in the U.S. Dr. De Rosa replied that there are cross-agency studies on hair in the U.S. population as it relates to fish/diet and that the vaccine issue was now on the radar screen. Dr. Fedson, of Lyons, France, asked if there were any data on which vaccines the Seychelles children received, how much thimerosal was in the vaccines, what the estimated exposure was in the first six months of life.

Dr. De Rosa replied that children are vaccinated in the Seychelles, but there was no information on the mercury content of vaccines. Dr. Risher added that they haven't tried to speciate ethylmercury in hair, but studies have looked at total mercury in hair and 95% is organic mercury. Dr. Rabinovich noted that they had been looking at vaccine-specific protocols to evaluate available specimens, including hair in infants with documented history, maternal hair, and validated dietary recalls to define different groups. It is still not clear whether it will be possible to distinguish methyl vs ethylmercury.

Dr. Jackson asked if there was any evidence that populations chronically receiving mercury through fish diet had become more resistant over long-term exposure. He also asked about breast milk content in mothers with high mercury levels. Dr. Risher said there was no evidence of mercury tolerance, but it had not been investigated. Both inorganic and organic mercury are passed to the infant through mother's milk. Fifty percent of the mercury passed on is organic, and 50% is inorganic. Dr. De Rosa pointed out that the population in the Seychelles is from Africa, China, India, and Europe. They began arriving in the 1600s, so no acquired resistance based on chronic exposure was possible in that amount of time.

Dr. Pickering asked how the MRL derivation was verified, and what the correlation has been between the calculations and actuality. Dr. De Rosa explained that a range of internal and interagency working groups look at the information. Identification of endpoints and key data gaps are the key issues.

Why is reducing or eliminating thimerosal-containing vaccines a worthwhile goal?
Dr. Bernier, NIP, OD. Calculations based on existing guidelines suggest that the total amount of exposure to mercury should be limited to 81 (EPA), 243 (ATR MRL) or 324 (FDA), compared to a total potential exposure of 187.5 micrograms. Tom Clarkson looked at blood levels from vaccines, calculating for low birth weight babies (1.8 kgs) and full term infants. They were below NOAEL levels found in the Seychelles.

What does it mean if you are over suggested limits? The ATSDR exposure guideline of 0.3 mcg would produce a blood level of 13. Average exposure in the high-risk group corresponds to a blood level of 61. The highest exposure documented in the Seychelles with no effect is eight times above that. At some level there is a level with a mild effect, and eventually a higher level with serious effects. The safety margin is the cushion above the health guidance value.

What are the possible ways children can be immunized, how many outcomes can you have?
There are about 100 ways to get vaccinated, from no exposure to thimerosal, up to 187.5 micrograms, the worst case scenario. Most combinations available would end up with exposures of 100 to 112.5.

What about actual populations? Using data on 85,000 children vaccinated by Kaiser on the West Coast, researchers found that about 63% received less than 100 mcg, 86.8% received less than 112.5 mcg, and 91.6% received less than 125 mcg. Thus the potential exposure is below ATSDR/FDA guidelines, but above EPA guidelines. Data on actual exposure give the same conclusions.

Based on these considerations, there was agreement to reduce or eliminate thimerosal in vaccines as soon as possible. However, during the transition, the benefits of vaccination far outweigh the risk, if any, of exposure to thimerosal. So the policy was no change for DTaP, Hib, hepatitis B for AG+ mothers at birth, unknown AG status, and infants in high risk populations. There was a recommendation to postpone the first dose until 2-6 months for infants of proven hepatitis B AG-negative mothers. Subsequently, the PHS expressed a preference for two months, while the AAP preferred six months, but agreed to two months if the vaccine is thimerosal free.

Areas of uncertainty and assumptions:

- Does Methyl Hg = Methyl Hg?
- Data from fetal risk are being applied to infant risk.
- The background level of exposure to Hg is negligible.
- Data from chronic exposure limits are being applied to an acute situation.
- Which are the best guidelines?
- Some people look at guidelines as lines that can't be crossed, others see them as screening tools.0

Overview of Hepatitis B Vaccine Issues

Dr. Eric Mast, NCID . The joint PHS/AAP statement says that clinicians and parents can take advantage of flexibility in the existing schedule for the hepatitis B vaccine and postpone the first dose until 2-6 months. The AAP subsequently indicated that if thimerosal-free vaccine was not available, the hepatitis B virus vaccination should be initiated at 6 months of age. CDC's supplemental guidance was that:

- Hospitals should continue existing policies to vaccinate infants of HBsAg-negative mothers at birth until procedures are or can be put in place to guarantee proper management of all births to prevent perinatal hepatitis B virus transmission.
- Hepatitis B vaccination at birth should be continued for infants born to HBsAg-negative mothers belonging to populations at high risk for hepatitis B virus infections.
- If a decision is made to delay the birth dose of hepatitis B vaccination for infants of HBsAg-negative mothers, CDC prefers that the first dose of hepatitis B vaccine be given at 2 months of age, according to current recommendations of the ACIP.

To assess changes in recommendations for policies and practices for hepatitis B vaccination at birth, surveys were conducted of birthing hospitals.

- Overall 79% of hospitals were aware of the joint statement on thimerosal.
- Of those that were aware, 74% had an existing hospital policy or practice to offer hepatitis B vaccine to all newborn infants before the infant was discharged.
- Of hospitals both aware of the statement and having policies, 46% changed their policy or practices to stop vaccinating HBsAg-negative mothers, 9% stopped their policy to vaccinate all infants, and 45% reported either no change or some other change. The 9% illustrates the confusion that has occurred from the thimerosal guidance. CDC has anecdotal reports where policies changed and infants born to HBsAg-positive mothers were not vaccinated within 12 hours of birth.

It is likely that birth dose coverage for infants of mothers with unknown HBsAg status could decline as a result of these changes in hospital hepatitis B vaccination practices. In many hospitals there are no procedures in place to identify infants born to mothers with unknown HBsAg status. It's also possible that increased rates of early childhood hepatitis B transmission could occur among infants born to HBsAg-negative mothers by delaying the first dose of hepatitis B vaccine.

The 1998 National Immunization Survey found that 97% of children received at least one dose of hepatitis B vaccine, and 87% completed the series by 19-36 months of age, but vaccine series completion decreased with age at administration of first dose. Based on data from the second and third National Health and Nutrition Examination Surveys, about 33,000 infants born to HBsAg-negative mothers were infected each year before routine hepatitis B vaccination was recommended. Data indicate that highest risk of infection is in Asian/Pacific islander children, but overall the majority of infections occur in white, black and Hispanic children.

FDA and manufacturers have been working to make a thimerosal-free hepatitis B vaccine available. A Merck product was approved and licensed by FDA in August. On September 10, MMWR published a notice to readers announcing availability of the vaccine. MMWR recommended first prioritization of limited supplies to newborn infants and second priority to infants under 6 months, with thimerosal-containing vaccine used for children over 6 months of age, adolescents and adults. On September 13, distribution started in the private sector; on October 13, a federal contract was signed for purchase of vaccine for VFC, and on October 15 distribution started in the public sector.

It will be necessary to monitor the reintroduction of birth dose policies/practices into hospitals and assess the impact of changes in birth dose policies and practices for vaccine coverage of infants of HBsAg-positive mothers and infants of mothers with unknown status. It will also be necessary to monitor vaccine series completion.

Discussion

Dr. Abramson asked whether those hospitals that were failing to implement policy correctly were also those giving the vaccine. Dr. Mast said there were no data on which hospitals have which policies. Dr. Abramson asked whether there was enough thimerosal-free vaccine now to go back to the original policy. Tom Vernon from Merck answered that there were enough doses for the two targets--birth dose and children less than 6 months of age.

Should the ACIP express a preference for DTaP and Hib Vaccines that do not contain thimerosal as a preservative?

Dr. Neal Halsey, Johns Hopkins University. The main focus in the presentations has been cumulative toxicity and the conflict with existing guidelines, particularly the EPA guidelines. WHO has the same guideline as EPA, i.e., 0.1 micrograms/kg for pregnant women, infants, and nursing women. Children of all weights who got all thimerosal-containing vaccines would receive more than the cumulative dose recommended by the EPA. There are about 200,000 births below the 5th percentile, and for them the ATSDR guidelines would be exceeded.

Vaccine exposures must be added to environmental exposures. The guidelines are for total exposure to organomercurial materials, including from breast milk. EPA estimates that 7% of women of childbearing age consume more than 0.1 µg/kg/d of mercury, and 1% consume more than 0.37 µg/kg/day.

There are differences between the Seychelles and Faroe Islands studies. Evaluation is at a lower age in the Seychelles and it is global IQ testing, whereas children in the Faroes were older and underwent domain-specific testing. Defects associated with mercury exposure involve fine motor coordination, visual and verbal learning problems. The dose was intermittent in the Faroe Islands; the largest effect was in people with the lowest quartile of PCBs. If problems are found in the follow up of the Seychelles cohort, there would be a lowering of the maximum exposure. If no abnormalities are detected, this could possibly be explained by the intermittent Bolus effect, i.e., it is more harmful to get all of your mercury at one time, rather than spread out evenly through a small daily dose.

Dr. Halsey shared a chart plotting actual doses in the worst case scenario, i.e., children getting all thimerosal-containing vaccines. The issue of the birth dose has been addressed, but the largest possible dose is at two months of age--several times the birth dose. The smallest infants get more than 20 µg/kg of mercury. When ATSDR guidelines are superimposed, the smallest infants receive three times the ATSDR daily guideline, and 100 times as much as the EPA daily guideline. Without the hepatitis B dose, or cutting Hib or DTaP to only a single vaccine, levels are much more reasonable. A month's worth of exposure is actually parallel to FDA guidelines. The European Union recommends adequate labeling for sensitization on all thimerosal

containing medicines: "For vaccination in infants and toddlers, the use of vaccines without thimerosal and other mercurial containing preservatives should be encouraged."

Ten to twenty percent of children now have some multi-factorial developmental disorders. The cause is unknown in the majority. If you tell pediatricians it is okay to exceed guidelines, you are creating problems down the road with parents of children with disorders from unknown causes. Mostly likely no harm is being done, however preference should be set for vaccines without thimerosal preservative for infants, and it should be limited to no more than one thimerosal preservative-containing vaccine per visit.

Discussion

Dr. Le commented that such a recommendation makes it very complicated for physicians who have decide which of 15 vaccines to use on each visit. Dr. Halsey explained that the decision is made in the ordering process, not with each individual child. Dr. Brooks asked if vaccines would be postponed if only one thimerosal vaccine is given per visit. Data show that delaying hepatitis B means some children do not conclude the series. Dr. Halsey said they were not proposing postponing. This recommendation would help alleviate perceived need to postpone.

Dr. Jackson asked how significant nephrotoxicity was. Dr. Halsey responded that toxicologists say ethymercury can cause nephrotoxicity, but it occurs later than mild neurologic effects. Dr. De Rosa clarified the WHO guidelines. Mathematically the value of 3.3 µg/kg/day comports with a daily intake 0.47 µg/kg/day. Dr. Halsey pointed out that WHO guidelines are for nonpregnant women and older children and adults. Levels are lower for pregnant women and infants. Dr. De Rosa said WHO guidelines were being revised. He added that nephrotoxicity is associated with ingestion of inorganic salts of mercury. If ethylmercury is metabolized in the body, it will lead to some nephrotoxicity, but it is of less concern than neurotoxicity.

Discussion of Availability Issues and Impact on Public Immunization Programs

Mr. Dean Mason, NIP, ISD. CDC has about 29 vaccine contracts, roughly split between thimerosal and non-thimerosal products, representing 55% to 60% of the U.S. market. CDC has two contracts for DPT/Hib that contain thimerosal, which will not be renewed. Three of four DTaP contracts do contain thimerosal. The only combination DTaP/Hib product contains thimerosal. All hepatitis B vaccines have thimerosal, except Merck's newly licenced vaccine. Through March, this vaccine is being rationed, only for newborns and infants. FDA is reviewing a new SKB vaccine for use in infants. All influenza vaccines contain thimerosal, as does the pneumococcal vaccine.

Contracts do not guarantee supply or availability. Reasons for supply interruptions include production issues, failure to obtain FDA approval in time, and consumer demand. SmithKline Beecham assures availability of DTaP through calendar year 2000, and Hib vaccines in various

combinations appear to be in sufficient supply. CDC estimates it will receive one third of the hepatitis B thimerosal-free vaccine needed to vaccinate all infants.

Thimerosal decisions will mostly affect DTaP, hepatitis B, P&A and Hib products. Actions taken by ACIP will directly affect different manufacturers' market share. For example, PMC has 44% of CDC's DTaP purchases. Prior to the introduction of Merck's preservative-free HB P&A vaccine, it had 32% of market share, with the majority belonging to SmithKline Beecham (68%). A shift to Merck is anticipated, at least until SKB's licence application is approved.

Practical issues for state and local immunization programs:

- In March 1999, NIP determined that 43 or 67% of the 64 immunization programs allow private provider choice in selecting vaccine brands supplied through public purchase.
- CDC estimates there is at least $5.9 million in thimerosal-containing DTaP vaccines purchased through CDC's contracts in state, local and providers' present inventories.
- There is no return credit for vaccines not used when supplied through public purchase.
- The number of vaccine manufacturers with whom CDC contracts for DTaP would be reduced from 4 to 1.
- One manufacturer would be excluded entirely from CDC's market.
- Another company's market share would drop from 44% to 0.
- The preservative-free hepatitis B (P&A) vaccine is not sufficient to meet national need, though consideration of a combination Hib-hep B vaccine could reduce this problem.
- There may be increased risk with respect to vaccine supply when the U.S. market is totally dependent upon one manufacturer.
- Sole source contracts eliminate competitive pricing.

Discussion

Dr. Rennels commented that there is presently no thimerosal-free DTaP with a fifth dose indication. Dr. Orenstein pointed out that there's one product licensed for all five doses. Dr. Vernon of Merck advised that there is plenty of Hib/hep B combination available for 6 weeks to 6 months of age and the amount will increase dramatically as months go forward. Mr. Mason added that the SKB project when licensed will alleviate concerns.

Dr. Offit noted that 9% of birthing centers chose to suspend all hepatitis B immunization, even though there is no clear evidence that thimerosal harms. By stating preferences, there is the potential for misinterpretation and some children may not receive beneficial vaccines. Dr. Abramson said the AAP was in agreement, except for the 2- and 6-month issue. However, once the thimerosal-free vaccine is available, it would be preferable to go to back to the original recommendation and give a birth dose. Dr. Rennels said it was logical to prefer thimerosal-free vaccines, but it creates logistical problems and confusion. Dr. Guerra noted that timing and wording were critical. This should happen gradually and over time, without calling attention to the theoretical risk of toxicity.

Dr. Fleming asked how long it would take for DTaP thimerosal-free vaccines to be available. Carlton Meschievitz from PMC said they expected to have preservative-free product available by next year. There are efficacy and safety issues to be considered, in addition to thimerosal. Dr. Paradiso from Wyeth Lederle added that they were also working on removing thimerosal.. Since it will be a new project license, they have to do stability and safety analysis, which will take time. Dr. Keith said that North American Vaccine had a thimerosal-free formulation in Europe, and anticipated availability in the U.S. next year. Barbara Howe of SmithKline Beecham said they had the indication for a fifth dose of DTaP and were working to file a supplement to it. Dr. Egan added that the upcoming vaccines advisory committee would be discussing the fifth dose for DTaP.

Dr. Bernier offered the following points in favor of the current policy (no preference expressed for Hib and DTaP):

- Helps avoid confusion/complexity for doctors and nurses caused by product-specific recommendations.
- Helps avoid a good vaccine/bad vaccine dichotomy, when all vaccines are FDA-approved for safety and are considered equally safe.
- May help maintain the existing number of vaccine suppliers and competition, and assure the greatest number of suppliers of vaccines and the lowest possible prices for those vaccines.
- May help avoid more complex storage requirements for providers and vaccination programs around single dose preparations.
- Reduces potential for loss of existing inventory.
- Supported by scientific models showing that blood levels of mercury following vaccination, i.e., acute exposures, do not exceed blood levels found to be safe in human studies from chronic exposures.

Points against the current policy:

- Continues to expose infants to small amounts of mercury, which may be avoided more easily than exposure to other sources in breast milk or in the environment.
- Does not add further momentum to the declared goal to replace vaccines that contain thimerosal as a preservative.
- Does not provide an additional step to maintain public confidence in vaccines.
- Maintains the false impression that the hepatitis B vaccine is somehow riskier than other vaccines.

Dr. Bernier then read the core paragraphs, which contain new information:

The ACIP has learned that the supply of hepatitis B vaccine that does not contain thimerosal as a preservative was made available for the first time in September 1999 when Merck Vaccine Division began distributing a single-antigen preservative-free hepatitis B vaccine in single dose packaging. In addition, SmithKline Beecham Biologicals expects to make available a similar vaccine in the near future.

For DTaP, the committee has learned from SmithKline Beecham Biologicals that it is now able to provide an adequate supply of its current DTaP vaccine which is free of thimerosal as a preservative to meet the needs of the U.S. market for the next 12 months. For Hib vaccines, four of the current single-dose, single-antigen products (two under CDC contract) do not contain thimerosal as a preservative. The supply from these manufacturers is adequate to meet national needs.

Discussion

Dr. Johnson expressed concern about the second paragraph, which seems to express a preference. He suggested that the second paragraph be modified to emphasize that most manufacturers are headed toward vaccines without thimerosal as a preservative. Dr. Rennels asked whether ACIP should consider the premature infant as a unique situation and state a preference for thimerosal-free DTaP and Hib vaccines. Dr. Abramson explained that the AAP did make such a recommendation for hepatitis B. However, the risk of pertussis is significant as soon as the infant is born, and the thimerosal risk is theoretical.

Dr. Bernier read **Option #1**, which recommends no change at this time:

Despite these recent and anticipated changes in the vaccine supply situation, the ACIP proposes to make no further changes in current ACIP and CDC recommendations for the use of hepatitis B, Hib and DTaP vaccines at this time. Vaccination policies to reduce the exposure of newborns, particularly low birth weight infants, to hepatitis B vaccines which contain thimerosal as a preservative have been issued previously by CDC and are being implemented. The Committee believes the risk, if any, from exposure to thimerosal is negligible, and wishes to avoid the disruption to the immunization system that could result from preferences expressed at this time for other vaccines that do not contain thimerosal as a preservative. Thus, Hib and DTaP vaccines containing thimerosal as a preservative may continue to be used in the routine schedule along with vaccines which do not contain thimerosal as a preservative.

Discussion

Dr. Fleming suggested saying that the goal is move over to thimerosal-free vaccine and to set a target date by which the goal would be achievable. Option #1 should not start out with "despite," but rather should say that these changes are good and the Committee endorses change. Dr. Le suggested deleting the phrase, "that could result from preferences expressed at this time for other vaccines that do not contain thimerosal as a preservative." Dr. Clover advised against using the word "eliminating," because some vaccines may have to retain thimerosal. Dr. Pickering suggested incorporating the second sentence, "Vaccination policies to reduce the exposure of newborns...," into the introduction because it has already happened.

Public Comment

Barbara Malarkey, spokeswoman for the Illinois Vaccine Awareness Coalition, said they were concerned about long-term studies on mercury-free vaccines. In addition, they don't see the difference among newborns, two-month-olds, and six-month-olds. If hepatitis B with mercury

is removed, it should be done for all ages and all vaccines containing mercury. They asked the Committee to investigate other ingredients as well, such as formaldehyde, fetal bovine serum, hydrolyzed gelatin, lactose, monosodium glutamate, neomycin, phenol, streptomycin, and others.

Carlton Meschievitz advised that PMC was going before the Advisory Committee for their fifth dose application for Tripedia. They are in the final stages of review of a different acellular pertussis-containing vaccine (Primarisol 3), which should be licensed before the thimerosal-free Tripedia. This raises the issue of interchangeableness of pertussis vaccines and its implications on efficacy.

Dr. Bernier explained that Option #2 states a preference for using vaccines with thimerosal if thimerosal-free vaccine is unavailable, whereas in Option #3 the ACIP recommends postponing vaccination until thimerosal-free vaccines can be obtained. It was decided to focus on the core paragraphs and some of the language of Option #1. Dr. Bernier summarized the suggestions made earlier, saying he would make the changes overnight and bring in the revised statement the next day.

Dr. Orenstein emphasized the need to talk about the success of where we are today, but that more needs to be done. Dr. Snider said he was hearing that ACIP does want to publish in MMWR, but there has to be a context--that there are thimerosal-free vaccines available, but not all vaccines are thimerosal free. Dr. Guerra said he would like to see a statement about what has been accomplished safely with vaccines containing thimerosal. Dr. Fleming noted that it may not be possible to say when thimerosal-free products will be achieved, but ACIP will continue to make recommendations as the process continues.

Decision
Dr. Fleming made a motion to adopt Option #1, with the additional modifications. Dr. Rennels, Dr. Clover, Dr. Le, and Dr. Guerra had potential conflicts. Dr. Word, Dr. Tomkins, Dr. Brooks, Dr. Helms, Dr. Offit, Dr. Johnson, Dr. Fleming, and Dr. Modlin were in favor of the motion. None were opposed. Dr. Rennels, Dr. Clover, Dr. Le, and Dr. Guerra abstained. The motion passed.

Dr. Harold Margolis, of NCID, suggested adding "hepatitis B" to the last sentence of the first paragraph of Option #1, and also adding "beginning at 2 months of age" after "in the routine schedule." Dr. Bernier pointed out that the joint AAP/PHS statement spoke about initiation at 2-6 months, and CDC then stated its preference for 2 months. This would be endorsing the previous CDC position, which would be different from the AAP position. Dr. Margolis read the revised sentence: *"Thus Hib, hepatitis B and DTaP vaccines containing thimerosal as a preservative may continue to be used in the routine schedule, beginning at two months of age, along with vaccines which do not contain thimerosal as a preservative."*

Dr. Offit made motion to adopt the change, which was seconded. Those in favor of the change were Dr. Word, Dr. Tomkins, Dr. Brooks, Dr. Helms, Dr. Offit, Dr. Johnson, Dr. Fleming and Dr. Modlin. None were opposed. Dr. Rennels, Dr. Clover, Dr. Le and Dr. Guerra abstained. The motion passed.

BIOTERRORISM WORKGROUP UPDATE

Dr. C. Helms, University of Iowa, Chair Bioterrorism Workgroup. The ACIP/NVAC Combined Bioterrorism Subcommittee was formed to assist CDC with the use of vaccines for prophylaxis and treatment diseases of highest concern. CDC asked for input on evaluation of risk/benefits of using vaccines for anthrax and smallpox, recommendations for the use of vaccines in pre- and post-exposure civilian settings, and vaccination recommendations for specific groups, such as laboratory workers, first responders, etc. Today's presentation is a preface to the statement coming in six months on anthrax recommendations. Dr. Snider added that CDC is responsible for establishing a stockpile of vaccines to use in the event of an actual accident. This is a long-term project for ACIP.

Background for Recommendations for Use of Vaccine for Anthrax in Civilian Populations
Dr. David Ashford, NCID. Anthrax is a zoonotic disease caused by the spore-forming *Bacillus anthracis*. The route can be cutaneous, gastrointestinal or inhalational. It occurs globally, but the overall incidence is unknown. The largest recent epidemic was in Zimbabwe. In the United States the number of cases in humans has declined, with the last case in 1992, but about 100 cases a year are still reported among domestic and wild animals. The spores survive in the soil for many years, grazing animals ingest the spores and become infected, and humans can become infected from animals or animal products. Inhalational contact, the form of concern for biological terrorism, results from inhalation of aerosolized spores. Anthrax is not transmissible from person to person.

Around 95% of all cases originate from cutaneous contact. The incubation period is 1 to 7 days for cutaneous and gastrointestinal cases, and is unknown for inhalation, possibly up to 45 days. Skin infection starts as a small papule, and progresses to necrotic ulcer with eschar. GI anthrax begins with nausea and progresses to bloody diarrhea and vomiting. Inhalational anthrax starts with general malaise, progressing to severe respiratory disease and shock within days or hours. The case fatality rate for cutaneous infection is rare if treated, gastrointestinal infection fatality rate varies from 25% to 60%, and inhalational infection is fatal 80% to 95% of the time.

Pathogenesis
Anthrax has three major virulence factors: an antiphagocytic capsule and two protein exotoxins--lethal factor and edema factor. Both require protected antigen (PA) to be transported into the cell. PA is considered the primary immunogen. Penicillin is the antibiotic of choice for naturally occurring anthrax, also tetracycline, erythromycin, chloramphenicol and ciprofloxacin--all of which are effective in animal testing and in vitro. Resistance is rarely reported. Human

anthrax is controlled by reducing infection in livestock, supervised animal slaughter in meat inspection, import restrictions, biosafety precautions and education. Vaccination has been used for high-risk occupations. Anthrax has practically been eliminated in the U.S. by a combination of these strategies.

The only licensed vaccine is produced by BioPort Corporation. It is a cell-free filtrate of a non-encapsulated, toxigenic strain. It stimulates humoral immunity against protective antigen, which is believed to confer protection, but there is no surrogate marker defined for protection in humans. The currently recommended schedule is a primary series at 0, 2 and 4 weeks, followed by boosters at 6, 12, 18 months and annually thereafter.

Development of Acellular Anthrax Vaccine

- In 1947 it was shown that culture filtrate provided protection in animal models.
- In 1954, the first vaccine based on alum-precipitated culture filtrate was defined and the precipitate was named protective antigen.
- In 1956, the efficacy of the alum-precipitate filtrate vaccine was demonstrated in macaques, and produced humoral response in humans.
- In 1962, this vaccine was used in one human trial among textile mill workers.
- In 1963, aluminum hydroxide was introduced as the adjuvant, and the final product was approved in 1970. This is the vaccine available in the U.S.

The efficacy of the vaccine is based on animal and human studies. Studies in rodents show protection ranging from 20% to 90%. Macaques are considered a better animal model for inhalational anthrax of humans. Efficacy was good in controlled trials among macaques. The first three studies used original vaccine, and the second two used the newer formulation. Vaccination was two doses at 10 and 14 days. Survival was 100% in each experiment, except in macaques challenged at more than one year. The last two studies used the intramuscular rather than subcutaneous route of introduction.

The one human study was a randomized adjuvant control trial using original alum-precipitated culture filtrate vaccine, the same as the current series. It was conducted in four textile mills processing goat hair, with 379 vaccinees and 870 controls. Three cases occurred in the vaccinated group, and 23 cases in the unvaccinated group, five of which were inhalational. Estimated efficacy was 93%. Protection against inhalational anthrax was not specifically assessed.

Post-exposure chemo-prophylaxis: Penicillin, doxycycline, and ciprofloxacin have been shown to decrease development of inhalational anthrax in animals. Use of antibiotics is complicated by the latency of spores in the host, which are resistant to antibiotics and may continue to germinate for several weeks after infection.

Vaccine in combination with antibiotics for post-exposure therapy: In macaque studies, 9 of 10 of those receiving only penicillin died, while all those receiving both penicillin and vaccine

survived. This suggests that the antibiotic provided protection long enough for the vaccine-induced immunity to develop. The lack of protection by penicillin only was presumably due to latent spores.

Longer term post-exposure with antibiotics: In a 1993 study, antibiotics were continued for 30 days post exposure, and compared with macaques receiving doxycycline plus two vaccines post-exposure. After 30 days, 9 of 10 macaques receiving only doxycycline survived, while all those receiving doxycycline plus vaccine survived. Protection was conferred by extending post-exposure prophylaxis to 30 days.

Adverse events: In Brachman's study, mild local reactions occurred in 30% of recipients, moderate reactions in 4%, and severe reactions less frequently. Systemic reactions occurred in less than 0.02% of recipients. In a study submitted for the IND application, observed reactions were similar.

Challenges for the subcommittee:

- The efficacy of the vaccine is unknown in humans.
- Reactogenicity and safety data for certain segments of the civilian population are limited.
- Specific pre- and post-exposure recommendations will be based on limited data and there are no surrogate markers for protection.
- Risk assessment is difficult to define for bioterrorism.
- Recommendations need to be made for the vaccination schedule and route of administration.

VAERS Data and Adverse Events

Dr. Miles Braun, FDA. The VAERS program started in 1990, but previously there were no reports of adverse events following anthrax vaccination. VAERS is a passive surveillance system which gets about 11,000 reports a year overall, of which 10-15% are serious (lower for anthrax), and about 2% are deaths (none for anthrax).

Before the Persian Gulf War, there were no reports to FDA of adverse events following anthrax vaccination and no deaths. The number of serious events (hospitalization, permanent disability, life threatening) remains relatively stable over time, with an increase in non-serious events. The number of doses has dropped recently, but there may be increased adverse event reporting. There have been 24 serious reports in persons vaccinated after the Persian Gulf War. Some of the conditions reported include: bronchiolitis obliterans with organizing pneumonia, angioedema, two cases of Guillain-Barre syndrome, systemic lupus erythematosus, transverse myelitis, multifocal inflammatory demyelinating disease, and two cases of atrial fibrillation. Various other diagnoses were hard to link to the vaccine, and some reported multiple symptoms without diagnosis. These conditions may represent temporal but not causal association with anthrax vaccine.

Anthrax vaccine expert committee: The DOD contacted HHS to facilitate an independent review of anthrax VAERS reports. HHS, in collaboration with FDA and CDC, established a committee of five non-government physicians with experience in evaluating adverse events. They review and categorize all anthrax VAERS reports for causality. They have not identified a problem with the vaccine, but recommended enhanced safety studies.

Conclusions:

- There is no clear signal of a serious problem with the vaccine.
- There are limitations with passive surveillance.
- Continued monitoring is required.

Use of Anthrax Vaccine in the Military

Dr. John Grabenstein, Deputy Director of the Anthrax Vaccine Immunization Program Agency, DOD. The military has given 1.1 million doses of vaccine to 340,000 service members. There are two patterns of adverse reactions. Injection site reactions were mostly transient and self resolving. Most people had lumps, and small reactions were more common in women than men. Additional studies are planned to see if changing from subcutaneous to intramuscular injections resolves problems. Systemic events were also transient and self-resolving. A case control study concluded that vision change was not associated with vaccination. At Langley AFB, a survey of personnel who had returned within six months from SW Asia found no elevated relative risks by ambulatory category.

Summary:

- Surveys generate more information than occupational health style data collection.
- Injection site reactions are seen more frequently than systemic events; most are transient and self-resolving.
- Temporary events occur more often in women than men, primarily by the subcutaneous route.
- No effect was found on ambulatory diagnosis, hospitalization or vision.

Discussion

Dr. Rennels asked if any local reactions were not resolved. Dr. Grabenstein replied that nothing had persisted so far. Dr. Peter asked if there was any association with later doses as opposed to first dose, regarding local and systemic reactions. Dr. Grabenstein said there were data in both directions. Dr. Jackson asked about the nature of the vision change. Dr. Grabenstein said it had to do with visual acuity, the ability of the aviator to see the runway. Dr. Le asked if any HIV-positive servicemen were vaccinated, and if so, were there any side effects. Dr. Grabenstein replied that HIV-positive servicemen were excluded. Dr. Chen noted there were discrepancies in safety data, and asked if some cases were not showing up in the system. Dr. Grabenstein explained that the media frequently take numbers out of context. Dr. Chen said there were allegations of hepatitis B vaccinations causing demyelinization in France, and asked if that had

been seen in the U.S. Dr. Grabenstein replied that there had been only one or two such cases here, which was hardly a trend.

Dr. Weniger asked if anyone had talked to the Soviet defector who was involved in biological warfare about the development of strains not protected against by the current vaccine. There was no one who was aware of such a debriefing. Dr. Johnson asked about the status of the issue of subcutaneous vs. intramuscular injection. Dr. Grabenstein answered that there was a 200-person pilot study of intramuscular vaccination at Ft. Deitrich. It was found that most reactions go away, but the FDA has asked for larger study. Dr. Johnson asked about the original reason for subcutaneous injection. Dr. Grabenstein replied that it was the route used in the 60s, and was on approved labeling.

HARMONIZED SCHEDULE ANNUAL REVIEW

Dr. Roger Burr presented the recommended childhood immunization schedule approved last year. He showed how the harmonized schedule could appear if rotavirus and pneumonococcal vaccine were left off. The proposed changes include recommendations for an all IPV schedule for polio vaccine, wording change for the DTaP footnote, pneumonococcal conjugate vaccine, and rotavirus vaccine. The first change in the footnotes is a recommendation for a fourth dose of DTaP, which may be administered as early as 12 months of age, provided six months have elapsed since the third dose and the child is unlikely to return at age 15-18 months. Also, DTP-Hib will no longer be available on public contract.

Dr. Livengood pointed out that last year's statement saying DTP vaccines were an acceptable alternative has been removed. No alternative statement has been proposed. They are talking about no longer having DTP vaccines under federal contract during the first quarter of 2000. To complete the transition, they will no longer list DTP as an acceptable alternative.

Dr. Burr read the recommendation for an all IPV schedule:

"To eliminate the risk of vaccine-associated paralytic polio (VAPP), an all IPV schedule is now recommended for routine childhood polio vaccination in the United States. Children should receive four doses of IPV at 2 months, 4 months, 6-18 months and 4-6 years. During the transition, OPV can be used only for the following circumstances: mass vaccination campaigns to control outbreaks of paralytic polio, unvaccinated children who will be traveling in less than four weeks to areas where polio is endemic, and children of parents who do not accept the recommended number of vaccine injections. These children may receive OPV only for the third or fourth dose or both. In this situation health care providers should administer OPV only after discussing the risk for VAPP with parents or caregivers."

Dr. Abramson said that the idea was to have a transition period of six months, at the end of which we would have an all IPV schedule. Therefore no more OPV should be ordered and this will be stated in the December issue of *Pediatrics*. However, OPV is still acceptable as the third

or fourth dose in the transition period. Dr. Katz wondered whether in fact there would be any more OPV available. Dr. Modlin clarified that Dr. Abramson was referring to existing supplies, and that it was more of an economic issue. Dr. Peter suggested a footnote referring to *Pediatrics*.

Dr. Jackson asked what happens when parents refuse IPV and there are no supplies of OPV. Dr. Orenstein replied that there were efforts underway to develop a stockpile, which would only be used in the event of a polio outbreak. Dr. Modlin noted that if a parent were to refuse IPV, it was unlikely that the child would be immunized. Dr. Peter wondered if the third footnote could say, "These children will receive OPV (if available)," as a reminder that the vaccine may not even be available for children whose parents refuse IPV. He also recommended saying, "...unvaccinated children going to areas where polio is endemic or epidemic."

Dr. Guerra asked if any concessions were being made to keep a supply available for infants who accompany families to endemic areas. Dr. Orenstein replied that there would be some stockpiles in health departments initially, but that the vaccine would be outdated sometime in the year 2000 and that he did not foresee having a vaccine available for such a limited circumstance.

Dr. Modlin said he thought there was reasonable agreement to add a statement regarding the use of existing supplies. He wondered whether it would be specifically an AAP recommendation because there was no language to that effect in the ACIP recommendation. Dr. Offit said he thought ACIP's interest was to move to an all 4-dose IPV schedule, to eliminate the risk of vaccine associated with paralytic polio in this country and that extending for an additional six months because physicians have existing stocks of OPV would go against what had been decided.

Dr. Snider emphasized that it was important that the harmonized schedule be published collectively by the ACIP, CDC, AAP, and AAFP. The ACIP would not change its position, but for the sake of harmony would acknowledge the AAP variation in a footnote.

Dr. Zimmerman explained that notification of physicians of the all IPV schedule began last summer, but it may take them a while to make the change. Phil Hosbock (PMC) added that private providers usually have a one or two month supply of vaccines. Dr. Livengood drew attention to the fact the AAP did agree to list the IPV in all four doses in the harmonized schedule.

Dr. Le asked about putting hepatitis A on the schedule, since 20% of children would be getting it routinely. Dr. Modlin replied that the working group agreed not to put it on the schedule, since it is considered a regional recommendation based on rates of hepatitis A infection. Dr. Abramson noted that for a truely joint statement, the first dose of hepatitis B should be moved from birth to up through 6 months. Dr. Fleming cautioned that this would be a problem in areas where hepatitis A is already on the routine schedule. It would need to be acknowledged that hepatitis

A is an issue. Dr. Orenstein suggested a footnote saying hepatitis A is routinely recommended for children in certain parts of the country and that hepatitis A schedules will vary by state.

Dr. Pickering suggested that footnotes on the schedule should give websites telling people where they can get further information when changes are made. Natalie Smith, from the California State Health Department, advised against creating separate schedules for states and recommended using some sort of asterisk on the harmonized schedule. In addition, she felt that as the schedule gets more complex, the whole format should be evaluated. Dr. Peter suggested a sentence at the top stating, "Specific states may require hepatitis A, consult local health department." Rotavirus and pneumococcus could be at the bottom. In addition, there needs to be some way to say that additional vaccines may be licensed in the coming year. Dr. Orenstein cautioned against saying too much about particular vaccines that are not yet available.

Dr. Livengood said the committee removed wording to the effect that DTP remained an acceptable alternative and mentioned a fourth dose that could be given at 12 months. They also tried several wordings for hepatitis B and finally left it unchanged so that hepatitis B would not be singled out for the thimerosal issue. He prefers a fully harmonized position on hepatitis B vaccine.

Dr. Abramson said that leeway was purposely written into the AAP statement so that both sides could come up with a harmonized statement. If left as is, he requested a footnote stating that AAP prefers six months. However, if it were certain there there was enough thimerosal-free vaccine for 0 and 2 months, he would prefer to go back to original statement. Dr. Modlin asked whether the AAP could live with keeping the original statement with a footnote and Dr. Abramson said he could not make that assurance. Dr. Zimmerman noted that the AAFP was more in sync with the CDC/ACIP position.

Dr. Vernon from Merck reiterated that there is now enough thimerosal-free hepatitis B vaccine to satisfy all necessary doses from birth to 6 months. There is plenty of combination of Comvax and thimerosal-free single antigen Recomvivax for that population. Dr. Abramson argued that unless one can guarantee that every state will buy Comvax, there is a problem.

Dr. Livengood pointed out that the current footnote for HBsAg-negative mothers is the only place where there is a difference. It does not refer to birth dose or exact timing, just that the second dose should be at least one month after the first dose, the third dose four months after the first, and so on. It also says the first dose at birth should be thimerosal-free. Dr. Orenstein suggested saying, "When thimerosal-free vaccines are not available for infants born to mothers known to be HBsAg-negative, the following recommendations apply:" Dr. Offit felt there should be a single policy, otherwise it could be misinterpreted. The thimerosal problem is theoretical, but it is known that hepatitis B virus causes hepatitis B infection and the vaccine prevents it. Dr. Abramson added that the data are compelling that by not giving hepatitis B at birth, harm is being done. Dr. Watson, from Philadelphia, said that because hepatitis B has been singled out, there is more refusal, even in the adolescent population. She urged the committee to

come to uniform agreement. Dr. Livengood asked whether the AAP would accept a footnote saying that the AAP prefers 6 months if the joint statement says 2-6 months and Dr. Abramson said he thought they would. Dr. Trudell from IVAX cautioned that the possibility of misinterpretation remains, even if HBsAg-negative mothers are put in again. He strongly suggested saying 2 or 6 months.

Dr. Guerra pointed out the need to build in a process to educate practitioners, many of whom have no idea this is still a significant disease. Dr. Le noted that fewer than 20 states have a hepatitis B prenatal screening law. Dr. Modlin said the voting members seemed to want to go with the harmonized schedule as is, with a footnote to be worked out. It was decided that the working group would make final decisions via conference call.

After the break, Dr. Abramson announced he had consulted with the COID liaison to the AAP Board, who gave permission not to make changes, leaving the recommendation at 0-2 months with no added footnote. Dr. Peter noted that the footnote on polio needed to be changed to be consistent. "During the transition OPV can only be used for the following circumstances" isn't correct because mass vaccination campaigns could occur any time, not just during the transition. He volunteered to work with Dr. Livengood on the wording.

MENINGOCOCCAL VACCINATION OF COLLEGE STUDENTS: SHOULD COLLEGE STUDENTS BE VACCINATED FOR MENINGOCOCCAL DISEASE?

Dr. D. Fleming, Oregon Health Division, Chair, Meningococcal Working Group. The topic was introduced at the last ACIP meeting, when Dr. Rosenstein presented new data on the increased risk among college students. The working group is proposing a permissive enabling recommendation, which acknowledges a modestly elevated risk, particularly for entering freshmen living in dormitories, balanced by a low absolute risk. There is a safe and efficacious vaccine, and the cost is high relative to the expected benefit. Health care workers should educate students entering college as well as their parents. The vaccine should be made available to those who wish to reduce their risk of disease.

Public Comment

Dr. Jim Turner, representing the American College Health Association, spoke in support of the ACIP recommendation as written, which underscores the ACHA recommendation made in 1997. Data to be presented clearly demonstrate that subpopulations of students are at increased risk. An ACIP recommendation is critical to educate the public and assure availability of preventative pre-exposure vaccinations to incoming freshmen, and it will prevent reactive vaccination and antibiotic campaigns when there are one or more cases on campus. Diagnosis is evasive, particularly early on, resulting in critical delays in treatment and adverse outcomes, and the infection is destructive, even with appropriate and sophisticated treatment. Some 10% to 20% of patients die and another 10% to 20% suffer permanent sequelae (amputation, renal failure and neurologic complications). This is one of a few diseases where otherwise healthy students with

flu symptoms can be in coma in a few hours. Many cases could have been prevented by the vaccine. ACIP has a moral and ethical responsibility to give parents and students accurate information for informed choices.

Lynn Bosoff. Her son Evan died from bacterial meningitis. He was hospitalized for 26 days, both arms and legs were amputated and he suffered multiple organ failure. After Evan died, she learned there was a vaccine available that would have saved him. It had been successfully used by military. It doesn't matter if it doesn't protect against all serogroups or offer long term immunity. It is not too late to protect other young people. Give parents and students the information and they will make the choice to be immunized. That choice was not given to her.

Melanie Venn, a student from San Diego and survivor of meningitis, became infected four years ago, living in the dorm as a freshman. Both arms and legs were amputated, she lost function of her kidneys and received a transplant from her father. She didn't know about meningitis or the vaccine. If she had known about the vaccine, she is not sure she would have taken it, but she wishes she had been given the chance. Because she did survive, she considers it her responsibility to educate others about the vaccine. She is 22 years old, a college graduate, and lives independently, but it has been a struggle. With this vaccine, it is unnecessary for anyone else to endure the same struggle. The bacteria is rare, but very real. It's important to educate people to take a proactive approach to their own health.

Background

Dr. N. Rosenstein, NCID, DBMD, presented a graphic showing the disease year by year. There were large scale group A outbreaks in the 1930s, often associated with military deployments. Rates have been relatively stable in the last 20 years, about 2600 to 3000 cases a year. It has a mortality rate of 12%, and an additional 10% have serious sequelae, including limb loss, hearing loss and mental retardation.

Changes in epidemiology, including changing serogroup distribution

In 1990-92, serogroups B and C made up most of the disease in the U.S.; serogroup Y was only 10%. In 1995-98, serogroups B, C and Y each accounted for one third of the disease. The current vaccine doesn't protect against serogroup B. There have also been changes in the age group affected. Rates are still highest in children under age one, but have been increasing among adolescents (ages 11-17 and 18-22). There is no specific information about whether rates among college students have increased because there is no information on rates in previous years. There has been an increase in outbreaks among serogroups C, B and Y, although each outbreak was relatively small. Between 1994-1997, there were four outbreaks among college students.

Military data: There are parallels between college students and military recruits. In 1964-70, the rate of meningococcal hospitalization among active duty service members was 25/100,000 person years. New recruits in training camps were at highest risk. Large civilian outbreaks also occurred, which led to the development of the meningococcal polysaccharide vaccine. Routine

serogroup C vaccination among military recruits was initiated in 1971, and in 1982 they switched to quadrivalent meningococcal polysaccharide vaccine. The vaccination campaign has been successful.

Current recommendations suggest anti-microbial chemoprophylaxis for close contacts to prevent secondary disease, vaccine for high-risk groups, and vaccine for control of serogroup C outbreaks. Routine childhood vaccination is not recommended.

Studies
A survey of 2000 universities (38% responded), found 43 culture-confirmed cases over a two-year period, for a rate of 1/100,000. Rates were higher among students in dormitories.

A retrospective cohort study was carried out among Maryland College students using active population-based surveillance. A total of 67 cases between the ages of 16 and 30 were identified. Fourteen attended Maryland College, and 11 were in four-year colleges. The rate for all 18-20 year olds in Maryland was 1.4/100,000, whereas the rate among students in four-year colleges was 1.7/100,000, and it was higher among students in dormitories--3.2/100,000.

There were two recent CDC studies, with CSTE and ACHA. The first was an enhanced surveillance of meningococcal disease. State health departments were asked to determine if cases between the ages of 17 and 30 years were college students. This revealed that between September 1, 1998 and June 30, 1999, 88 cases were detected among college students, with 8 deaths. Of these cases, 50% were serogroup C, 20% were Y and 1% were W-135, suggesting that 70% of cases could have been preventable with the current vaccine. Of the deaths, four were C and one was B. The rate among 2-5-year-olds during same period was 1.7/100,000, and the rate among 18-23 year olds was 1.1/100,000. Overall rates for college students were not elevated, but they were slightly higher for freshmen and dormitory residents, and highest for freshmen in dormitories (5.2/100,000).

The second was a case control study. Cases were identified through college health centers and state health departments, and randomly matched to three controls by school, sex, and age group. The study found that freshmen in dormitories had an independently elevated increased risk of meningococcal disease compared to other college students. Radiator heat, white race, and upper respiratory infections were risk factors.

A recent study in the UK, where rates of meningococcal disease are higher than in the U.S., compared rates of meningococcal disease among students who live in districts with universities, with students in districts without universities. Colleges students in the UK do have elevated rates of meningococcal disease compared to the general population. Rates were higher in students living in universities with catered halls.

The American College Health Association has recommended that students consider vaccination to reduce their risk for potentially fatal meningococcal disease, and that health providers take a

proactive role in providing information and access to the vaccine. Parents and college student advocates have encouraged more widespread use of vaccine in college students. In a survey, 8% of 691 schools had non-outbreak vaccination campaigns. In the case control study mentioned previously, 3%-5% of controls were vaccinated in 1998/99. Multiple schools sent out information packets this past summer, some recommending vaccination, others merely informing students. There are no data on the proportion of students vaccinated.

A cost/benefit analysis conducted by CDC used 1998/99 rates of meningococcal surveillance data to model what would happen if 2.3 million freshmen or the subset of freshmen living in dormitories were vaccinated. They found that if freshmen in dorms were vaccinated, it would cost about $0.5 million to $1.6 million per case prevented, and the cost per death prevented would be approximately $5-17 million. At the higher value of life lost ($4.8 million), with cost of vaccine $88.00, there would need to be a lot more cases for vaccination to be cost effective. What mostly affects the analysis is cost of the vaccine and the number of cases occurring on college campuses.

ACIP statement:

Freshmen, particularly those who live in dormitories, constitute a group at modestly increased risk of meningococcal disease relative to other persons their age. Immunization with the currently available quadrivalent meningococcal polysaccharide vaccine will decrease the risk for meningococcal disease in individuals who choose to be vaccinated. Immunization will not eliminate risk as the vaccine confers no protection against serogroup B disease, and although it is highly effective against serogroups C, Y, W-135 and A, efficacy is less than 100%. The absolute risk of meningococcal disease among college students is low; therefore, immunization of all college students, of freshmen or of freshmen who live in dormitories or residence halls is not likely to be cost-effective from a societal perspective.

Individuals who provide medical care to freshmen, particularly those who live in or plan to live in dormitories or residence halls, should provide information about meningococcal disease and the benefits of vaccination to these students and their parents. Immunization should be provided or made easily available to those freshmen who wish to reduce their risk of meningococcal disease. Current data suggests that risk among non-freshmen college students is not elevated compared to the general population; however, vaccine can be provided to non-freshman undergraduates (traditionally those less than 25 years of age) who wish to reduce their risk of meningococcal disease.

ACIP further recommends that colleges provide information about meningococcal disease and the availability of a safe and effective vaccine to freshmen, particularly those who plan to live in dormitories or residence halls. Public health agencies should serve as a technical resource regarding meningococcal disease and vaccine for colleges and providers, including serving as a source of information regarding how to obtain vaccine.

Additionally, revaccination is indicated for individuals vaccinated more than 3-5 years earlier. There are no data indicating that other closed civilian populations are at similarly high risk, e.g., preparatory school students.

The polysaccharide vaccine is very effective for control of outbreaks and subgroups of college students at higher risk. The number of cases is relatively small in both groups. Because the serogroup B capsule is not immunogenic, serogroup B vaccine development has lagged behind vaccines for other serogroups. Several companies are working on the problem and a vaccine for serogroup B may be available in the next 5-10 years. In contrast, licensure of conjugate A/C/Y/W135 vaccine is expected much sooner, with a potentially large impact on meningococcal disease in the U.S. FDA is considering licensing them based on immunogenecity. The UK is poised to use a conjugate C vaccine next month.

Issues:

- Meningococcal disease has a broad age distribution, so a vaccine focusing on infants may be less efficient in reducing disease.
- Use of vaccine in toddler or adolescent populations could have significant impact on the disease, especially if it also prevents carriage.
- Decisions about vaccine formulation are complicated by multiple serogroups, specifically whether to include serogroup Y in the U.S.
- Because of the already crowded infant immunization schedule, combination vaccines are attractive.

Activities: Active surveillance data from the U.S. were used to model the potential impact of possible strategies, regarding age group, formulation and combination. Results were shared with vaccine companies to advocate for strategies that would maximize impact. They are now working on development of a ten-year strategic plan.

Discussion

Dr. Guerra asked whether there were any regional differences in college students, or by race, ethnicity, and SES. Dr. Rosenstein replied that rates were higher among white than black college students, and there were some differences by state and region, but it's only a single year of data. Dr. Modlin wondered if the higher rates in England reflected methodological or geographic differences. Dr. Rosenstein confirmed that rates in the UK were overall higher than the U.S. Ours are about 1/100,000, whereas theirs are 3.8/100,000 overall.

Dr. Fedson asked if any cases occur during flu season and whether influenza vaccine would be more cost effective if it might help prevent meningococcal disease. Dr. Rosenstein said that a high proportion of college students reported upper respiratory tract infections during their illness, but that meningitis cases occurred all school year long, not just during the peak of flu season. Some studies have shown influenza and upper respiratory tract infections are risk factors for

meningococcal disease. Dr. Abramson added that the best data are in serogroup A, which show a clear association with influenza.

Dr. Gardner asked how many of the 10,000 to 20,000 deaths a year from influenza in the U.S. are in the 18-20 age group and what influenza recommendations were made for college students. Dr. Turner of ACHA said there were sporadic disease clusters when students reconvene after summer, and around Thanksgiving, holidays and spring break. Occasionally there are cases during flu season, but they can occur throughout the school year. Dr. Gardner asked about flu itself as a morbidity and mortality factor. Dr. Turner responded that he had never seen a college student die from influenza. ACHA is pushing influenza vaccination as strategy for meningitis prevention. Dr. Nichol added that in a healthy adult population, excess deaths would be about 1 per 100,000.

Philip de Wells from Quebec offered some data on the efficacy of the polysaccharide vaccine in Quebec. They did a comparison of over five years of cumulative incidents among those who had the vaccine and those who refused it. After five years, there is still a clear advantage to be vaccinated because of potential of immuno-suppression.

Dr. Katz asked if there were any colleges or universities that require pre-matriculation vaccination for meningitis. Dr. Turner said there may be one or two small liberal arts colleges. ACHA estimates about 150-170 colleges recommended the vaccine this fall; two years ago there were fewer than ten. Dr. Modlin pointed out that in one college where it was offered, about 50% accepted the vaccine. Dr. Katz responded that in another college, 5000 out of 7000 students chose to be immunized. Dr. Modlin asked whether parents or students were paying for the vaccine, and whether any students say they can't afford it. Dr. Turner said that students are paying and cost has not been raised as an issue.

Dr. Fleming commented that this was not a cost effective strategy from a societal perspective. However, the working group felt there should be an obligation to help health care providers educate freshmen about risks of meningococcal disease and the benefits of vaccination. They also recommended an encouraging but permissive statement that the vaccine should be available to freshmen, but it shouldn't be a requirement, nor should public resources pay for this vaccine. Dr. Plotkin argued that when talking of cost effectiveness, one should determine cost to whom. The statement didn't take into account the destructive effects of outbreak and subsequent panic. It may not be cost effective from a public health point of view, but it is from a societal point of view. He recommended substituting "public health" for "societal," and would also add at the end of that sentence, "although individual protection may be provided." In the third paragraph, he would say "College health services and private physicians [instead of Individuals] who provide medical care to freshman....should provide written information about meningococcal disease and the benefits of vaccination before the freshman enters college." Dr. Fleming replied he had no problem with more specificity around individuals, but was concerned that if the information comes in written form [brochures], no conversations occur between patients and doctors.

Dr. Gardner argued that if the concern is about public health, then one should go back to the list of people at increased risk, including household crowding, chronic underlying illness, active and passive smoking, black race, alcohol use, etc. Dr. Zimmerman preferred informing parents and students about options and colleges providing this information, but was concerned about implementation. What about people who came in at age 15 for a sports physical? Should they be called in? Or those coming in at Thanksgiving for something else? How does this fit in with other prevention services?

Dr. Word asked whether the committee had addressed other at-risk groups. Dr. Fleming replied that the Committee was only asked for recommendations for college students. The conjugate vaccine is probably a long-term solution to the issue of other at-risk groups. Dr. Trump, DOD, wondered whether the ACIP should be more permissive with colleges about recommending the vaccine. The military takes living conditions, radiators and other factors into consideration.

Dr. Jackson noted that the committee should be recommending more research leading to a vaccine for serogroup B. Dr. Orenstein thought the Committee could consider financing vaccines for poor students. Dr. Peter was concerned that some colleges have had low rates of acceptance of the vaccine and wondered what could be done to facilitate implementation before a case takes place. Dr. Modlin asked Dr. Turner if colleges would need a recommendation from ACIP and was told that the way the recommendation is currently written would facilitate putting it on pre-matriculation and immunization forms.

Decision

Dr. Helms moved approval of the statement presented by the working group, with the understanding that the final language decisions would be made by the working group. Dr. Rennels and Dr. Guerra had a conflict with PMC. Dr. Brooks seconded the motion. Those in favor of the motion were Dr. Word, Dr. Tomkins, Dr. Brooks, Dr. Helms, Dr. Offit, Dr. Johnson, Dr. Le, Dr. Fleming, and Dr. Modlin. None were opposed. Dr. Rennels and Dr. Guerra abstained. The motion passed.

Introduction of Group C Conjugate Meningococcal Vaccine into the UK

Dr. D. Salisbury presented epidemiological data in England and Wales from 1912 to the 1990s. In 1997 there were 59 deaths in children under one year of age, a rate of 10/100,000. There were 54 deaths in children ages 1-4 years, or 3/100,000. The proportion of group C isolates was falling until 1994-95, when it started rising and now represents 40% of isolates. The remainder are group B. There is no significant presence from other strains. For group B, most cases are occurring in ages 0-4, with a small secondary peak in ages 15-19. For group C, there is a lower proportion of cases in ages 0-4, and more group C than B in the 15-19 age group.

Case fatality rates: Deaths from C are higher than for group B, especially in the 10-14 and 15-19 age groups. In 1997/98, deaths from group C peaked in age 15-19. Last winter, the burden of deaths increased even more. Numerically there are more cases in the 0-4 age group, but more deaths in the 15-19 age group.

Present overall estimates: We are estimating roughly 1530 cases/year for group C and 150 deaths. The public perception is that it is a serious problem though rare, however meningococcal disease is the number one killer of children in the UK.

In 1994, the Vaccine Evaluation Consortium changed its research focus to investigate group C meningococcal conjugate vaccines, based on the success of the Hib vaccine. This was done in advance of any changes in the epidemiology. They were aware of shifts elsewhere to higher proportion and virulence of group C. Public interest was high, but there was an absence of interest in manufacturers. The epidemiology now fully justifies the commitment.

Data from some studies: Immunization with doses of meningococcal C conjugate vaccine at 2, 3 and 4 months results in very high levels of antibodies by 5 months, but they fall rapidly and by 13 months are almost undetectable. If children are given a challenge at 13 months, there is a huge boost response, showing immunizational memory. The same study looked at one dose of vaccine given at 12 months, at the same time as the MMR. There were very low levels of antibodies beforehand and huge titers after one dose. Six months later there were low levels, but given a tiny boost, functioning immunological memory was demonstrated on all tests.

Reactogenicity: Some local reactions were seen, but the attributable burden of systemic reactions was almost zero.

Vaccination program: The objectives of the program are to reduce the number of cases and number of deaths, optimize supplies of vaccine, and utilize health services efficiently with minimal disruption. The goal is to immunize 14 million people within one year. The campaign starts November 1st, subject to satisfactory licensure, supplies, and implementation arrangements. Supplies are coming from three companies, which will enter the market sequentially.

There are two phases and two implementation routes, all publicly funded. Phase 1 is November to December 1999, and Phase II is January 2000 onward. Route I is children ages 0-5, and first-year college and university students. Route II is age 5 to school leavers (18). The first phase will be part of routine immunization for children ages 5 to 12. This year's freshman intake at universities has already been done and next year's freshmen will have gotten the conjugate vaccine this year.

Workloads: The target population in November is two million 15-17-year-olds. One nurse covers 150 children per day, over a six-week period. For Phase II, children ages 1-5 will receive one dose through primary care. Children ages 5-15 get one dose in school. The target population is 6.5 million children and immunization will take 25 weeks.

Resources needed: The campaign is funded centrally. The budget includes vaccine purchase, payment to GP's, and promotion work. Other resources are needed for information materials for health practitioners, parents, young people, students, teachers, schools, universities and colleges, TV and advertising, a parents' telephone health line, and data collection on implementation and impact.

Cost effectiveness issues: We looked at cost per dose, number of doses, giving younger ones three doses vs older ones one dose, delivery costs, and burden of hospitalization. We used age-specific mortality rates from PHLS data, and looked at rate of major complications by age. Life years gained were discounted to base year by age of immunization, and costs were discounted by 6%. It was found that the younger children are immunized, the more life years are saved. Older children are more likely to have sequelae. If one is being hardnosed, it is less cost effective to give three doses, but you can't <u>not</u> immunize on the basis of cost.

Outcome: The UK is the first country in world to introduce group C meningococcal conjugate vaccine.

Discussion

Dr. Offit commented that there seemed to be memory in the absence of circulating antibodies and wondered if there was adequate time to reactivate memory in time to prevent disease. Dr. Salisbury replied that the Hib example suggests there is high antibody avidity even with the low level of antibodies that remain and the response is rapid with a single booster dose. Dr. Mark Nutzer, CDC, wonder if the meningococcal vaccine might suppress one set of strains which would allow another strain to come in. Dr. Salisbury replied that there is already an ongoing study on carriage strains in advance of the vaccination. It is looking for a replacement effect from taking group C strains out of the environment or switching, so that B starts to express C epitopes. It's a theoretical concern.

Dr. Chen asked if there were any formal plans for the next phase. Dr. Salisbury responded that data had already been collected from Phase II studies and that a large reactogenicity-specific study was unlikely. If new hypotheses are raised from passive surveillance, they would quickly turn to large-link databases. Dr. Egan asked if there were any data from the trials on the efficacy of the vaccine to support not giving a booster shot. Dr. Salisbury said he was not aware of any case of invasive disease in any recipient of conjugate vaccine. Within six months of giving a dose to a one-year-old, circulating antibody levels are very low again, but one would not boost every six months. The same is true with Hib.

Dr. Paradiso of Wyeth Lederle wondered if the apparent increase of disease after 1994/95 was simply an increase in surveillance. Dr. Salisbury replied that the shift to higher proportion of group C is a biological observation being seen in other countries. Dr. Paradiso asked if that meant an increase in total meningococcal disease as well. Dr. Salisbury said yes, but it may be real and/or a reporting effect.

Dr. Ball asked how they established their serologic correlate of protection. Dr. Salisbury replied that the licensing authority was prepared to accept surrogates of protection based on immune correlates, against the data on plain polysaccharide and the data on antibodies after infection. Dr. Ball asked if this was established in ages other than infants and Dr. Salisbury replied that it was.

Dr. Katz asked whether they had used conjugate and polysaccharide for the boost. Dr. Salisbury responded that they had used plain polysaccharide, and conjugate as well. They also used conjugate in young people who had plain polysaccharide before. They do not see the same hyper-responsiveness when plain is followed with conjugate. Dr. Katz commented that a polysaccaride challenge would be more akin to what happens with natural infection. Dr. Orenstein asked how they got funding for all the activities listed, other than vaccines. Dr. Salisbury's response was that the UK has a National Health Service.

Thursday, October 21, 1999

ACIP Review of the Risk of Exposure to Thimerosal and Progress Toward Obtaining a Supply of Vaccines Free of Thimerosal as a Preservative (revised wording)

On October 20, 1999, the ACIP reviewed information about thimerosal in vaccines and received updates from the National Immunization Program and several vaccine manufacturers on the current and anticipated availability of vaccines that do not contain thimerosal as a preservative.

This review of thimerosal in vaccines and of the vaccine supply was prompted by a joint statement about thimerosal issued on July 8, 1999, by the American Academy of Pediatrics (AAP) and the Public Health Service (PHS) and a comparable statement released by the American Academy of Family Physicians (AAFP). Thimerosal is a mercury-containing preservative that has been used as an additive to biologics and vaccines since the 1930's because it is effective in preventing bacterial and fungal contamination, particularly in open multi-dose containers. Given the widely acknowledged value of reducing exposures to mercury, vaccine manufacturers, the Food and Drug Administration, and other PHS agencies are working together to replace thimerosal preservative-containing vaccines with vaccines that do not contain thimerosal as a preservative as soon as possible without causing unnecessary disruptions in the immunization system

The Committee was encouraged by the licensure of a single-antigen preservative-free hepatitis B vaccine (Merck & Co., Inc.,) on August 27, 1999 and by the report that a second hepatitis B vaccine (SmithKline Beecham Biologicals) which does not contain thimerosal as a preservative is under consideration for licensure. The FDA has committed to an expedited review of manufacturers' supplements to their product license applications to eliminate or reduce the mercury content of vaccines. Also, the Committee welcomes the information that the supply of DTaP vaccine from one manufacturer (SmithKline Biologicals) which does not contain thimerosal as a preservative could be increased significantly to meet any increased demand over the next year, and that other manufacturers are also developing similar vaccines that could be licensed in the future. For Hib vaccines, the Committee was pleased to confirm that multiple Hib vaccines that do not contain thimerosal as a preservative are already licensed and that the supply of these projects is adequate to meet national needs.

The Committee re-examined information presented earlier this year to the AAP and the PHS and at a public workshop held at the NIH in August 1999. The Committee reviewed the thimerosal content of vaccines used in infants and the health risk, if any, that infants might experience from vaccination with these products. The Committee believes the risk, if any, from exposure to thimerosal is negligible, and concurred with the evaluation of the AAP, AAFP and PHS and their conclusion that the large risks of not vaccinating children far outweigh the theoretical risk of exposure to thimerosal-containing vaccines over the first six months of life.

Given the progress that is being made in the development and availability of vaccines that do not contain thimerosal, and given the conclusion reached by the Committee on the risk, if

any, of exposure to thimerosal, the Committee judged that Hib, hepatitis B, and DTaP vaccines that contain thimerosal as a preservative should continue to be used in the routine infant schedule beginning at two months of age along with the vaccines that do not contain thimerosal as a preservative. For newborns, the Committee is concerned about reported failures to immunize high-risk infants following misinterpretation or poor implementation of the recommendations in the joint statement by AAP and PHS to postpone hepatitis B vaccination only for lower risk infants. Concerned by this development, the Committee strongly endorses the CDC recommendation issued on September 10, 1999 to resume vaccination at birth for all infants with vaccines that do not contain thimerosal as a preservative.

The Committee resolved to review progress towards achievement of the national goal to obtain a vaccine supply free of vaccines that contain thimerosal and to issue additional recommendations when appropriate to further promote this goal.

There was continued discussion about wording, and then it was agreed that the final document would be E-mailed to members of the committee and ex-officio members.

Dr. Chinh Le raised the following questions for future consideration:

- Can we reduce the number of doses for some routine immunizations? There are 23 injections by the time a child reaches kindergarten, sometimes 25.
- Do we really need four doses of IPV when two doses give 99%-100% seroconversion?
- Can we re-examine the need for two doses of hepatitis A vaccine? One dose has stopped outbreaks, the Israeli army uses one dose and we know we get 99% conversion with one dose. This would cut the cost of the program in half.
- Can we resolve the issue of DT booster for adults? After age 50 (ACP) vs. every 10 years (CDC)?
- Can we learn from other countries, and can the U.S. licensing of some combination vaccines already available elsewhere be accelerated?
- We have achieved 90% immunization rate, which is no worse than other industrialized countries.
- Can we drop one or two doses and still maintain a very good immunization program, drop costs, put breathing room in the schedule for other vaccinations to be introduced later, and avoid the pin cushion syndrome--five shots a visit.
- When we look at the immunization schedule next year, let's look at diseases one by one.

REPORT OF ADULT WORKING GROUP

Dr. Clover noted that Dr. France of the American Association of Health Plans should be added to the working group. They were unable to get acellular pertussis on agenda, so it will be on the agenda of the February meeting. The group is planning to begin the revision of the adult immunization recommendations before the February meeting. There were discussions at the last ACIP meeting about where standings orders for immunization should be implemented. The most

significant change in the current draft recommendation is limiting standing orders to nursing homes and skilled nursing facilities.

Dr. Shaffner reported that in reviewing published data on utility and efficacy of standing orders, the working group found a strong recommendation that standing orders be implemented in long-term care facilities, but there was very little information for acute care, corrections, assisted living, etc.

Dr. Nichol agreed that it was important to distinguish among facilities, and felt the data on direction and magnitude of effect were more convincing in the in-patient and outpatient setting, as well as long-term care. However, there is no reason to expect standing orders wouldn't be effective in other venues. Dr. Clover suggested focusing on skilled nursing and home facilities first, acknowledging that the recommendations will change. Dr. Fleming thought the data in the *Guide to Preventative Community Services* should be considered and Dr. Guerra added that the American Pharmaceutical Association was not mentioned either. Pharmacists are part of the community-based health effort and linkages should be broadened.

Dr. Zimmerman cited an article by Dr. Nichol saying the sensitivity of patient (elderly, managed care and VA setting) remembrance of vaccination was 97% to 100%. That means the negative predictive value is very high, which is key to the safety issue. Dr. Nichol added that sensitivity and specificity are extremely high for influenza vaccine, but not quite as high for pneumococcal vaccinations. Dr. Fedson supported not diluting language that would encourage hospital-based vaccinations. People hospitalized for influenza-related illness account for less than 10% of the elderly population but account for half of the influenza-related hospitalizations, and two thirds of the influenza-related deaths. For pneumococcal illness, two thirds of deaths occur among people previously seen by hospitals.

Dr. Word said she had difficulty with the concept of recording the patient's refusal, because in some cases patients cannot verbalize their wishes. She suggested wording indicating that the guardian refuses. Also, she suggested that patients going to long-term care facilities should be given adequate information in the admission package on the risks and benefits of immunization. Dr. Gardner pointed out that pharmacists enjoy an extremely high approval rating by the public, so this venue should be encouraged. Also, pharmacists do send records to doctors. Dr. Mast added a number of other settings, such as STD clinics and drug treatment centers.

Decision

Dr. Clover moved that the committee accept the working group draft on standing orders. The motion was seconded by Dr. Guerra. No one was in conflict. Those in favor were Dr. Word, Dr. Rennels, Dr. Tompkins, Dr. Brooks, Dr. Clover, Dr. Offit, Dr. Johnson, Dr. Le, Dr. Fleming, Dr. Guerra and Dr. Modlin. None were opposed. None abstained. The motion passed.

Yellow Fever Vaccine and the Elderly: Age-specific Risk of Adverse Events
Dr. M. Cetron, NCID, DQ. Yellow fever 17D vaccine is one of the safest vaccines, with 60 years of recorded history. Adverse events are mostly in young children and infants. In August 1998, there were two reports of severe systemic illness in elderly YF vaccine recipients. The objective of the study was to determine if the elderly are at increased risk of systemic adverse events from YF vaccine

Yellow fever is an acute flaviviral infection from a mosquito-borne flavivirus, which can cause multi-systemic hemorrhagic fever with hepatitis, renal failure, encephalitis, etc. It occurs in tropical regions of South America and Sub-Saharan Africa. The vaccine is a live attenuated vaccine prepared from the 17D strain of the virus. Protective immunity occurs in over 95% of vaccinees within 10-14 days. There are rare reports of vaccine-associated encephalitis, exclusively in infants.

Summary of two index cases: The first was a 76-year-old male with an onset of fever, myalgias and headache four days after receiving the vaccine. He spent two weeks in the hospital, characterized by confusion, renal failure, mild hepatic disfunction, and thrombocytopenia. The patient fully recovered. The YFV-17D + mutant was detected by PCR. The second case was a 70-year-old female, who experienced diarrhea, cough, shortness of breath, and confusion two days after receiving the vaccine. She spent 16 days in the hospital, with respiratory failure, renal failure, hypertension, leucopenia and thrombocytopenia. She died on day 16, three weeks after vaccination. The 17D strain was detected as well.

Risk of adverse events: Age-blinded reports submitted to VAERS from 1990 to 1998, restricted to the civilian population, were reviewed. Hepatitis A reports were used as a comparison vaccine. Each of the events was categorized as systemic, other or clearly not related to YFV. Characteristics included neurologic and multi-system events, GBS, new onset seizures, encephalitis, alternated mental status, etc. Onset was within two weeks, with duration $\geq$ 72 hours. Multi-system events included GI events, elevated liver transamanases, respiratory distress, and others. Onset was within two weeks, $\geq$ 24 hours after vaccine and with a persistent duration of three days. The "other" category included hypersensitivity, rash, local reactions, onset within 48 hours.

The denominator was the annual number of YFV doses sent to providers by manufacturers from 1990-1994. U.S.-based geo-sentinel clinics provided the number of YFV recipients by age and the distribution by age group was extrapolated. Very little wastage of vaccine was assumed. There were 5000 YF recipients and 25,000 hepatitis A recipients.

Results: The study found the rate of adverse events was about 3-4 per 100,000 population. When comparing systemic and local hypersensitivity, they found systemic adverse events increased with age, but not local adverse events. Using hepatitis A as a comparison, there was a slight increase in the higher age group, but nothing like YFV. When looking at the relative risk

of YF administered alone and in combination, the effects were more pronounced when taken in combination.

Reported risk calculation: Using 25-44 years as a reference group, there was a 4- to 12-fold increase in risk in 65 to 74-year-olds. When the definition was restricted to events requiring hospitalization or resulting in death, there was a strengthening of statistical association by age.

VAERS deaths following YFV: Three deaths occurred. Most illnesses were characterized by fevers and myalgias, which progressed to renal failure, hepatitis, encephalopathy, and coma. There was a fairly consistent pattern of presentation.

It is important to contrast these VAERS findings (rare event) with the real risk of YF if one is not vaccinated. The dramatic increase in the amount of international travel to YF endemic areas increases risk. Dr. Cetron reviewed four cases of imported YF in last the four years, all with lab evidence of yellow fever and no vaccination. He presented two maps, one showing distribution of YF endemic areas and another showing YF vaccination requirements and recommendations. Sometimes the vaccine is given for political reasons; many countries require a stamp on health cards for border entry. This creates confusion among providers about when to give the vaccine.

Limitations:

- Estimated age distribution for 1998 is assumed to apply to the whole study.
- Possible age related reporting bias
- Age-specific SAEs to YFV may be a general age-related response to vaccination.
- The proximity of an adverse event does not prove causality, but plausibility.

Conclusions:

- There is an increased risk of systemic adverse events among the elderly.
- This may reflect age-related changes in immune response to flaviviral infections.
- The risk of systemic reaction of YFV in elderly travelers must be balanced against the YF risk.

Potential Follow-up Activities

G. Mootrey

- Enhance follow up of serious VAERS reports, including retrieval of medical records
- Periodically review of VAERS cases by CDC
- Administer questionnaire to VAERS reporters, providers, vaccinees
- Distribution of VAERS postcards to all YF vaccinees
- Convene expert panel for clinical review and causality assessment of serious YF VAERS reports
- Develop protocol for pathologic investigation of deaths following YFV
- Dissemination of information, using Internet, travel media, VAERS web site, travelers health web site, etc.

Discussion

Dr. Tomkins said she was struck by fact that they could isolate the YF virus and asked about the proportion of people who don't develop adverse events but are viremic after YF vaccination. Dr. Cetron explained that the virus itself wasn't isolated, rather footprints of the virus were identified and sequenced. Data indicate that viremia is expected with vaccine strain virus after immunization. Finding slight variations on the genotype is probably not that uncommon. Having a protocol available to get specimens from autopsies would be very valuable.

Dr. Chen noted that the safety issue is difficult because travelers often get vaccinated right before they depart. Dr. Gardner commented that the incubation periods seemed remarkably short. He encouraged the surveillance system to document mild symptoms as well as severe. Dr. Modlin asked whether any of these travelers had received vaccine before. Advanced age may be a marker for repeat vaccination. Dr. Cetron replied that prior vaccination wasn't documented. Dr. Guerra noted the similarity between dengue fever and yellow fever symptoms. He wondered if those who were vaccinated with YF actually had dengue. Dr. Cetron said there was overlap in some areas, but not everywhere. Also, if one is exposed to one flavivirus and then has another, there are higher titers to the first flavivirus because of non-specific cross-reaction. Lisa Weld, DQ, pointed out that none of the index case people who died had traveled. All died before they left the country.

Carlton Meschievitz informed the group that PMC was developing warning labels. Also, their French counterpart reported eight cases of encephalitis since marketing of their YFC product began. In over 100 million doses, only one case occurred in an elderly man, who recovered. Dr. Modlin suggested that the warning be balanced with YF risk language. Phil Brunell asked whether the elderly individuals were immunocompetent. Dr. Cetron replied that they appeared to be, but that many elderly have pre-existing medical conditions. Dr. Chen pointed out that most of the 100 million doses of PMC vaccine go to EPI programs in Africa, where it is difficult to conduct surveillance.

Combination Hepatitis A/B Vaccine

Dr. Betsy Abraham, SmithKline Beecham, presented a clinical profile of Twinrix, the world's first combination hepatitis A/B vaccine. It is composed of hepatitis A antigen and hepatitis B surface antigen, with 0.45 mg aluminum salts. It is already approved in several countries, including the European Union, Canada and Australia and is currently under review with the FDA for adults aged 18 and above. It is given on a three-dose schedule, at 0, 1 and 6 months. The target population is adults ages 18 and over who have not previously been vaccinated with either vaccine.

Over 5000 doses were administered in clinical trials and blood was drawn five times. At month 7 (one month after the third dose), seroconversion was 99.9%, with GMTs of over 5000. In the U.S. trial, they compared subjects given Twinrix with subjects given the monovalent vaccines. A total of 773 subjects were vaccinated, randomized into two groups. One group received 3

doses of Twinrix, the other received a total of 5 shots--two Havrix and three Engerix-B. For hepatitis A, the monovalent group showed 99.3% seroconversion, with titers of 3000. The Twinrix group had 99.6% seroconversion, with GMTs of 5000. For hepatitis B, monovalent seroconversion was achieved in 92%, and Twinrex had 95% protection.

For antibody persistence, 129 subjects in two clinical trials were followed up for four years, and the persistence of anti-HAV and anti-HBs titers were comparable. The rate of decline was fairly consistent for Havrix and Twinrix. For local reactogenicity, the rate of local injection site pain was 44%, all transient. General systemic side effects were felt in 17%, including headache and fatigue. The most frequent adverse events were soreness, headache, and fatigue. Rates were comparable for Twinrix and Havrix.

In summary, less than two percent of all doses were followed by grade 3 events. There were a total of 29 serious adverse events, 8 in non-U.S. studies, and 21 in U.S. studies, none related to the vaccine. There were no unsolicited adverse events attributable to the vaccine and no deaths.

Post-marketing surveillance reports (non U.S.). A passive surveillance system is maintained by SKB in a single global safety database. Out of 2.4 million doses, 273 adverse events were reported, 50 of which were serious.

Since the safety profile of Twinrex is comparable to that of monovalent vaccines, protection against both infections can be achieved with three shots instead of five. Target groups are travelers to endemic areas, MSMs, patients with hepatitis C or other chronic liver disease, drug users, and members of the armed forces.

Future steps:

- Consider vaccination of individuals at clear risk of either infection or at potential risk of the other (health care workers, public safety workers, patients who attend STD clinics, personnel and inmates in correctional facilities, people in long-term care facilities, staff of day care centers, residents of high endemic areas, close contacts of carriers or infected individuals, and patients who require regular transfusions of blood products).
- Consider vaccination of individuals at clear risk of one infection and who desire to be protected against the other.

Discussion

Dr. Le asked whether the post-marketing surveillance included pediatric patients and was told the pediatric formulation was different. Dr. Gardner asked if they had considered giving two doses of Twinrex, which takes care of hepatitis A, then a straight hepatitis B shot. Dr. Abraham replied that it took three doses to get 99% seroconversion. However, they do have two doses of Twinrex outside the U.S. Dr. Nichol asked if there were data comparing vaccine to placebo for side effects and was told there were none. Dr. Jackson asked if the number used in reporting antibody response to combination was additive, and how they knew what the response was from. Dr. Abraham explained that they measured A and B separately, even when given together.

Dr. Clover commented that if PMC is going to change their insert for yellow fever, maybe the adult working group should look at the YF statement and change it appropriately. This idea was accepted, and the working group will make minor revisions at their next meeting.

UPDATE FROM DECISION RULES WORKGROUP

Dr. Guerra said this issue had been postponed because of vaccine safety issues. They hope to finalize the recommendation for the February meeting. Dr. Bernier announced that Bill Atkinson would be taking the lead, working with Dr. Le.

The latest version was distributed at the National Immunization Conference, where it received supportive comments from AAP and the Association of Immunization Managers (AIM). It has been field tested with focus groups. Overall there seems to be strong support for the flexibility the new approach will bring to immunization decision-making at the clinical level. There is a recommended age of vaccination for the first dose of DTP, with no flexibility. There is also an accelerated schedule. That recommended age has been doing double duty, functioning as accelerated age to vaccinate, but also interpreted as a cut-off. The committee wants to create a period of flexibility no matter which schedule is used. They will send the committee a table with the new values.

Discussion

Dr. Fleming and Dr. Clover both felt that flexibility would be appreciated, although Dr. Bernier was concerned that people might take advantage of the zone of flexibility. He suggested saying "on time, early, too early, and too late." Dr. France pointed out that problems arise when the child is 11 months 3 weeks old and is told to come back in a week for MMR. He asked why the yellow zone couldn't be extended for MMR and Varivax to a couple of weeks before the first birthday. Dr. Bernier explained it was enshrined in school laws. The committee decided the gain from universal application of the model was not worth the pain and made an exception for MMR. The plan is to take four days off the interval and present it for final approval in February.

INFLUENZA VACCINE

The working group met over the summer, especially because thimerosal is an essential ingredient in influenza vaccines. They were also looking at new neuraminadase inhibitors and older antiviral agents.

Use in Pregnancy and Young Children

Dr. Fukuda explained that currently ACIP recommends an annual flu vaccination for women in the second and third trimester of pregnancy during influenza season, also for children over six months with several chronic medical conditions, including asthma. Children from age 6 months to 18 years on long-term aspirin therapy should also be vaccinated. During the summer, thimerosal concerns were raised and discussed. The working group decided no change in recommendations was indicated for pregnant women and high-risk children. Dr. Ray Strikas,

NIP, added that CDC has had relatively few inquiries about the influenza vaccine, thimerosal and recommendations for infants and pregnant women.

Dr. Snider said he was concerned earlier that raising the thimerosal issue might do more harm than good, going into vaccination season. Some felt it was a non-issue, but Dr. France said it was an issue in some locations. As flu season goes forward, more people will be asking about thimerosal. He felt a statement strongly in favor of the flu vaccine would allay any questions. Dr. Zimmerman asked what the projected timetable was for the potential of removal of thimerosal from flu vaccine, and was told that one company says next year, another says it isn't possible, the other two have not been asked. However, there is limited chance of any thimerosal-free vaccine next fall. Dr. Modlin asked if there were any strong feelings about a separate publication. Dr. Fleming responded that it was important to have a statement for immunization programs. An alternative would be to put a couple of lines in the thimerosal statement approved this morning. Dr. Le noted that in California they promoted flu vaccine for pregnant women with a consent form for thimerosal, and there was not a single objection. Dr. Siegal this was an issue for employee health services in hospitals, because people are so aware of infant and fetal issues.

Decision

It was agreed to incorporate a sentence about flu vaccine in the thimerosal statement. No voting members were conflicted with flu vaccine manufacturers. A motion was made by Dr. Clover, and seconded by Dr. Guerra, to accept the following draft statement:

Annual influenza epidemics result in an average of approximately 20,000 deaths and 110,000 hospitalizations per year, many of which are preventable through vaccination. Annual influenza vaccination is recommended for persons who are at increased risk of serious complications from influenza, including persons greater than or equal to 65 years, persons residing in nursing homes or long-term care facilities, anyone aged ≥6 months of age with certain chronic medical conditions such as heart or lung disease (including asthma); diabetes; renal insufficiency; hemoglobinopathies; immunocompromising illnesses or conditions requiring the use of immunosuppressive medications; women who will be in the second and third trimester of pregnancy during the influenza season; and children and adolescents aged 6 months to 18 years receiving long-term aspirin therapy who may be at risk for developing Reye syndrome after influenza. In addition, health-care providers, family members, and others in close and frequent contact with high-risk persons should be vaccinated to diminish virus transmission.

Some vaccines, including all currently licensed U.S. manufactured influenza vaccines, contain thimerosal, a mercury-containing compound used as a preservative. This compound has been used for over 60 years in vaccines and is a very effective means to prevent bacterial and fungal contamination. The Food and Drug Administration Modernization Act of 1997 called for the FDA to review and assess the risk of all mercury-containing food and drugs. On July 8, 1999, the U.S. Public Health Service and the American Academy of Pediatrics issued a joint statement about the use of vaccines containing thimerosal, and the American Academy of Family

Physicians released a comparable statement. The July 8 statement recommended changes only in the hepatitis B vaccination schedule for children born to hepatitis B surface antigen-negative women, but not for other vaccines routinely given to children. A subsequent statement by CDC on September 10, 1999 recommended resumption of the previous hepatitis B vaccination schedule, because of the availability of thimerosal-free hepatitis B vaccine. These statements did not discuss recommendations for use of influenza vaccines.

There is clear evidence that children with medical conditions such as cardiopulmonary disease, including asthma, are at substantially increased risk for complications of influenza. In a study of children enrolled in a health maintenance organization, children with high-risk medical conditions were almost six times more likely to be hospitalized with influenza-related illness than those without high-risk conditions. High-risk children aged 0-14 years has an excess rate of 290 hospitalizations per 100,000. Influenza vaccine is licensed and recommended for such children beginning at 6 months of age. There are no data or evidence of harm associated with the level of exposure to mercury in thimerosal-containing vaccines that some children may have encountered in following the existing immunization schedule. Based on these considerations, the risks of not vaccinating high-risk children far outweigh the unknown and probably much smaller risk, if any, of neurodevelopmental effects posed by exposure to thimerosal-containing vaccines.

However, because any potential risk is of concern, the PHS, the AAP and the vaccine manufacturers agreed that thimerosal-containing vaccines should be replaced with thimerosal-free vaccine whenever possible. Vaccine manufacturers, FDA, and other PHS agencies are working together to expeditiously replace thimerosal preservative-containing vaccines with vaccines that do not contain thimerosal as a preservative while ensuring maintenance of high vaccination coverage levels and prevention of disease.

Routine influenza vaccination is recommended for pregnant women who will be in their second and third trimesters of pregnancy during the influenza season because they are at substantially increased risk for complications of influenza. During the influenza season, the rates of cardiopulmonary hospitalizations for otherwise healthy women in their second or third trimester of pregnancy are similar to those among persons aged 65 years and older who do not have a chronic medical illness and for whom influenza vaccination is also recommended. In addition, pregnant women with chronic medical conditions have a hospitalization rate more than two times higher than among pregnant women without other high-risk medical conditions. The issue of possible fetal vulnerability to mercury exposure deserves special consideration, because the rapidly developing brain of the fetus is much more susceptible to mercury effects than the adult brain. However, there is a significant safety margin incorporated into the health guidance values for daily mercury exposure developed by the Department of Health and Human Services. The health guidance value was based on studies of infants born to women whose average daily mercury blood levels, including throughout pregnancy, exceeded by more than 20-fold the maximum mercury blood level that a pregnant woman would receive from a single annual dose of thimerosal-containing influenza vaccine. The amount of mercury in the vaccine is equivalent

to the amount that a pregnant woman would ingest in three days from an average daily diet in the United States. After review of available data, CDC recommends no changes in the current influenza immunization guidelines, including those for children and pregnant women.

Those voting in favor of the motion were Dr. Word, Dr. Rennels, Dr. Tomkins, Dr. Brooks, Dr. Clover, Dr. Offit, Dr. Johnson, Dr. Le, Dr. Fleming, Dr. Guerra and Dr. Modlin. None were opposed and no one abstained. The motion passed.

Neuraminadase Inhibitors

Dr. K. Fukuda, NCID, DVRD. Influenza recommendations traditionally covered both vaccine and antiviral agents. There is now a new class of influenza-specific antiviral drugs, the first since amantadine and rimantadine. In July 1999, the FDA approved zanamivir for treatment of acute, uncomplicated influenza. Oseltamivir is in submission for FDA approval. Other NI's are under development. The Influenza Branch drafted guidelines for the use of these agents for the 1999-2000 flu season, which they plan to publish in mid-December in MMWR. They will then be incorporated into ACIP recommendations in February. Dr. Snider emphasized that the ACIP charter does not include recommending the use of specific drugs. Dr. Fukuda added that this is a new class of drugs, there has been considerable media attention and intense marketing efforts, and CDC has received many questions about their use.

Andrea Winquist, Influenza Branch, explained that two versions of the statement were prepared. The version used will depend on the status of oseltamivir. The focus is on the use of the agents for treatment, with minimal discussion of prophylaxis. The guidelines will be revised to reflect the fact that they are not an ACIP recommendation. The indication emphasizes the importance of the influenza vaccine and states that antiviral agents are an important adjunct to vaccine.

The trials of zanamivir and oseltamivir enrolled patients with recent onset of influenza. Results were presented as reduction in duration of symptoms for the treatment group as compared to the placebo group. Results of efficacy studies varied widely. For zanamivir, in the influenza-positive population with no fever, results varied from a less than one-day reduction in duration of symptoms to a 1.5-day reduction. For the febrile-positive population, reduction in duration varied from less than one day to 2.5 days. The oseltamivir studies found a 1.2 to 1.4 day reduction in duration of symptoms (febrile, influenza-positive population). In summary, when initiated within two days of illness onset in otherwise healthy persons, zanamivir can reduce the duration of symptoms considered moderate or severe due to uncomplicated influenza by approximately one day. A similar statement can be made for oseltamivir, leaving the time blank currently.

Some reviewers felt reports of no significant benefit in patients treated more than 30 hours after onset should be cited. However, it was not clear the study had the power to detect a significant benefit in this group. The degree of precision possible in measuring the time of symptom onset is questionable. For zanamivir, the wording in the package states that it should be used for

treatment of patients symptomatic for no more than two days. If oseltamivir is approved, wording will be used to match the package insert.

Some reviewers suggested saying that the reduction in duration of symptoms is 1 to 1.5 days, instead of one day. However, we felt that citing the range from 1 to 1.5 days would give a false impression that one day was the lower end of the spectrum. There were suggestions we should state that treatment with these agents can reduce symptom severity. However, since duration and severity were not entirely separable in these studies, we elected not to make a separate statement about severity. We plan to add that efficacy appears greatest among febrile patients.

Limited clinical data suggest that zanamivir is effective for treatment of infections due to influenza B viruses as well as influenza A. Some reviewers suggested that statements regarding influenza B should be stronger. In a zanamivir meta-analysis, only 220 influenza-infected subjects had influenza B, compared to 1,352 patients with influenza A. For oseltamivir, information about type of influenza is limited to one study, in which 92% of subjects had influenza A.

For persons at high risk for serious complications, data are limited and not conclusive concerning the effectiveness of zanamivir for treatment of influenza. No published data are available on effectiveness of oseltamivir on high-risk populations. Three zanamivir studies included persons at high risk for complications of influenza. Two found a statistically significant reduction in duration of symptoms among persons at high risk for complications. Most patients were considered high risk because of asthma or age. A meta-analysis found a 2.5 day reduction of symptoms in this group, but this was not statistically significant. Neither zanamivir nor oseltamavir has been shown to be effective in preventing serious complications of influenza. Two studies reported that zanamivir reduced complications (primarily bronchitis, pneumonia and other chest infections) and/or associated antibiotic use. One study found oseltamivir significantly reduced complications.

Prophylaxis: Amantadine and rimantadine are both approved for prophylaxis (primarily bronchitis and sinusitis), while zanamivir is currently only approved for treatment. If oseltamivir is approved, it will probably only be for treatment. We chose to only briefly summarize the results of the major prophylaxis studies. Prophylactic dosages differ from treatment dosages.

Pharmacokinetics: When administered by oral inhalation, only 4% to 17% of zanamivir is systemically absorbed. Absorbed zanamivir is excreted in the urine. Oseltamivir is well absorbed after oral administration, metabolized by hepatic esterases to GS4071, and excreted in the urine via the anionic pathway.

Clearance of zanamivir is reduced in persons with renal impairment and limited data are available regarding safety and efficacy in these patients. However, oral inhalation at recommended doses should result in serum levels below levels well tolerated in healthy persons given zanamivir intravenously. Therefore the manufacturer does not recommend dose

adjustment for persons with renal impairment. For oseltamivir, a dose reduction is recommended. The manufacturer does not expect the metabolism to be altered in persons with hepatic disease, but we do not know what the package insert might state if it is approved.

Side effects and adverse reactions: For treatment, the main concern for zanamivir is decreased FEV1 in patients with asthma or COPD. For oseltamivir, the main concerns are nausea and vomiting. There are no known or expected drug interactions for zanamivir, and it does not impair the immunologic response to influenza vaccine. For oseltamivir there is a potential for interaction with agents that are excreted via the anionic pathway.

Resistance to zanamivir and oseltamivir can be induced in vitro, but requires several passages in cell culture. It is unknown whether these findings indicate that clinical drug resistance will occur less frequently with zanamivir and oseltamivir than it does with amantadine and rimantadine. No resistance to zanamivir has been found in clinical trials to date, but resistance was identified in a case in which the drug was used on a compassionate basis. For oseltamivir, resistance has been identified in clinical trials, but it appears to be rare. We concluded that development of viral resistance to both drugs during treatment has been identified but does not appear to be frequent.

Amantadine and rimantadine inhibit only influenza A, while zanamivir and oseltamivir inhibit both A and B viruses. There are also differences in side effects and cost. In conclusion, all four agents are roughly comparable in reducing the duration of uncomplicated acute illness due to influenza A when treatment is started shortly after onset of symptoms.

Discussion

Dr. Le mentioned an unpublished study by Glaxo in North America, which showed no significant cost benefit of zanamivir. He was bothered that the data won't be published and that publication of negative studies is not encouraged. Barbara Styrk, from FDA, said the Glaxo study was discussed by FDA and is reflected in the package insert. Joan Tomlin from Glaxo added the data were presented at the ICC in Birmingham in July and are publicly available.

Dr. Abramson said the AAP was concerned about zanamivir being used in children. The document should highlight that it was not approved for use in children because of the amount of cooperation required to use the device. Second, he asked if physicians should do a lab test every time the drugs are used, or could clinical factors be used (i.e., father or mother with flu). Third, a cost comparison in the table would be helpful. Dr. Gardner commented that recommendations were needed for pregnant women, since pregnancy is a high-risk condition. Dr. Winquest replied that zanamivir is pregnancy category B.

Dr. Le recommended stating that there are no data on combination use of Amantadine/Rimantadine with the neuraminadase inhibitors. Doctors may try to use all available drugs for very sick patients. Dr. Word suggested saying patients have "activity," not "influenza A and B." Also, the wording about cost implies one is more expensive than another. Dr. Guerra noted that this was an opportunity to educate communities about flu. Often

companies create epidemics to market products. Also, the importance of early diagnosis and confirmation should be stated, to minimize inappropriate and over-use of antibiotics. Dr. Plotkin urged that the prophylaxis section be strengthened. Although zanamivir is not yet recommended for prophylaxis, the data are impressive. Dr. Rennels felt practitioners needed to know more about the bronchospasm following an asthmatic attack and safety issues. Dr. Le noted that pharmacists' involvement in patient education would be important.

Dr. Tomkins asked whether ACIP would take up other antiviral drugs and get involved in treatment recommendations. Dr. Snider replied that CDC's major concern would be for chemo-prophylaxis, with no major emphasis on treatment. Dr. Le pointed out that there is an ACIP statement on prophylaxis and treatment of Lyme disease.

Recommendations for Routine Influenza Vaccination for Healthy Young Children

The risk of serious complications from influenza is elevated in young children, based on several old and new studies. Dr. Fukuda showed a table with hospitalization rates, by age, during separate periods dominated by influenza viruses on RSV (CDC study). Among Healthy children younger than age two, rates of excess hospitalization attributable to influenza ranged from 86 to 112 hospitalizations per 100,000 person months using a periinfluenza baseline to 127 to 151 hospitalizations per 100,000 person months using a summer baseline.

Data show that trivalent inactivated vaccine (TIV), and live attenuated, cold-adapted vaccine (LAIV) are effective in preventing illness in children. It is uncertain if TIV and LAIV are comparably effective. There are questions about the risk of reversion of live attenuated vaccines to a more virulent strain, reassortment with circulating viruses, and development of secondary infections. The risk to immunocompromised populations is unknown. There are several questions about the logistical feasibility of vaccinating this group. Can pediatricians' offices handle the increased visits? Who will pay for the effort and how would it affect the vaccine supply? Would this be cost effective over a several year period of time?

In summary, regarding young children, there is no licensed LAIV at this time and certain issues remain open, such as safety of LAIV, feasibility, cost effectiveness, what age group would be targeted, and what the cumulative effect of another recommended childhood vaccine would be. There are several studies underway or planned to look at these safety issues. Another consideration concerns AAP recommendations.

Considerations for the 50-65 Age Group--Healthy Adults

Influenza mortality begins to increase in the 50-65 age group and rates of high-risk conditions begin to increase as well, but the risk for serious complications in healthy persons is uncertain.

CDC plans home-based studies of healthy and high-risk persons ages 50-64.

- Data on vaccine effectiveness indicate both TIV and LAIV are effective.
- There are no additional safety issues for this group.

- Feasibility questions are the same, such as who would administer and who will pay. There are 39.8 million people in the age group and people in close contact with flu patients are already included in ACIP recommendations.
- Manufacturing capacity and effect on demand and distribution, and cost effectiveness over time will have to be assessed.

Reasons to recommend vaccination of healthy adults:
- Prevalence of high-risk conditions increases in this group.
- 50 years is the time to begin preventive care.
- Age-based recommendations are effective.
- Condition-targeted recommendations are not as effective.
- No new safety concerns.
- AAFP has made this recommendation.

Counter-considerations:
- The burden of disease in healthy persons in this age group remains unclear.
- Has targeted vaccination been given an adequate opportunity?
- Can vaccine supply reliably meet the demand?

Discussion

Dr. Clover stated that the AAFP has endorsed this recommendation, as have other professional organizations. Dr. Guerra noted that many people in this age group don't have access to primary care systems. The burden will fall on health departments, which don't have systems and capacity in place. In a large work force, when vaccine is offered free, only 10% accept. Dr. Clover noted that risk-based targeted programs are still needed. Mr. Graydon said many people in that age group were already being vaccinated in different ways. Dr. Fukuda explained that high-risk adults make up about 25% of that group, and vaccine coverage generally ranges below 30%. Dr. Nichol added that vaccination rates in Minnesota for all people ages 50-64 was about 39%. For people 18-64, it's about 29%.

Dr. Modlin asked about cost effectiveness specifically in this population. Dr. Nichol said she was working on a cost-effectiveness analysis looking at healthy people ages 18-64, with net savings based on productivity. Dr. Zimmerman felt the question was not whether, but how and how quickly and how intensely to make this recommendation. Carlton Meschievitz commented that, from the manufacturers' point of view, the earlier the decision is made the better. February would be a bit late. Dr. Fedson noted that the total number of doses of flu vaccine distributed in 1997 in the U.S. accounted for 25% of the population. We're vaccinating 70% of the over-65 population, who represent 12% of the population. So the majority of vaccines are going to people under 65.

It was decided to postpone a decision until the next morning.

Public Comment

Carla Newby, Meningitis Foundation of America. Her son died a year ago from pneumococcal meningitis. Doctors needed to do a spinal tap, but didn't act quickly enough to diagnose and start proper treatment. Other children survive, but suffer lifetime disabilities. She strongly supports the new vaccine for all children as part of the routine immunization schedule. She also urged inclusion of children up to 5 or 6 years old, with a strong, clear recommendation. We can't assume parents or doctors will figure it out without a recommendation to vaccinate all children. Some say it is not cost effective to vaccinate all school-aged children, but look at your own children and grandchildren and tell them their life is not worth the cost of the vaccine.

Barbara Malarkey, Illinois Vaccination Awareness Coalition. She shared Rep. Dan Burton's grandchildren's adverse reaction to vaccines. His granddaughter almost died after a hepatitis B shot and he would appreciate an investigation of VAERS reports. His grandson became autistic after nine vaccines, four shots and the OPV at one time. He compared it to an overloaded circuit. What long-term safety studies have been done regarding the receipt of nine vaccines at once and what are the synergistic effects? The flu vaccine insert packets state there are no data on fetal harm when injected in pregnant women, and that there are no studies of flu vaccines injected together with pediatric vaccines. Is a child injured or killed following a vaccine less important than one injured or killed from a disease?

RECOMMENDATIONS FOR THE USE OF THE PNEUMOCOCCAL CONJUGATE VACCINE

Dr. Johnson, Michigan Department of Health
Dr. Chris Van Beneden, NCID, DBMD

Development of Recommendations: Factors taken into consideration by the working group

Three levels of strength of evidence exist:

A. There is strong epidemiologic evidence, including efficacy studies, to support use of the vaccine.
B. There is moderate evidence, including immunogenicity and safety data, to support use of vaccine.
C. Effectiveness has not been supported by efficacy or immunogenicity studies, but is anticipated based on studies among other groups. Other data used to support a recommendation are burden of disease (rates of disease and severity, infection by antibiotic-resistant organisms), lack of or questionable efficacy of PPV23 in younger children, and expected cost effectiveness.

After looking at all the evidence, we came up with four levels of strength of recommendation:

A. *Strongly recommended:* efficacy, immunogenicity and safety are demonstrated, and there are high rates of disease.

B. *Recommended*: immunogenicity and safety are demonstrated in some studies, very high rates of disease, and questionable efficacy of PPV.

C. *Recommended in the context of limited data*: groups with increased risk of disease, lack of or questionable efficacy of PPV, and safety data on use of conjugate vaccine in studies of similarly aged children.

D. *Groups that may benefit from immunization (permissive)*: increased risk of disease, increased risk of infection or colonization with drug-resistant organisms, and safety of conjugate vaccine demonstrated by studies of similarly aged children.

Strongly recommended:

- The working group strongly recommends that all healthy children less than 36 months should be immunized with PCV7 at 2, 4 and 6 months of age, with a fourth dose at 12-15 months. A catch-up schedule is included for children over 7 months old at first immunization. Strength of evidence: A

Immunization recommended:

- The working group recommends that all children less than or equal to 59 months with sickle cell disease (SCD), including those with hemoglobin HbSS, HbSC or hemoglobin HbS-betathal, or who have functional or anatomic asplenia, should be immunized with the conjugate vaccine. The schedule for children less than or equal to 23 months, is the same as for healthy children. The schedule for children 24 to 59 months is two doses of vaccine given two months apart, followed by one dose of polysaccharide vaccine a minimum of two months after the second dose. It is also recommended that penicillin prophylaxis be continued up to age 5. Strength of evidence: B

- The recommendation is that all HIV-infected children less than or equal to 59 months should be immunized with conjugate vaccine. The schedule for those less than or equal to 23 months is the same as for healthy children. Schedule for those ages 24-59 months is the same as for the sickle cell patients. Strength of evidence: B.

Immunization recommended in context of limited data:

- The ACIP recommends all children less than or equal to 59 months who are immunocompromised, excluding those who are HIV infected, or who have chronic illness should be vaccinated with the conjugate vaccine. The schedule for those who are less than or equal to 23 months is the same as for healthy children. The schedule for those who are 24-29 months is one or two doses of the conjugate vaccine given two months apart, followed by one dose of polysaccharide a minimum of two months after the second dose. Strength of evidence: C.

- The ACIP is recommending in the context of limited data that children aged less than or equal to 59 months who have received a bone marrow transplant should be immunized with the conjugate vaccine, regardless of whether they have been immunized prior to the bone marrow transplant. The proposed schedule is two doses of the conjugate vaccine

given two months apart, starting at 12 months after the bone marrow transplant. Health care providers should also consider giving a third dose of the conjugate at 24 months after the bone marrow transplant. One dose of polysaccharide should be given a minimum of two months after the last dose of conjugate vaccine. Strength of evidence: C. One study on immunogenicity and safety is pending.

- Immunization is recommended in the context of limited data for Alaskan natives and American Indians aged less than or equal to 59 months should be immunized with the conjugate vaccine. The schedule for less than 23 months of age is the same as for healthy children. The schedule for those 24-59 months of age would be one dose of the conjugate, followed by one dose of the polysaccharide a minimum of two months after the conjugate. Strength of evidence: C. There are studies pending.

Dr. Van Beneden presented a table showing that rates of invasive pneumococcal disease for Alaska natives and American Indians are higher than for whites, but lower than for children with SCD and HIV. They did not consider recommending use of the conjugate vaccine for children over age five because 1) proposed licensure was for up to age five, 2) the rates fall progressively after age two, and 3) the conjugate vaccine is a 7-valent vaccine, which covers most serotypes in young children but the coverage begins to decline after two years of age.

After two years of age, African Americans have higher rates than white Americans, but they decided not to single out African Americans for the following reasons: 1) the total burden of disease is still much lower in this age group, 2) the serotype coverage has decreased in all higher age groups, and 3) there are only two years of catch-up vaccination. African Americans have never before been singled out for a recommendation.

Permissive statements:

- Providers should consider administering a single dose of conjugate vaccine to unvaccinated children aged 36 to 59 months who have had frequent or complicated episodes of acute otitis media (AOM) during the previous year. The recommended schedule is a single dose of conjugate vaccine and the strength of evidence is B. These children have an increased risk of tympanotomy tube placement and antibiotic prophylaxis, and they are at increased risk for antibiotic resistance. Efficacy and safety have been demonstrated in younger children with AOM, including recurrent AOM.

- Providers should consider administering a single dose of conjugate to unvaccinated children aged 36-59 months who attend group child care. The specific definition of group child care is a setting outside the home where the child regularly spends four or more hours per week with at least two unrelated children under adult supervision. Recommended schedule is one dose of conjugate vaccine. Strength of evidence: B. Other support includes increased risk of invasive disease and increased risk of infection and colonization of antibiotic-resistant S. pneumoniae. There is potential for cost effectiveness among this group.

- Persons 5 years and older who are at high risk for pneumococcal infection: Conjugate vaccine is currently only being evaluated for those up to age five, but small studies have shown immunogenicity of the conjugate vaccine in older children with HIV infection and with sickle cell disease. In contrast, small immunogenicity studies among elderly and HIV-infected adults ages 18 to 65 showed no increased benefit of conjugate over polysaccharide. Therefore, the working group recommends that administering the conjugate to older children with HIV infection or sickle cell is not contraindicated, but it is not being recommended. Current data are inadequate to recommend replacing the polysaccharide with conjugate in older high-risk children and adults.

- Use of PCV7 among children previously vaccinated with PPV23: The working group suggests that health care providers should consider immunizing high-risk 24 to 59-month-old children who have already received PPV23 with a single dose of conjugate, a minimum of 2 months after vaccination with polysaccharide. There is still questionable efficacy of the polysaccharide among certain age groups. Also, the PCV7 generates immune memory.

- Use of PPV23 among children previously vaccinated with conjugate vaccine: The suggested ACIP statement is that children who have completed the conjugate immunization before two years of age and are in risk groups for which the polysaccharide is already recommended should still receive one dose of polysaccharide at the age of two years, a minimum of two months following the last conjugate dose. There is expanded serotype coverage from PPV23, especially as children age. Safety of PPV following PCV has been demonstrated by five studies.

- Revaccination with PPV23: The suggested ACIP statement is that immunocompromised children or children with sickle cell disease or functional or anatomic asplenia should be revaccinated with the polysaccharide as previously recommended by the ACIP in a Red Book committee. If the child is less than 10 years of age, revaccination with the polysaccharide is recommended three to five years after the previous dose of polysaccharide.

Addition to draft submitted to ACIP: If a child receives the polysaccharide and then receives the conjugate vaccine, either one or two doses, any potential dose of polysaccharide should be given at least three years following the first dose of polysaccharide.

Discussion

Dr. Johnson explained that the draft statement recommends universal vaccination with conjugate vaccine up through 35 months of age. The working group discussed whether to recommend universal vaccination for the 36 to 48-month age group, and for four-year-olds. They turned to rates of invasive disease in those age groups for targeted vaccinations. Dr. France asked about safety and immunogenicity information for primary series beginning after 7 months. Dr. Johnson replied that there was less evidence, that the best data were on those who were started at

less than six months. Dr. Van Beneden added that the data on efficacy were for age two months to 120 days. Children were followed up to 36 months, but the entry date was up to age 120 days.

Dr. Offit gave grounds for a universal recommendation up to 59 months. The rate of invasive disease for *Neisseria meningitis* in incoming college students was 5/100,000, while the rate for invasive *S. pneumoniae* disease in 2-5 year olds was 49-53/100,000. Dr. Van Beneden replied that they weighed the benefits of immunization against the potential side effects in groups with lower rates of disease. Dr. Johnson commented that cost played a role as well. Also, there's a disconnect between the conjugate vaccine and the serotypes that are causing the disease as children age. Rates are high, but mortality rates are low in these age groups. Dr. Modlin asked about the relative contribution of various types of serious invasive disease to these rates. Dr. Van Beneden replied that it is primarily bacteremia, with a low percentage of meningitis and pneumonia.

Dr. Fleming asked about expectations for aggressiveness of the catch up. Should children over 15 months be recalled or provided with the immunization when they come in for other reasons? Dr. Johnson said they felt there were fewer but still opportunities in the third year of life, when children interact with health care providers. Dr. Abramson pointed out that the recommendation must deal with parents who want the vaccine but whose children fall outside the age range. An option would be a permissive recommendation, such as we have for the meningococcal vaccine.

Dr. Egan asked if there was an age at which the polysaccharide becomes a more effective prophylaxis than the conjugate. Dr. Van Beneden replied that serotype coverage by age group falls rapidly and Dr. Modlin added that data aren't sufficient to be precise enough. Dr. Peter suggested putting the table [showing rates of invasive pneumococcal disease] in the draft statement to explain why vaccine for children over age three is not routinely recommended, but it's not contraindicated either. Second, he was not convinced that two doses were needed in the second year of life. Seroconversion is more important than comparing antibody titers. Dr. Van Beneden explained that the recommendation for two doses was based on comparing GMTs to Kaiser data. [She showed an overhead with geometric mean concentrations for all serotypes, ages, and dose regimens.] Even if antibody levels are correlated exactly with protection, there are no data to set a lower limit because of the vaccine's high efficacy.

Dr. Word wondered if eligible children would be reimbursed for something in the permissive recommendation category. Dr. Orenstein replied that if it's in the VFC resolution, it would be covered. Dr. Word noted that with the original cutoff at 35 months, some children still have high rates. To be more permissive, she suggested dropping the cut off even lower to clearly identify children at high risk for invasive disease. Dr. Johnson explained that it is only in the 36-59 months age group that we have either recommendations or permissive recommendations, i.e., those who attend day care or have re-occurrent otitis. He asked if Dr. Word was suggesting a permissive recommendation for African American children. Dr. Word said that the rate of 46/100,000 jumps out. Dr. Johnson said the data include children with SCD, but even if they are excluded, there is still an increased rate for three-year-old African Americans. Ben Schwartz

explained that the working group did consider the higher risk of disease in African Americans. SCD accounts for about 10% of increased rate, and he was not sure how many fell into the HIV, day care, or otitis categories. In a case/control study of children with invasive pneumococcal disease, significant risk factors included crowding but not race. Perhaps the higher rates in African-American populations are due to SES or living conditions. Dr. Orenstein said the data show a one-year difference between whites and African Americans, so one would either have to recommend the vaccine for 4-year-old African Americans or make it permissive for all children through age five. His second point was that there will be competition among public sector providers for resources, and decisions will have to be made when some children are covered by VCF and others are not.

Dr. Zimmerman shared Kline's review of the epidemiology of pneumococcus. In the first year of life the incidence range is 3-8/100,000, in the second year of life it is 1/100,000 and for ages 3-4 it drops to 0.3/100,000.

Dr. Katz thought bone marrow transplant patients should get vaccines before the transplant, not afterwards, although Dr. Modlin thought many wouldn't respond very well. Dr. Katz said it varies depending on the type of transplant. Clare Dykewicz, NCID and editor of the draft Bone Marrow Transplant Guidelines, said there are not a lot of data about immunogenicity and efficacy of immunizing pre-transplant patients. Many lose immuno-memory cells after the transplant. Some studies indicate the best way is to immunize donors, so they have a surge of antibodies before donation. But donor-acquired immunity also wanes, so one still has to re-immunize the patient after the bone-marrow transplant.

Dr. Jackson said he preferred a recommendation up to 59 months in order to raise immunization rates, and because of the emergence of resistant pneumococci. Certain minority groups remain at greater risk after 36 months, but the NMA strongly recommends this vaccine for all children disproportionately impacted by this disease, including but not limited to African American, native American and Alaskan native children through 59 months. It further recommends that conjugate and polysaccharide vaccines be considered for inclusion in the VFC program.

Dr Modlin asked about the implications of raising universal vaccination to five years of age. Dr. Johnson said there were several options: 1) permissive recommendation for all children not already recommended under this statement in the 36-59 months group, 2) permissive or stronger recommendation for African American children, or 3) recommendation for a catch-up dose for all children. Regarding financing, Dr. Orenstein said about 60% of vaccines in this country are purchased with public funds. About 60% of that is VFC, about 25% is the 317 program, and the remainder is state purchase. If Congress does not give the President what he has requested, the public sector might have to prioritize.

Dr. Breiman said it would be useful to have data showing why the conjugate is superior to 23-valent in older children. Dr. Van Beneden replied that there were no direct comparison studies, but polysaccharide studies showed the response to some serotypes was lower than expected (ages 2.5 to 4). Also there is maturation of the immune response. Dr. Paradiso of Wyeth Lederle added that the data suggest that children 2-5 years of age are responsive to some types of polysaccharide and not responsive to other types, especially Types 6 and 23, whereas they are responsive to the conjugate.

Dr. Fedson noted that the wording for healthy children is "strongly recommended," whereas for children with sickle cell and functional or anatomic asplenia, whose risk of disease is 60 times that of healthy children, the vaccine is just "recommended." He felt public health concerns ought to have greater weight in the wording of a recommendation. Dr. Johnson explained they were trying to communicate strength of evidence, including burden of disease and efficacy.

Neal Halsey, of Johns Hopkins, recalled that last year the consensus was not to have differences in age for African Americans. Dr. Jackson replied that much had happened since those discussions, including the emerging of resistant pneumococci. Dr. Santosham from Johns Hopkins noted that rates for African Americans were similar to those for Hib disease in European countries. He urged increasing the age to 4 or 5 years. Dr. Brunell, from NIH, noted that there was a tendency to give polysaccharides to children over age two, but data show they do not respond to the common serotypes that infect kids this age.

Dr. Modlin asked voting members to state their opinions about the age of universal immunization, and any substantial changes in proposed recommendations for other risk groups. Dr. Guerra supported universal recommendation for the younger age group. Dr. Fleming supported keeping the recommendation for universal immunization as it is, but would support a permissive recommendation for all children up to age five. Dr. Le would vote to expand the recommendation to five years of age. Dr. Offit said it makes sense from the best medicine standpoint to extend age of immunization to five years, but was not sure it could actually be done. Dr. Livengood was concerned with what to do if the supply of vaccine is limited, but would go with one dose through 59 months and hope for the best. Dr. Orenstein said the risk is a one-year difference between blacks and whites, so he favors a generic recommendation. Dr. Mawle thought it should go for 59 months, for a short period of time. Dr. Clover preferred a more permissive statement for the group aged 3 years and under. Dr. Brooks recommended universal immunization up to 36 months, with a permissive statement after that, and to identify special groups by overcrowding or poverty, not race. Dr. Tomkins agreed with universality up to 36 months, using "top priority" for that age group and another word for up to 59 months. Dr. Rennels preferred universal up to 36 months, permissive up to 59 months, and some language to acknowledge limited resources and prioritization guidelines. Dr. Words supported 48 months when rates are similar across groups, with the exception of high-risk groups, and more permissive beyond that. Focusing on SES may be better than race.

Dr. Modlin asked how prioritization would work and was told that states would set priorities. Dr. Snider suggested saying that the desire is to make it universal through 59 months, but given implementation limitations, initial priorities should given to specific groups. He also reminded the group that there is still no licensed vaccine. Additional data may come up in the next FDA meeting or economic information might become available.

Decision

Dr. Modlin asked for a straw vote regarding the concept of universal recommendation up to 59 months of age with a clear statement of priorities for implementation. This is only for the first two to three years of program. Members conflicted with Wyeth included Dr. Rennels, Dr. Brooks, Dr. Clover, and Dr. Le. This still left a quorum. Those in favor were Dr. Word, Dr. Tomkins, Dr. Offit, Dr. Johnson, Dr. Fleming, Dr. Guerra, and Dr. Modlin. None were opposed. Dr. Rennels, Dr. Brooks, Dr. Clover and Dr. Le abstained.

Dr. Rennels asked if the AAP had established a cut-off for penicillin prophylaxis in children with SCD, and what fever rates were when this vaccine was given with the DTaP vaccine. Dr. Jill Hackel from Wyeth presented an overhead with composite [fever] rates across all trials after the primary series for 7-valent pneumococcal conjugate vaccine.

Dr. Le commented that it could be interpreted from the table in the draft that the fourth dose should not be given after 15 months of age, and he was worried about the child over 16 months of age. Dr. Johnson emphasized that they would recommend the fourth dose for those who had missed it. Dr. Le then asked for a definition of recurrent otitis media, and was told that it wasn't defined on purpose. They preferred to let the practitioner define recurrent or persistent otitis media.

Dr. Modlin suggested leaving the number of doses given to older immunocompromised children up to the practitioner, given the lack of data. Dr. Zimmerman pointed out that, based on Hib, one dose wouldn't work in the immunocompromised group. Dr. Modlin then suggested saying, "two doses until more data is available."

Regarding procedure, Dean Mason explained that an announcement would be published in the Commerce Business Daily, after which they were required to wait for public comment. Then they will discuss accelerating the solicitation process with the manufacturers so they can respond quickly. It is important not to effectuate recommendations in the public sector until a contract is established, otherwise it puts pressure on state health programs.

It was decided to draw up a list of priorities and put off the final vote until the next morning.

PREVENTION OF PNEUMOCOCCAL DISEASE IN ADULTS ≥65

How well do ACIP recommendations address those at risk for pneumococcal disease?
Dr. C. Whitney, NCID, DVRD. In the U.S., there are about 62,000 cases of invasive pneumococcal disease every year, about one third in the over-65 age group, a third in children under 18, and a third in the age 18-64 population. Of the latter, two thirds have an ACIP indication, mostly HIV or alcohol abuse. About 30%-40% of this age group do not have indication, i.e., about 11%-14% of all invasive pneumococcal disease in the U.S. occurs in adults without indication for vaccine. Racial disparities exist, with African Americans having higher rates than whites in this age group, especially among the 18 to 64-year-old group. The risk is 3 or 4 times higher for blacks than for whites, and the rate for African Americans over age 35 is higher than for whites over 65. Some but not all of the difference is due to chronic disease. For both groups, the incidence of disease either remains high or increases with age, and the case fatality rate increases with age.

Issues with protecting adults:

- Polysaccharide vaccine efficacy for high-risk groups remains a question. HIV and alcohol abuse may be the most common indications for vaccine. Efficacy of polysaccharide vaccines is low for HIV patients with low CD4 counts and the efficacy is unknown for those with alcohol abuse.
- Vaccines need to provide long-term protection, since the risk of infection and death increases with time. The polysaccharide vaccine does not induce immunologic memory and antibody levels wane after 5-10 years. The duration of protection is unclear.
- Safety, cost and efficacy of revaccination are unclear.
- Should we evaluate the use of other vaccines that induce immunologic memory for use in this age group?

Dr. Butler, NCID, AIP. The highest rates of invasive pneumococcal infection in the U.S. are among the very young and the very old, and these age groups have already been addressed. About 60-70% of those in the 18-64 age group with invasive pneumococcal disease are non-immunocompromised. There is increased risk, but how much is uncertain. In 1993, data show that 90% of people with invasive pneumococcal disease in that age group already had vaccine indications. More recent data suggest the proportion is lower and that only 60% adults aged ≥65 with invasive pneumococcal infection have vaccine indications. In studies of those without indications, 53% were smokers.

The objective of the study was to assess the contribution of various factors to the risk of invasive pneumococcal infection in immunocompetent adults in this age group, including chronic medical conditions, tobacco smoke exposure and household crowding. A case control study was done, with the sample drawn from ongoing ABC surveillance. Dr. Butler described the research methodology and defined cigarette exposure, consumption of alcoholic beverages, and crowded

households. People who were immunocompromised were excluded from the study, as were those with no telephone. A total of 228 cases participated, with 301 controls.

Results of univariate analysis: Cases were more likely to be black and male, and more likely to have COPD, cirrhosis, diabetes, and asthma. Overall, 28% of cases had a pneumococcal vaccine indication and 12% had been vaccinated. Cases were more likely to have been diagnosed with pneumonia in the past year and report URI in the past month. Compared to controls, cases were more likely to have lower educational attainment, live at lower income levels, and live in crowded households. There was a trend toward higher risk for people with a child six or younger, and for those with a child in a day care center.

There are higher rates among current tobacco smokers (58% of cases vs 24% of controls). Former smokers generally are not at increased risk, but exposure to environmental smoke did increase risk. Heavy drinking and alcohol consumption point to a tendency for more disease. The study controlled for age, study site, educational attainment, sex, race, and chronic illness. Also included were smoking and children in the household. The risk for disease was greater for males, blacks, chronic illness, current smokers, environmental smoke exposure, and children in day care.

Regarding the dose response relationship between cigarette smoking and invasive pneumococcal disease, the risk of disease increased with the number of cigarettes smoked per day. The risk also increased with the number of pack years. Former smokers showed no increased risk, but if the interval since quitting smoking was stratified, there was a significant risk for those who quit more recently. Increased risk disappeared after about eight years. Daily exposure to environmental smoke was also stratified. One to four hours of exposure daily increased risk slightly, but it was higher for those with four or more hours.

After multivariable adjustment, the population-attributable risks were calculated: i.e., the predicted reduction in incidence if the factor associated with the disease were eliminated through either vaccination or behavior change. In the multivariate model, the population-attributable risk for cigarette smoking was 51%, environmental smoke exposure among nonsmokers was 17%, black race was 32%, and chronic illness was 14%. If the prevalence of cigarette smoking were reduced from 25% to 15%, 18% of pneumococcal disease in immunocompetent, non-elderly adults would be prevented.

Conclusion: Cigarette smoking is the strongest modifiable independent risk factor for invasive pneumococcal infection in immunocompetent adults. Increased risk was also associated with black race, environmental smoke, living with children in day care, and chronic medical conditions.

Relevance for ACIP

- Current vaccine indications for chronic illness appear to be appropriate.
- Should there be broader use of polysaccharide vaccine among blacks?

- Is there an indirect effect of vaccination of children with conjugate vaccine?
- What is the role of polysaccharide vaccine for cigarette smokers?
- Should the polysaccharide vaccine be incorporated into smoking cessation programs?

Discussion

Dr. Gardner cited the study's relevance to the influenza recommendation and asked if there was any breakdown within the 18-64 age group. Dr. Guerra asked if there was any information on attributable risk in occupation and/or prior history of pneumonia. Dr. Butler replied that no one occupation stood out. They were interested in occupational exposure to children and health care workers, but the numbers were too small to draw any firm conclusions. Prior history of pneumonia didn't hold up after controlling for underlying illness. Dr. Modlin asked about attributable risk for people with children in day care centers and was told it was about 10%.

The study will be referred to the adult workgroup.

ALTERNATE HEPATITIS B VACCINE SCHEDULE FOR ADOLESCENTS

Dr. H. Margolis, NCID, DVRD
Dr. T. Vernon, Merck

Dr. Vernon showed a cross sectional analysis done in March 1998. It was a nationally representative sample concentrating on 11-12 and 13-18-year-olds.

- Of adolescents ages 11-18, 53% never received any hepatitis B vaccine.
- Of those who began the series, 67% completed all 3 doses.
- Of those who completed the series, 94% did finish but late.

On average, doses were given at 0, 4, and 10 months. This data is consistent with previously published reports on immunizing adolescents. Compliance to the three-dose series ranged from 11%-88%.

Dr. Murray Abramson, Merck.

The purpose of the study was to explore adolescent regimens of hepatitis B vaccine that would lead to enhanced compliance by being more convenient, have a more flexible schedule, fit within school semesters, have low administrative costs, and improve coverage of hard-to-reach cohorts. Specifically, the objective was to determine, in healthy adolescents, whether a two-dose regimen as well as a three-dose regimen was either similar or more immunogenic than the licensed standard three-dose regimen. The study also assessed the safety and tolerability profile of the investigational two- and three-dose regimens. It was an open randomized study, with over a thousand 11-19-year-old healthy subjects.

Regimens:

- 5 micrograms, 0, 1, 6 months (standard FDA approved, ACIP recommended)

- 5 micrograms, 0, 2 and 4 months (licensed, shorter administration, ACIP recommended for school-based vaccination programs)
- 5 micrograms, 0, 6 months (licensed, fewer shots)
- 10 micrograms, 0, 4 months
- 10 micrograms, 0, 6 months

Hypothesis: The percentage of vaccinees who are seroprotected and greater than 10 million international units per milliliter in one or more of the investigational regimens will be similar to or better than the standard 0, 1, 6 month regimen.

A table was presented showing results one month after the last dose, looking at post-dose anti-Hbs response in ages 11-19.

- Seroprotection was between 95% and 99% for all groups compared to control. All were in excess of the historical target for seroprotection for hepatitis B.
- The 10-microgram 0-4 month regimen sandwiches the FDA-approved dose with the other 10 microgram GMT.
- All regimens were statistically similar to the standard regimen of 0, 1, 6 months with respect to the proportion of vaccinees who developed seroprotection one month after the last injection.

The study also assessed the impact of demographic factors, such as gender, smoking, weight, weight/height index, and age. Only age was an independent variable. Data was summarized separately in two age groups. In a table showing post-dose anti-Hbs response one month after the last dose by age group, age had the following impact on seroprotection:

- 11-15 year olds were similar to control and similar to the 0-4 regimen.
- Ages 11-15 were slightly higher than the ages 16-19 group.

Relative immunogenicity of single 5 microgram dose vs 10 mcg: The study compiled all single doses before any additional doses were given, so they were only looking at people who received one dose.

- The 10 mcg dose appears more immunogenic than the 5-mcg dose for the 11-15 group.
- For older adolescents ages 16-19, enhanced immunogenicity is less apparent.

Safety: They vaccinated 1026 subjects, 97% of whom received all doses. No serious adverse event was attributable to any vaccine regimen. There were two SAEs. They compared the 5 mg to the 10 mg, shot for shot. Injection site adverse events were typically soreness of the arm. There were slightly greater frequencies of injection site AEs, but systemic AEs were about the same.

Individual regimens: 10 mgm regimens were not statistically different from the standard one, at 0, 1, 6 months. The increased frequency of soreness of arms was balanced by the fewer number

of vaccinations given. The most common systemic adverse events were headache, fatigue and pharyngitis.

Conclusions: The final percentage of seroprotection of each alternate regimen is statistically similar to the control in the 11-19 age group. The 2x10 mcg regimen in 11-15 age group most closely approximates the 3x5 regimen at 0,1,6 months, in terms of final percent seroprotection and GMT. A single 10 mcg dose of Recomivax appears to be more immunogenic than a 5 mcg dose, which may be important with respect to compliance. A single 10 mcg dose induces slightly more soreness of arm, but overall frequencies of injection site and systemic reactions were similar in 2x10 vs 3x5.

Dr. Vernon advised that product circular changes were submitted to the FDA, seeking two doses at 0 and 4-6 months, 10 mcg/1.0, for ages 11-15, regardless of individual risk of infection. It was approved by FDA. This is an optional regimen. Providers can still use 2x10, and 5 mcg is also still approved. This is an alternative regimen ideal for certain segments where compliance is an issue or resources are limited. It is an excellent option for providers vaccinating adolescents and helps to better meet middle school entry requirements. Health economic studies have been done, but it is essentially equivalent to the currently recommended dose.

Discussion

Dr. Rennels asked if there was increased severity of local reactions with the higher dose, and was told there was not. Dr. Clover asked if there were any data on efficacy if the interval was greater than 4-6 months, say at 0 and 12 months. Dr. Murray Abramson said no, but some follow-up data were available. Dr. Offit asked if there were any data on memory, on a booster dose years later. He also wondered if a two-dose regimen would be of value in older adolescent and adult populations. Dr. Abramson replied that seroprotection and GMTs following the two-dose regimen tended to be higher than the three-dose currently used in school-based programs. GMTs for both 10 mcg regimens exceed the international unit that has demonstrated immune memory with other regimens. Long-term immunity for any hepatitis regimen is not known. There are some data on adolescents given a 5 mcg booster about two years after the primary dose. Seroprotection was very good after one month, one week after the booster it was 100%, and after four weeks it was still 100%. But seroprotection beyond two years is unknown. As for seeking an indication for the 16-19-year-old group, in separating the data, it was a little lower for the older group, so Merck took a conservative stance.

Dr. Guerra asked whether they did a second 10-mcg dose when starting with a 5-mcg dose. Dr. Abramson said there were no booster doses, except in a subset of individuals two and a half years later. Dr. Breiman asked if there were plans to look for adverse events a year or two later. Dr. Abramson said yes, but mainly to look at booster long-term immunity. Dr. Fedson asked if it would be possible to follow 16-19 year olds and give them a booster dose after two or three

years, to check memory and protection levels. Dr. Abramson replied that they would want to look at long-term immunity, but had no reason to believe there woul be any differences.

Dr. Neal Halsey, Johns Hopkins, advised that they had another alternative schedule, the 0,12,24 month schedule, which has been approved for adolescents who are seen annually. They had 90% seroconversion after two doses, and 100% after the third dose. The only downside is complexity for the decision-making physician.

Dr. Le asked if this would be a written footnote in the harmonized schedule. Dr. Modlin replied that it may not be important enough. Dr. Abramson said the AAP would put it in their Red Book. He then asked about the cost of the vaccine and was told that the decision hadn't been made, but it should be at least comparable to alternative regimens. Dr. Guerra asked whether this recommendation would be covered by VFC and was told there would be no VFC vote today.

Decision
Several people were conflicted with Merke and SmithKline, so Dr. Trump, Dr. Egan, Mr. Graydon, Dr. Evans and Dr. Rabinovich were deputized. A motion was made to accept the draft language. Those in favor were Dr. Breiman, Dr. Word, Dr. Tomkins, Dr. Brooks, Dr. Johnson, Dr. Fleming, Dr. Evans, Mr Grayden, Dr. Egan, and Dr.Trump. No one was opposed. Dr. Rennels, Dr. Clover, Dr. Offit, Dr. Le, Dr. Guerra and Dr. Modlin abstained. The motion passed.

UPDATES
National Vaccine Program
Dr. Breiman announced that an international symposium on combination vaccines was planned for February. The goal is to continue to elucidate key issues in the development and licensure of combination vaccines. We're continuing to work toward an enhanced vaccine safety system, for greater surveillance, investigation of adverse events, targeted laboratory research on vaccine safety, and improved information exchange on risk communication.

Dr. Peter reported that the last NVAC meeting was in September. The agenda included:

- Vaccine safety and communication, including creative means of funding
- Recommendations regarding immunization registries. A plan has been approved, but confidentiality remains a major issue.
- Review of the process for using advisory committees to address crises. A working group was formed.
- Program for strategies to sustain success in child immunization, referred to July JAMA article
- Subcommittee on future vaccines, which will work on IOM vaccine R&D priority setting process
- Adult immunization coverage, particularly programmatic issues

- Grant 317 funding.

The next meeting is February 28-29th.

National Center for Infectious Diseases
Dr. A. Mawle, NCID, OD.
Two labs were expanded last year.

- The varicella lab was set up 18 months ago in response to the huge need for serologic and molecular assays for varicella. The gold standard is fluorescent antibody membrane antigen or Farmer test, which does not lend itself easily to epi studies. Several different ELISA assays have been set up, all compared against a panel of standardized sera. To distinguish between the vaccine strain and wild types, two digests were previously required. The new system takes only one digest and reduces the time from two days to about four hours.
- Pertussis lab: A pertussis enhanced surveillance project was established using six sites and the most prevalent profiles of *B. pertussis*; 65 profiles have been identified.

The incidence of pertussis has been increasing in the Netherlands since 1966, despite the high rate of vaccine coverage. One possible explanation is that different strains are appearing. The Netherlands group has analyzed pertussin toxin and pertactin genes of their isolates and found three different strains. CDC sent a representative to the Netherlands to learn their technique, in order to determine whether the same thing is happening in the U.S.

Jerry Sado from Merck wanted to clarify that the GP ELISA has been correlated with protection following vaccination and is the standard in long-term follow up. Dr. Mawle added that the lab group is working with Merck. Dr. Brunell said that the major question is whether people who are seropositive and vaccinated can still get modified varicella when exposed. From CDC data, they are not totally protected. The PSD-1 marker is fine to separate American vaccine from wild strains.

Dr. Katz urged all participants to communicate with friends in Congress to save and augment the 317 program. The dollars are shrinking while needs go up. Dr. Shaffner from Vanderbilt added that funding of adult immunization will be examined by the Institute of Medicine Committee.

National Immunization Program
Dr. Orenstein, NIP, OD. National coverage for varicella vaccine is now 43.7%, and in some places is reaching 70%. He showed some data from the National Immunization Survey, broken down by quarter; last quarter it was 51%. Philadelphia has the highest immunization coverage--

68.6%. Data from active surveillance sites for varicella shows a decrease in cases and no hospitalizations in 1999.

National immunization coverage figures were just released in MMWR, and for 1998 they are higher than ever. However, 1998 data refer to children born between February 1995 and May 1997, when there was more funding, This doesn't mean rates will decrease, but these are retrospective data, not current data.

Regarding the funding status of Section 317, there have been major cuts in infrastructure and the carry over is virtually gone. The President asked for flatline for operations, but even this will translate into an $11 million cut. The polio/measles line is for eradication, to support the global effort. There have been concerns about political support for hepatitis B. While there is controversy, there is still substantial support.

Food and Drug Administration

Dr. W. Egan, FDA, CBER. There was a workshop in September on cell substrate issues, specifically the use of neoplastic cells as substrates for viral vaccines. It was organized by NIH, National Vaccine Program, FDA, WHO and IAPS. The proceedings will be coming out in book form, with a transcript on the website.

Vaccine approvals have included thimerosal-free hepatitis B and a two-dose schedule for adolescents.

The Vaccines and Related Biological Products Advisory Committee will meet November 4 and 5, addressing:

- Product license application for Wyeth Lederle's pneumococcal 7-valent conjugate vaccine
- Safety data following the fifth successive dose of DTaP (Tripedia)
- Ways to demonstrate attenuation of chimeric strains of cytomegalovirus and candidate vaccines to support proceeding into clinical trials.

Vaccine Injury Compensation Program

Dr. G. Evans, HRSA. The largest number of claims under the post-1988 program were received this year, reflecting the fact that there was a filing deadline for hepatitis B claims. Hepatitis B was just added to the compensation program two years ago, along with Hib and varicella.

- *Total to date*: 270 hepatitis claims, 7 varicella claims, 2 Hib claims, and 7 DTaP claims. Only one injury–anaphylaxis.
- *Under adjudication*: only 118 claims left.
- *Awards*: over one billion dollars paid to date, with $1.4 billion in a trust fund.

Legislative activity: The Vaccinate America's Children.Now Act is still pending in Congress. A couple of bills have pneumococcal vaccine excise tax language. The ACCD met Sept 9th and got an update on rotavirus. Claims that have intussusception as the injury can be presented and try prove by causation, but the statute requires that the effects last six months. We're going to try to change the statute to require inpatient hospitalization and surgical intervention, and they would be eligible for compensation.

Congressional oversight: A GAO investigation is pending, The Subcommittee on Drug Policy, Criminal Justice and Human Resources had a hearing entitled "Compensating Vaccine Injuries: Are Reforms Needed?" They addressed three questions: how to change the adversarial nature of the hearing process, are evidentiary and adjudicative standards for determining compensation too strict, and have enough funds been allocated to ensure preservation of the program? There was bipartisan agreement that the program could be more user friendly.

The vast majority of DTP claims were adjudicated under the original table. There have been no significant drop offs of claimants, but we're seeing a decline in DTaP claims. There is no basis for media claims. Congress may go back to the original table, so that anything possibly caused by vaccine could be compensated.

In response to a question about what happened in 1990, Dr. Evans explained that it was the filing deadline for claims for vaccinations administered prior to the start of the compensation program. The oldest claim went back to 1917. He added that it had been his pleasure to work with Dr. Rabinovich and invited her to come up and update them on NIH.

Dr. Rabinovich (NIH) said there was a lot going on and Congress was giving NIH more money than anticipated. It's an exciting opportunity and challenge to use funds to support research that will advance the health of the public.

Friday, October 22, 1999

Old Business

Influenza Vaccination for Healthy Adults

Dr. Modlin reminded the group that there was broad agreement on Thursday to recommend lowering the age from 65 to 50 for routine influenza immunization of healthy adults for 2000/1. Dr. Fleming and Dr. Tomkins had expressed reservations about making a decision today, because if a recommendation were made in advance of the current season, there would be issues in vaccine programs and supplies. Carlton Meschievitz of PMC added that manufacturers need lead time to make sure they have an adequate supply of eggs, etc. They could probably increase production in the short run by 20% for next year by re-routing current supplies, increasing

efficiency of production, and lengthening the production season. Dr. Rennels asked what was known about the length of immunogenicity and protection and whether we could get the vaccine earlier. She was told it depended on the strain for the year, but there was a fair amount of leeway.

Dr. France was concerned about how to delay communication of this recommendation to the public. Dr. Snider felt manufacturers only needed a sense of how the committee would vote in February, but Dr. Meschievitz worried that February was a bit late and the ACIP is not always predictable. Dr. Zimmerman pointed out that the AAFP recommendation was already in press. Regarding logistics for next fall, the ACIP could include a statement that implementation would take time and resources.

Decision
Dr. Offit moved that the ACIP recommend that influenza vaccine be given to all healthy individuals 50 and over beginning in the 2000/2001 flu season. Several voting members had conflicts, with PMC, Glaxo, Park Davis, and Wyeth Lederle, so Mr. Graydon, Dr. Trump, and Dr. Egan were deputized. Those in favor were Dr. Word, Dr. Helms, Dr. Offit, Dr. Modlin, Dr. Breiman, Mr. Graydon, Dr. Egan, and Dr. Trump. Opposed: none. Abstaining: Dr. Rennels, Dr. Brooks, Dr. Le, and Dr. Guerra. The motion passed.

Pneumococcal Conjugate Vaccine Statement
Dr. Modlin reminded the group that they had already voted to recommended pneumococcal conjugate vaccine for children up to 59 months. The next step was to develop a set of priorities because of logistical or resource limitations.

Dr. Johnson offered the following set of priorities for consideration:

- Priority 1: All children ages ≥23 months, including those in high-risk categories (sickle cell disease, functional or anatomic asplenia, or HIV infection)
- Priority 2: Children with high rates of pneumococcal disease, ages 24-59 months, those with sickle cell disease, functional or anatomic asplenia, or HIV infection
- Priority 3: Children ages 24-59 months who are immunocompromised or have chronic illness, Alaska natives, or American Indians.
- Priority 4: All healthy children ages 24 to 35 months, and children 36 to 59 months at increased risk for pneumonococcal infection, including frequent or complicated episodes of acute otitis media, socio-economically disadvantaged, or attending group day care
- Priority 5: Children ages 36-59 months, not included in the groups mentioned above.

Dr. Abramson thought this was too complicated for pediatricians. Dr. Word did not find it confusing, but noted that the majority of Priority 2 children are followed in specialty clinics anyway. Dr. Brooks added that most of the socio-economically disadvantaged were also going to get vaccinated anyway.

Dr. Siegal asked if prevalence of resistant strep/pneumo in certain geographic areas should be considered. Dr. Le responded that resistance was widespread. Dr. Word worried that the order that subgroups are listed might send a message to practitioners. Dr. Livengood suggested calling priority groups 1, 2, and 3 "children at high risk for pneumococcal disease;" and calling priority 4 "children at moderately increased risk for pneumococcal disease." Priority 5 would be "all other children."

Dr. Breiman asked whether the 23-valent vaccine two months following conjugate vaccine and the lack of safety data would be included in the vote, and was told the plan was to vote on the entire statement. He requested that more information be included about the safety of the combination of conjugate and polysaccharide. Also, since there are no data about efficacy in high-risk groups, it will be important to evaluate those populations post licensure.

Decision
A motion was made that the committee accept the conjugate pneumococcal vaccine statement, with provisions written into the introduction. Changes suggested Thursday and Friday morning will be added and a final draft will be given to working group. Dr. Rennels, Dr. Brooks, and Dr. Le had conflicts. Those in favor of the statement were Dr. Word, Dr. Helms, Dr. Offit, Dr. Johnson, Dr. Guerra, Dr. Modlin, Dr. Evans, Dr. Rabinovich, Dr. Breiman, Mr. Graydon, and Dr. Trump. None were opposed. Dr. Rennels, Dr. Brooks, Dr. Le, and Dr. Egan abstained. The motion passed.

ROTAVIRUS VACCINE AND INTUSSUSCEPTION

Does Rotavirus Vaccine Cause Intussusception?
Dr. J. Livengood, NIP, ESD. *Background*: Rotavirus gastroenteritis is the most common cause of severe diarrhea in infants and children. Worldwide there are an estimated 600,000 to 800,000 deaths per year. In the U.S., there are 20 deaths, 50,000 hospitalizations, and 500,000 physician visits. The vaccine is a live, oral, rhesus/based, tetravalent vaccine, licensed August 1998, and recommended by ACIP and AAP for routine vaccination at 2, 4 and 6 months. High efficacy has been shown in preventing severe diarrhea and hospitalizations. There is less efficacy for infection and mild disease.

Intussusception is an obstructive bowel disease. One segment of the bowel telescopes into a distal segment of the bowel, most commonly at the end of the small intestine. It can be reduced by barium enema or surgery. Delays result in bowel necrosis, loss of bowel or death. The basic etiology is unknown, but it has been associated with respiratory adenovirus infection. The natural rotavirus itself has not previously been associated with intussusception. Rotavirus has a distinct winter peak, while intussusception does not.

The ACIP statement was published in the spring of 1999, at which time there were three cases reported to VAERS. By May, ten cases had been reported, so CDC started a review of the literature and presented it at the ACIP meeting in June. Data from California and Minnesota suggested a causal relationship between the rotavirus vaccine and intussusception, so CDC decided to postpone any use of the vaccine. The decision was published July 16, in MMWR.

Melinda Wharton, NIP, ESD. As of October 15, VAERS had reports of 113 cases of intussusception, of which 93 were confirmed, nine were presumptive, nine did not have intussusception, one did not receive rotavirus vaccine, and one had insufficient information. Of the 102 confirmed and presumptive cases, 57 occurred within seven days of vaccination, and of these 29 underwent surgery, seven underwent bowel resection, and there was one fatality. Eighty-six of the 94 cases had received other recommended vaccinations simultaneously. The MMWR publication in July prompted an increase in reports. There were 15 reports before MMWR, and 87 afterwards.

There were 44 confirmed or presumptive cases within 7 days following receipt of the first dose, 10 cases within 7 days following dose 2, and one case within 7 days following dose 3. There was wide distribution in age at receipt of dose 1 among recipients who developed intussusception within one week of dose 1. Two other deaths were reported that were not related to intussusception. One was a 3-month-old child with a history of previous abdominal surgeries. The autopsy revealed necrotic cecum with perforation and lymphoid hyperplasia. The second death was a child who had received rotavirus six weeks before developing diarrheal illness and suffered a cardiac arrest. No intussusception was found at autopsy.

Active Surveillance Data

Dr. P. Kramarz, NIP, ESD, presented the preliminary results of a population-based cohort study of intussusception and rotavirus vaccination. The Vaccine Safety Datalink (VSD) is a collaborative project between CDC and four HMOs, which has data on about 2% of the U.S. population, based on linkages between computerized vaccination, medical outcomes and covariate records, and which allows computation of incidence rates and attributable risks.

Methodology: Cases were found by search of automated data bases and radiologic procedures. A case of intussusception is defined as diagnosed by radiologic procedure, or directly at the time of surgery or autopsy in a child aged 1-11 months. The incidence rate in vaccinated children was computed and compared to the incidence rate in unvaccinated children and vaccinated children outside risk intervals.

Updated results of Northern California Kaiser cohort study: The risk for ever-vaccinated children is 1.7 compared to never-vaccinated children. That risk is greatest in the first week after vaccination. While this is statistically significant, it was based on only two cases. Because of the rarity of intussusception, more HMOS were included for an extended study.

Extended study: We selected HMOs that administered more than 1000 doses of rotavirus vaccine and that have computerized databases with discharge diagnoses and vaccination data. We also had access to medical records for abstraction. In six HMOs, 62 cases of intussusception were identified, out of 85,000 RV doses administered to more than 50,000 children.

During the period from December 1998 to March 1999, the study found no risk of intussusception during the first three days, and the rate was highest between the third and seventh days. For the whole period of the study, results were consistent with the first period, but data are still incomplete. When vaccinated children are followed up throughout the whole period of the study, the overall relative risk of intussusception in ever-vaccinated children is 2.37, compared to never-vaccinated children and the risk is highest after the first dose. The attributable risk was calculated to be one case per 7,104 children vaccinated, using the first period of study.

Conclusions: Preliminary results suggest that RV is associated with an elevated risk of intussusception, and the greatest risk is 3-7 days after vaccination.

Next steps: medical record abstraction, search of radiology records for additional cases, and follow up and re-analyze cohort (for triggering) in six months. A study of background rates and potential risk factors of intussusception is in progress.

Methods and Design of Case Control Study

Dr. M. Massoudi, NIP, ISD. The study was a collaborative, multi-state investigation. The primary objective was to estimate the relative risk of intussusception among vaccinated and unvaccinated infants for specific risk periods. The ancillary objective was to estimate the change in incidence of intussusception among cases over post-vaccination windows of time, by age and by dose.

Sample size estimate: We used a 1% vaccination level among controls and an odds ratio of 4. We selected 19 states with a large number of doses distributed and/or a high ratio of doses distributed per child; these states accounted for 80% of all doses distributed in the U.S.

Subjects: Cases and controls both had to come from the exposed population. Children were aged 1-11 months. The study period was November 1, 1998 to June 30, 1999. To avoid diagnostic or detection bias in case ascertainment, we used the following guidelines:

- Cases occurring before MMWR publication
- Sites not informed of cases reported to VAERS
- Thorough systematic identification of cases performed.

Hospitals were ranked by number of cases. States targeted hospitals that had treated at least 50% of historic cases of intussusception. A systematic review of medical and radiology records was

performed in targeted hospitals. *Case definition*: diagnosis confirmed by radiological exams, surgery or autopsy. *Controls*: infants born ±7 days of case at same birth hospital. All vaccine providers were determined from parents and vaccine history was ascertained from written records.

A total of 447 cases were identified, of which 96% were available for analysis, providing 1281 completed questionnaires. The study had 397 cases, 1619 controls, and 3238 questionnaires.

Case Series Analysis
Trudy Murphy, NIP, ESD (Principal Investigator)
In both analyses, the following issues were addressed with regard to the risk of intussusception:

- In ever- vs never-vaccinated infants
- Effect of Rotashield vaccine for dose 1 and for dose 2.
- Effect of RRV-TV dose 1 within age categories.

The case series analysis examines whether adverse events following vaccination are clustered shortly after vaccination or occur randomly through time. It compares incidence rate of adverse events in vaccinated cases with the rate in unvaccinated cases to determine the incidence risk ratio.

In the ever/never analysis, the incidence rate is the number of cases that occurred after vaccination over their cumulative post-vaccination time. A similar incidence rate is computed for unvaccinated cases.

Dr. Murphy showed the incidence risk ratio for intussusception after RRV-TV in the ever/never analysis. There were 69 cases of intussusception after vaccination among 312 child months of cumulative time. There were 358 cases who did not receive vaccine during 2592 child months of cumulative referent time. The incidence rate risk ratio for vaccinated children was 1.6, representing a 60% increase overall in incidence of intussusception after vaccination, compared with incidence without vaccination.

To examine whether there is clustering of adverse events, we defined relevant risk windows based on timing of fever after Rotashield vaccination; those windows were 0-2, 3-7, 8-14, and 15-21 days. The numerator is the number of cases of intussusception occurring after vaccination in any one risk period. The denominator is the amount of person time in that risk window. The denominator of the ratio is the number of cases in unvaccinated infants over their person time.

Cases identified in case control study by day since vaccination:

- There were no cases for days 0 to 2 after vaccination with any dose.
- Dose 1: a cluster of cases between days 3 and 7, a smaller cluster during the second week, no clustering of cases after day 14.

- Dose 2: a small cluster between days 3 and 7.
- Dose 3: no clustering observed.

Incidence risk ratios by times since vaccination for dose 1 :
- There were 351 cases of intussusception in unvaccinated cases.
- No cases occurred in the 0-2 day window.
- 34 cases occurred 3-7 days after vaccination; the incidence risk ratio = 18.9, representing a 19-fold increase in incidence risk.
- Nine cases occurred 8-14 days after vaccination; the incidence risk ratio = 3.6, an almost fourfold increase.
- Risk was no longer elevated 15 days after vaccination.

Incidence risk ratios by times since vaccination for dose 2: There were six cases 3-7 days after vaccination; IRR = 5.8, with no significant increased risk 8 days after vaccination.

Summary: Increased risk was observed after both dose 1 and 2 at 3-7 days after vaccination, and in the 8-14 day period after dose 1.

Effect of age on risk of intussusception after dose 1:
Children receiving dose 1 at 1-2 months:
- Reference group included 14 cases in unvaccinated infants.
- Six cases in vaccinated infants 3-7 days after vaccination. IRR = 27.
- Two cases 8-14 days after vaccination, IRR 6.9.
- No increase in risk 15 days after vaccination.

Children receiving dose 1 at 3-5 months of age:
- Reference group included 106 cases in unvaccinated infants.
- 19 cases at 3-7 days, IRR = 24.8.
- 5 cases at 8-14 days, IRR = 4.6.
- No risk after 15 days.

Children vaccinated at 6-8 months of age:
- Reference group included 155 cases in unvaccinated infants.
- 9 cases at 3-7 days, IRR = 16.5.
- No significant risk after 8 days.

Summary: The overall the risk of intussusception is increased 60% after RRV-TV among ever-vaccinated cases vs never-vaccinated cases.
Dose 1: The risk is increased 19-fold in the first week, and almost fourfold in the second week after vaccination, in all age categories.
Dose 2: The risk is increased sixfold in the first week.

Case Control Analysis

Aisha Jumaan, NIP, ESD

Descriptive vaccination information for cases and controls:

- There were 427 cases and 1619 controls, with similar distribution for vaccination by calendar month.
- Dose 1 received between 1-6 months, mostly 2-4 months.
- Dose 2 received between 1 and 9 months, mostly 4-6 months.
- Dose 3 received between 3 and 9 months, mostly 6 months.

Results: When comparing ever-vaccinated vs never-vaccinated infants, the odds ratio was 1.8, which means an 80% increase in the risk of intussusception among those infants vaccinated compared to those infants who were never vaccinated.

Risk windows:

- Dose 1: There were no cases 0-2 days after vaccination, but at 3-7 days after vaccination, there was a 25-fold increase in the risk of intussusception. The increased risk persisted 8-14 days after vaccination, with a 7.1-fold increase. There was no significant statistical association beyond that.
- Dose 2: There were similar results at 3-7 days after vaccination, with a 13.4-fold increase in intussusception among vaccinated infants compared with unvaccinated infants. Beyond that, there was no significant statistical association between vaccination and intussusception.

Dose 1 by age:

- Age 1-2 months: at 3-7 days, there was a 28.1-fold increase in intussusception among vaccinated infants, and no statistically significant association beyond that.
- Age 3-5 months: at 3-7 days, there was a 20.6-fold increase in intussusception, and at 8-14 days there was a 7.1-fold increased risk of intussusception.
- Age 6-8 months: at 3-7 days, there was a 31.4-fold increase in intussusception. The wide confidence interval indicates that the estimates were based on small numbers.

In summary, for the case control study, the overall risk of intussusception increased 80% after receiving RRV-TV.

- For dose 1, the risk increased 25-fold 3-7 days after vaccination, and 7.1-fold 8-14 days after vaccination.
- For dose 2, the risk increased 13.4-fold 3-7 days after vaccination.
- For dose 1, an increased risk of intussusception was present for each age group examined, 3-7 days after vaccination.

Case control and case series studies had similar results, which were similar to the VAERS data set. Both showed an elevated risk of intussusception after receiving rotavirus vaccine, especially 3-7 days after receiving vaccination.

Summary of Evidence

Dr. J. Livengood, NIP, ESD. The data from all sources demonstrate a strong association for rotavirus vaccine and intussusception. For VAERS, the relative risk is four to fivefold over expectation in the first week. The HMO and Kaiser studies show a significant overall increase. The case series/case control analyses have remarkable consistency, with the largest effect after dose 1, and some effect after dose 2. The highest risk is in days 3-7 following immunization. The association appears to be causal, based on strength of association, and the temporal sequence is consistent and biologically plausible. These conclusions are based on comparison of case series, case/control, and managed care analyses.

Discussion

Dr. Offit asked whether there were enough children in the Kaiser study to look at whether the vaccine caused a triggering effect and increased overall intussusception. Dr Kramarz replied that they followed up the vaccinated children for a shorter period of time. If the study is extended, they could make a comparison and look for any protective effect.

Dr. Modlin was intrigued that the risk did not appear to change with age, which seemed to indicate that the degree of viral replication may not be a direct factor. Dr. Livengood responded that the basal risk is very different at 2 and 5 months, and no one was immunized after six months. Dr. Le asked if there was any overlap of cases and whether they had talked to any other countries. Dr. Livengood replied that no other country is administering rotavirus right now. Approximately 40% of cases were entered into VAERS and the Northern California Kaiser data were excluded from the case control study.

Regarding the issue of biologic plausibility, Dr. Gardner wondered if there could be a more precise study of intussusception cases and careful viral work to understand why this attenuated virus produces disease. He also commented that there is still a case to be made for use of the vaccine in areas where rotavirus is a mortality issue, rather than a morbidity issue. Dr. Livengood responded that intussusception was an uncommon adverse event. Dr. Abramson asked if they had looked for protective or risk factors, such as breast feeding. Dr. Livengood responded that right now rotavirus vaccine was the only risk factor for which they had data.

Dr. Offit said he understood that vaccination changed rotavirus to a milder infection. So if natural infection occurring in the younger age group was associated with intussusception, could one go back to the New York data and sub-stratify them for the younger child? Dr. Livengood replied that the rate in 2-month-olds is about 37/100,000. There are only about 1000+ cases of intussusception in the NY data set, which is quite sparse when broken down by age. He suggested they might do a composite analysis for seasonality. Dr. Helms asked if there were any manufacturing or provider issues with the vaccine itself and was told they were not aware of any.

They do have lot numbers, but haven't attempted to proof that yet. Dr. Helms felt there might be an issue with public confidence in rotavirus vaccines in future.

Dr. Katz asked if there was anything determinable from the 29 cases with surgery, and the seven bowel resections. Dr. Wharton replied that specimens will be reviewed. From a review of histopathology reports, a number of children were reported to have lymphoid hyperplasia, which is thought to be a major predisposing cause of intussusception. Dr. Le commented that the shift in age of the peak shown on the graph gives the impression that a certain number of children are already predisposed to intussusception and the vaccine brings it on sooner. Dr. Livengood replied that over 50% of affected children had surgery, which is extremely uncommon. Maybe intussusception is happening at younger ages, when it's harder to diagnose and has a higher case fatality rate. Dr. Jackson wondered if one saw hyperplasia in children who got intussusception without rotavirus but did get DTaP, Hib and IPV, then rotavirus might cause even more. Dr. Livengood said there was no statistical difference in use of OPV or IPV between cases and controls. Dr. Guerra asked if there were any differences based on race, SES, or ethnicity, and whether there were any data on infant formulas. Dr. Livengood said there were extensive data on what children were being fed, but race and ethnicity data were not yet cleaned.

Rotavirus Vaccine Recommendations: Does the ACIP wish to change its recommendation on the use of rotavirus vaccine?

Attributable Cases

Dr. J. Livengood, NIP, ESD. In the ever/never analysis based on the New York baseline study, if the risk were 1.6, there would be about 1200 excess cases. In the Kaiser study, the ever/never risk is 1.7, which would be 1400 excess cases. From the case/control study, risk is 1.8, which would be 1600 excess cases over the New York baseline, which is about 2000 intussusception cases/year in the U.S.

The baseline changes rapidly over the first year of life. CDC developed a model of mature program to estimate excess cases, where all first doses are given at 2-3 months, and the second dose at 4-5 months. Based on a case/control analysis, there would be 76 baseline cases, and if using rotavirus vaccine there would be 301 excess cases, which is an almost 400% increase due to the effect of the vaccine. At 3-5 months, even though the effects are a little less, the total of attributable cases is higher because the baseline rate is higher, i.e., 678 baseline cases and 588 excess cases, for an 87% increase. There would be no excess cases in the 6-8 month and 9-11 month groups with a third dose. This works out to one vaccine-attributable case of intussusception per 4323 infants.

Assumptions: 80% of children received their first dose at 2 months and 20% at 3 months; 60% received the second dose at 4 months and 40% at five months.
From the case series analysis, we found a total of 838 cases for a 41% increase, and one vaccine-attributable intussusception for every 5483 children.

Caveats: In the ever/never projections, we had an altered age distribution of vaccinees, there was inadequate observation time, and all rates are sensitive to baseline yearly rate. For the case series/case control model there was limited observation time, it was sensitive to the baseline monthly rate, and the model assumes baseline risk resumes after the vaccine effect is over.

Theory of compensatory decrease: After the vaccine effect is over, the baseline risk is lowered for those who did not develop intussusception. Infantile spasms after DTP are a classic example of compensatory decrease. Among previously normal cases, there is a slight increase in cases in week one after DTP, which decreases over the next two weeks, then there is a fairly normal pattern after 21-28 days. The excess risk in the first week is due either to triggering or earlier diagnosis. Another example is febrile seizures after DTP: the vaccine caused fever, some children have predisposition to seizure with high fever, and fever brings forward in time events destined to happen anyway, but with no change in outcome.

Hypothesized mechanisms:

- Protection against rotavirus disease decreases intussusception due to natural rotavirus.
- Some unknown factor predestines infants to intussusception, timing is changed by early infection (vaccine), and the overall impact diminished.

Could such a compensatory decrease be present at this time, which would ameliorate the projected overall impact? For the rotavirus protection hypothesis, there is evidence for a possible effect, it's effective in preventing severe disease, and there is biologic plausibility that rotavirus is associated with intussusception. Evidence against a possible effect includes:

- No documented evidence of a relationship. The size of the effect would need to be 800 excess cases, i.e., rotavirus disease would have to be causing nearly half of all intussusception in the U.S.
- Vaccine is not that effective against milder disease infection.
- Rotavirus is seasonal in the U.S., so every case of intussusception from November to April would have to be due to rotavirus.

Protection against some other factor:

- Evidence for possible effect: This could have sufficient magnitude since background risk rises with age, e.g., anatomic factors.
- Evidence against possible effect: Our ever/never comparisons are quite strong. There is >3-week interval data from Kaiser, and those children continue to have some elevated risk. In VAERS, cases continue to occur at remote intervals after vaccination.

Hypothetical cohort illustration: If we took one million children, whose risk is 9.8 cases per week, the total risk in the first year of life would be 510 cases. Using the vaccine effect from the managed care example (December-March), there were four cases of intussusception within three weeks among 25,000 children vaccinated. So for one million children, there would be 160 cases in a three-week period, and the excess over a normal three-week period would have been 130 cases. The baseline risk would be 480, so the total risk in the first year of life would be 640

cases. Under these circumstances, you would see an increase in intussusception if you vaccinated children.

We are continuing to look at other risk factors for intussusception, including other vaccines.

Cost Effectiveness and Economic Impact of Intussusception
Mr. Robert Deuson, NIP, ISD, Health Economist. To determine cost effectiveness and economic impact, we first obtained the number of excess cases resulting from one million doses administered. Costs included direct medical costs, parental time, and value of life. We didn't include vaccine injury compensation and possible lawsuits.
Vaccination costs were 61% UTD coverage. The JAMA model was modified to include the new vaccine cost (weighted price of $38.00), administration costs and cost of intussusception and other adverse events. The big increase was in vaccine cost. This assumed a coverage rate of 61%. Assuming coverage rate of 90%, the picture is about same.

Composition of costs: 71% value of life lost, 28% medical care, and less than 1% for caregiver time. In looking at 61% UTD coverage in the original model and modified model, one can calculate cost effectiveness ratio, (net savings). Based on the JAMA article, for each case of diarrhea one would save $280. Today, with the change in price and adverse events, one would save $9, but still it's a cost saving. Based on 90% coverage, the same pattern would develop.

Bottom line: For the JAMA model, the benefit cost ratio would be around 2. Today, the benefit cost ratio would be marginally acceptable, but one would break even. It's not an economic issue, but a medical issue whether to continue with the vaccine. This analysis is based on U.S. conditions, and may be different in developing countries.

Dr. Livengood added that they didn't add the potential cost of every child with diarrhea running to emergency room to rule out intussusception, and Dr. Guerra noted that it would change with compensation and liability dimension.

Domestic Perspective
Roger Glass, NCID, DVRD. These have been "the best of times and the worst of times" for rotavirus vaccines. It took 25 years to discover the virus and make a vaccine that has demonstrated its efficacy. Then we discovered a possible association between rotavirus vaccine and intussusception.

The burden of rotavirus disease
Each year in the United States, there are approximately 3 million episodes of rotavirus diarrhea among children in their first 3-5 years of life. One in seven children will visit a doctor for treatment (500,000 doctor visits per year) and another 60,000 will be hospitalized. Between 30% and 40% of all hospitalizations for diarrhea are due to rotavirus. In the past, an estimated 20-40 deaths occured each year from rotavirus. However, now that there is an ICD code for rotavirus, it appears that approximately one in 800 children hospitalized with specific diagnosis of rotavirus

dies during hospitalization. This would increase the estimated number of rotavirus-associated deaths to 60-100 per year. Of these, about one half are associated with rotavirus itself and the other half are related to other severe conditions.

Eight studies of hospital discharges for intussusception in the U.S. indicate a wide range of baseline estimates, from 30 hospitalizations per 100,000 children to 75 per 100,000 children. This means that the estimated numbers of intussusception using the excess relative risk from the vaccine could range widely, depending upon the state in which the relative risks are applied. In addition, while intussusception used to be a common cause of intestinal obstruction with fatalities, in 1997 only seven children died of intussusception in the U.S. These were all children of mothers who were under 20 years of age, had not completed high school, and were from racial minorities. In other words, they represented problems of social access rather than unusual medical disease.

Fifteen years ago rates of intussusception within the Indian Health Services were several times higher than those of the rest of the U.S. population. Since then, those rates have declined to U.S. levels. The cause of the decline is unknown, but it may indicate that intussusception is infection-related. It also suggests that rates of intussusception in developing country populations could be higher or lower than U.S. rates.

Intussusception events associated with rotavirus vaccine
The exact number or rate of intussusception events that are truly associated with the rotavirus vaccine is unknown. It is possible that there could be compensatory decrease in intussusception among vaccinees following rotavirus immunization, similar to the compensatory decrease in febrile seizures following DTP immunization. We do not actually know if children vaccinated against rotavirus have a higher rate of intussusception than children who were not vaccinated. These studies could come from a follow up of the HMO cohorts, but full data may never be available because the immunization program was stopped abruptly.

Which children get intussusception?
For every 9,999 children protected against rotavirus without adverse events, one child could develop intussusception. This child may be unusual in some way. Since we know that children who get vaccine-associated polio have a high likelihood of being immuno-suppressed or immuno-incompetent, we need to examine how children who get intussesception from rotavirus vaccine differ from those who do not.

Could rotavirus vaccine be administered safely? Intussusception is uncommon in children in the first three months of life. It is therefore conceivable that immunizing children at a younger age (less than 3 months) could significantly decrease the attributable risk. It is also possible that the risk of intussusception could be lowered by changing the timing of immunization, the links of intussusception to feeding practices, introduction of solid foods or breast-feeding, or the presence of other intercurrent infections. Furthermore, we could educate physicians and parents alike to treat intussusception more conservatively, but aggressively, in the week following rotavirus

immunization, to decrease the need for surgery and the likelihood of a fatal disease. We will need to seek other vaccine candidates as well.

The risk of intussusception associated with the vaccine must be balanced with the benefits of protection against rotavirus infection. In the United States, failure to vaccinate could lead to 10,000 to 15,000 rotavirus hospitalizations per million children and 10 rotavirus-associated deaths. The importance of the rotavirus vaccine is even greater in developing countries, where an estimated 600,000 to 800,000 deaths from rotavirus occur each year. In India, for example, one in 250 children will die with a rotavirus infection. Other countries need the opportunity to decide whether this vaccine is an important prevention tool in their settings. Clearly much more work and research is needed to address these important issues.

WHO's Position on Rotavirus Development

Dr. B. Ivanoff, WHO. The estimated mortality per year in the world is due to five pathogens, and rotavirus is the highest. Even if you improve sanitation and sewage, you cannot decrease rotavirus. The United States has the same percentage of rotavirus as Indonesia. Clearly there is a strong need for effective health intervention to prevent rotavirus diarrhea. WHO is working with CDC on surveillance in Africa and Asia. In a few years, we'll have an update on disease burden and mortality and morbidity of rotavirus in these two continents.

WHO has two important goals on its agenda: 1) an effective vaccine able to prevent severe rotavirus diarrhea in infants from developing countries, and 2) to see if neonatal immunization with BCG would be immunogenic and protective. We are concerned about achieving major coverage.

Questions: What is the balance between risk and benefit in developing countries? What is the risk of dying from rotavirus vs the risk of dying from induced intussusception? If the use of oral rotavirus vaccine should not be recommended in the U.S., what about its use in developing countries, where there is a substantial risk of death?

Don't close the door on the development of other oral vaccines. There is a strong need for the vaccine in developing countries. We know a little about incidence and risk factors for intussusception among infants from developing countries. Evaluation of other vaccine candidates could be hampered if a strong decision were taken by ACIP. Therefore, we would request that any recommendation the ACIP makes on the use of the vaccine in the U.S. leave open the option for further considering and testing of live oral rotavirus vaccines in countries where assessment of risks and benefits might be substantially different.

Update from Wyeth Lederle

Dr. P. Paradiso, Wyeth Lederle. In July, when increased reports of intussusception in children vaccinated with rotavirus vaccine were received through VAERS, Wyeth Lederle, with CDC and FDA, decided to stop distribution of the vaccine. A letter was sent out to 100,000 health care

providers informing them of the recommendation to suspend use of the vaccine. Follow-up visits were made to reconfirm suspension of immunization and proper storage of vaccine supplies. Wyeth Lederle provided CDC with shipping addresses of everyone who had ordered vaccines and met with CDC to review VAERS information. It then became apparent that resumption of routine vaccination would not occur during the winter rotavirus season, so we requested return of vaccine still in the field. We will continue to work with CDC to further understand the relation between rotavirus and intussusception, and the risks and benefits of vaccination. Rotavirus is a serious illness and Wyeth Lederle will continue to work toward prevention throughout world.

Public Comment

Lars Hansen, Sweden. The newborn's immune system is much less developed than the adult's. It has to be colonized with bacteria and flora. Gram negatives are essential for balance of the immune system of the gut, so we have an abnormal situation, which might relate to these unusual responses. Second, breast feeding provides some protection. Vaccination might be very different in developing countries where babies are breast-fed.

The Draft Statement:

The Advisory Committee on Immunization Practices (ACIP), after a review of currently available information from several sources, has concluded that intussusception occurs with significantly increased frequency in the first one to two weeks following vaccination with rhesus rotavirus vaccine - tetravalent (RRV-TV), particularly following the first dose. Therefore, the ACIP no longer recommends routine immunization of infants with RRV-TV and withdraws its recommendation that RRV-TV be administered at 2, 4, and 6 months of age.

Rotavirus causes a substantial health burden for children in the United States. It accounts for 20 to 40 deaths annually, and more than 50,000 hospitalizations from severe diarrhea and dehydration. Vaccination against rotavirus would be the optimal means to prevent this health burden. Rhesus rotavirus vaccine was recommended because it was shown in pre-licensure trials to be a safe and effective vaccine. In those trials, RRV-TV was shown to prevent at least 50 percent of the cases of diarrhea from rotavirus and an estimated 90 percent of the hospitalizations. Post-licensure evaluation, however, has identified intussusception as a rare, serious adverse event associated with the vaccine.

Many important questions regarding the relationship between intussusception and rotavirus vaccine remain to be answered, and merit further research. These answers could impact directly on the use of this and other rotavirus vaccines in the future. In addition, the worldwide burden of rotavirus disease remains substantial. Thus, the ACIP's decision may not be applicable to other rotavirus vaccines or the use of RRV-TV in other settings, where the burden of disease is substantially higher and where the risks and benefits of rotavirus immunization could be different. Other countries might reasonably choose to proceed with rotavirus vaccination based upon their own assessment of risks and benefits.

In the United States, rotavirus remains the primary cause of parents seeking health care for children with severe dehydrating diarrhea, particularly in the winter months. In light of the withdrawal of this vaccine recommendation, the ACIP recommends that educational efforts directed at parents and health care providers be undertaken. These efforts should focus on the early diagnosis and treatment of dehydrating rotavirus diarrhea, particularly among those children who would have benefited most from the availability of a rotavirus vaccine (i.e., 3 months to 35 months of age).

Discussion

Dr. Livengood commented that this was a recommendation about this vaccine at this time on this schedule. There are issues of alternate schedules, alternate doses of this vaccine, and alternate settings. Dr. Jackson noted that the first paragraph by itself slammed the door on the vaccine, and urged the committee to leave some reservations. Dr. Livengood explained that CDC is very reluctant to urge developing countries to do things that do not meet the U.S. standard of care. Dr. Rennels suggested adding "to US infants" at the end of the last sentence. Dr. Orenstein explained that the other paragraphs were designed not to slam the door. Dr. Guerra asked about U.S. infants who are going to the developing world. Dr. Modlin replied that the vaccine would not available to them.

Dr. Johnson commented that other developed countries need information on the risk of intussusception. This is a real finding that has to be taken into consideration. Dr. Guerra asked whether there was a need to mention ongoing observation of those who have already received the vaccine. Dr. Livengood replied that CDC intended to perform additional analyses and continue surveillance. Dr. Abramson said that the AAP would go along with this statement. However, he felt it was important to say something about ORS in order to impact hospitalization rates. Dr. Guerra suggested that for those who are at greatest risk and not easily able to access services, we should recommend a specific resource, such as ORS through WIC programs. Dr. Jackson said he would like to see specific evidence for some of the comments made by speakers, such as 2000 deaths per day in developing countries. Surveillance around the world is not sophisticated enough to say the cause was rotavirus.

Decision

Dr. Guerra made a motion to adopt the statement with modifications and suggested changes in emphasis in the final paragraph. A number of voting members had conflicts with Wyeth Lederle The executive secretary designed the ex officios members as voting members. Those in favor were Dr. Word, Dr. Johnson, Dr. Guerra,

Dr. Modlin, Dr. Breiman, and Mr. Graydon. Opposed: none. Abstaining: Dr. Rennels, Dr. Brooks, Dr. Offit, Dr. Evans, Dr. Rabinovich, and Dr. Egan. The motion passed.

The meeting adjourned at 12:05 pm.

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

John F. Modlin, M.D., Chair — DATE

22 Feb 00