Table of Contents

OPENING COMMENTS 10

INFLUENZA VACCINE 12
Estimates of Vaccine Effectiveness 13
Vaccine Supply Issues 13
ACIP Response to the Delay 13
PRO Survey 14
Program Response to the Delay 15

NIH HALF-DOSE INFLUENZA VACCINE STUDY 16
Jet Injector Study 17
Cost Effectiveness Study in Health Adults 18
Update on Use of LAIV and Pediatric Issues 20

IMMUNIZATION OF FOREIGN ADOPTEES 21
Progress Towards Recommending Immunization of Foreign Adoptees . . . 23

RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE 27

SMALLPOX VACCINE RECOMMENDATION 29
Smallpox Vaccination for Laboratory Workers 29
Smallpox Vaccine for Bioterrorism Preparedness 30

SUBCOMMITTEE ON OVERSIGHT OF THE VACCINE
HEALTH CARE NETWORK 31

FDA UPDATE ON USE OF BOVINE-DERIVED MATERIALS IN THE
MANUFACTURE OF VACCINE 32
Recommendations of the FDA Joint TSEAC and VRBPAC Meeting . . . 32

UPDATE ON NIP VACCINE SAFETY INITIATIVES 33
Vaccine Safety Initiatives 33

UPDATES
National Center for Infectious Diseases 35
National Immunization Program 35
Food and Drug Administration 36
Vacugfycine Injury Compensation Program 36
National Vaccine Program Office 37

ADULT IMMUNIZATION WORKING GROUP 38
Pertussis Among Adolescents and Adults 38
SmithKline Beecham Data on Boostrix™ 39
Criteria for Making Recommendations for the Pertussis Booster 40

MENINGOCOCCAL CONJUGATE VACCINATION IN THE UNITED KINGDOM 42

UPDATE ON MEASLES VACCINE AND OUTBREAKS OF DISEASE IN THE UNITED KINGDOM. 44

PERSISTENT EXCRETION OF POLIO VIRUS IN B CELL IMMUNE DEFICIENCY DISORDERS 45
Overview of Polio Eradication 45
Polio Virus Excretion and B Cell Immune Deficiencies 45

ANAPHYLAXIS DUE TO GELATIN AFTER MMR VACCINATION 47

UPDATE FROM MANUFACTURERS ON THIMEROSOL-FREE VACCINE UPDATES 49

TD VACCINE SHORTAGE 49

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GEORGIA
October 18-19, 2000

Agenda Item	Purpose/Action	Presider/Presenter(s)
October 18		
8:30 Welcome		Dr. J. Modlin (Chair, ACIP)
Disclosure by Committee Members		Dr. D. Snider (CDC, OD)
9:00 Influenza vaccine	Information	Dr. C. Bridges (NCID,DVRD)
Overview of Seasonal Activity	Discussion	Dr. K. Fukuda (NCID,DVRD)
Vaccine supply issues	Decision	Dr. Marika Iwane (NIP, ESD)
NIH half dose influenza vaccine study		Dr. Linda Lambert (NIH)
Vaccine effectiveness estimates		Dr. Roland Levandowski (FDA)
Cost effectiveness study in healthy adults		Dr. Lance Rodewald (NIP,ISD)
Update on LAIV and pediatric issues		Dr. Ben Schwartz (NIP, ESD)
10:45 BREAK		
11:15 Immunization of foreign adoptees	Discussion	Dr. Wm. Atkinson (NIP, ISD)
Progress towards recommending	Decision	Dr. M. Hostetter (Yale)
immunization of foreign adoptees		Dr. J. Modlin (Dartmouth)
		Dr. J. Schulte (NIP, ESD)
		Dr. Ben Schwartz (NIP, ESD)
		Dr. M. Statt (Chisdren's Hosp.)
1:15 LUNCH		
2:15 Recommended Childhood Immunization	Discussion	Dr. J. Cono (NIP, ESD)
Schedule	Decision	Dr. T. Murphy (NIP, ESD)
Does ACIP approve the proposed schedule?		
3:15 Smallpox Vaccine Recommendations	Information	Dr. C. Helms (Univ. of Iowa)
Recommendation for smallpox vaccine use in Bioterrorism event involving smallpox	Discussion	Dr. L. Rotz (NCID, DVRD)
Revised recommendations for smallpox vaccination in laboratory workers using attenuated vaccinia virus strains		
Alternatives to VIG for treatment of adverse vaccine reactions		
3:45 Subcommittee on Oversight of the Vaccine	Information	Dr. M. McNeil (NIP, ESD)
Health Care Network	Discussion	
4:00 BREAK		

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Agenda Item		Purpose/Action	Presider/Presenter(s)
4:30	FDA Update on Use of Bovine-Derived Materials in the Manufacture of Vaccines Recommendations of the FDA joint TSEAC and VRBPAC Meeting	Information Discussion	Dr. K. Midthun (FDA,CBER)
5:00	Anaphylaxis after MMR due to gelatin Alter guidance for vaccinees with MMR anaphylaxis history Include gelatin food allergy as a precaution to immunization	Information	Dr. V. Pool (NIP, ESD) Dr. T. Vernon (Merck)
5:30	Public Comment		

5:45 ADJOURN

October 19

Agenda Item		Purpose/Action	Presider/Presenter(s)
8:00	Unfinished Business from Previous Day		Dr. J. Modlin (Chair, ACIP)
8:30	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. K. Midthun (FDA, CBER)
	Vaccine Injury Compensation Program		Dr. G. Evans (HRSA)
	National Vaccine Program		Dr. M. Myers (NVPO)
9:30	Adult Immunization Working Group	Information	Dr. K. Bisgard (NIP, ESD)
	SmithKline Beecham data on Boostrix	Discussion	Dr. R. Clover (Univ of Louisville)
	Pertussis among adolescents and adults in the US: Data from the APERT trial	Decision	Dr. T. Murphy (NIP, ESD) Dr. J. Ward (UCLA)
	What data are needed by ACIP to help make a decision about a recommendation for adolescent or adult pertussis booster dose?		Dr. P. Willems (SKB) Dr. L. Zanardi (NIP, ESD)

10:15 BREAK

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Agenda Item		Purpose/Action	Presider/Presenter(s)
10:45	Meningococcal conjugate vaccination in the United Kingdom	Information	Dr. D. Salisbury
11:15	Update on Measles vaccination and outbreaks In the United Kingdom	Information	Dr. D. Salisbury
11:45	Persistent polio virus excretion in patients with B cell immune deficiency disorders	Information Discussion	Dr. R. Sutter (NIP, VPDED) Dr. N. Halsey (Johns Hopkins Univ.)
12:30	Update on NIP Vaccine Safety Initiatives Update on IOM Vaccine Safety Initiatives	Information	Dr. R. Chen (NIP, ESD)
1:00	Update from Manufacturers on Thimerosal free vaccine	Information	Dr. P. Hosbach (Aventis Pasteur) Dr. M. Kempf (Baxter Hyland Immuno) Dr. P. Paradiso (Wyeth Lederle)
1:15	Public Comment		
1:30	**ADJOURN**		

ATTENDEES:

Committee Members
Dr. John Modlin, (Chair)
Dr. Dennis Brooks
Dr. Richard Clover
Dr. Charles Helms
Dr. David Johnson
Dr. Paul Offit
Dr. Margaret Rennels
Dr. Lucy Tompkins
Dr. Bonnie Word

Ex Officios
Dr. Dana Bradshaw, DOD
Dr. Jeffrey Evans, NVICP
Randolph Graydon, HCFA
Amy Groom (IHS)
Dr. Karen Midthun, FDA
Dr. Martin Myers, NVPO
Dr. Kristin Nichol (UMVAMC)

Liaison Representatives
Dr. Jon Abramson (AAP)
Dr. Eric France (AAHP)
Dr. Stanley Gall (ACOG)
Dr. Barbara Howe (PhARMA)
Dr. Rudolph Jackson (NMA)
Dr. Samuel Katz (IDSA)
Dr. Victor Marchessault (DNACI)
Dr. Martin Mahoney (AAFP)
Dr. W. Paul McKinney (ATPM)
Dr. Georges Peter (NVAC)
Dr. Larry Pickering (AAP)
Dr. William Schaffner (AHA)
Dr. Jane Siegel (HICPAC)
Dr. H. David Wilson (AMA)
Dr. Richard Zimmerman (AAFP)

Executive Secretary (Acting)
Dr. John Livengood

Office of General Counsel
Kevin Malone

Epidemiology Program Office
Dr. D. Fishbein

National Center for Environmental Health
Susan Gorman
Gillian Hamilton
Anne Huang
Marika Iwane

National Center for Infectious Diseases
Carolyn Bridges
Scott Campbell
Christy Cianfrini
Nancy J. Cox
Debbie Dotson
Sarah Foster
Keiji Fukuda
Olen Kew
Rima Khabbar
Alexander Klimor
Nina Marano
Allison Mawle
Brad Perkins
Lisa Rotz
Anne Schuchat
Cindy Whitney
Elizabeth Zell

National Center for STD, HIV, and TB Prevention
Dr. Tim Mastro

National Immunization Program
Curtis Allen
Debi Ashman
William Atkinson
Sharon Balter
Roger Bernier
Kris Bisgard
Sharon Bloom
Bob Chen
Susan Chu
Gary Cole
Joanne Cono
Kristen Drusuelas
Elizabeth Fair
Bill Gallo
Karen Galis
Paul Gargiullo
Edith Gary
Stephen Hadler
Toni Habeour
Beth Hibbs
Penina Haber
Sonya Hutchins
Laurie Johnson
Sheila Jones
Sharon Katz
Duane Kilgus
Karin Kohl
Mary Lambert
Kim Lane
Charles LeBaron
Randy Louchart
Hugh Mainzer
Tasneem Malik
Dean Mason
Mary McCauley
Mike McNeil
Gina Mootrey
Trudy V. Murphy
Bill Nichols
Glen Novak
W. Orenstein
Jeri Pickett
Robert Pless
Bette Pollard
Kristen Poydence
Dianne Quarterman-Ochou
Susan Reef
Lance Rodewald
Susan Scheinman
Judy Schmidt
Joanne Schultz
Ben Schwartz
Jane Seward
Kristine Sheedy
Abby Shefer
Jim Singleton
Vismnu-Priya Sneller
G.G. Somerville
Bob Snyder
Ray Strikas
Kathy Trevers
Fran Walker
Donna L. Weaver
Bruce Weniger
Craig Wilkins
Skip Wolfe
Ed Yacovone
Lynn Zanardi
Laura Zimmerman

National Vaccine Program Office
Sandra Browning
Alicia Postema
Greg Wallace

Public Health Practice Program Office
Luis Kun

Other Government Attendees
Norman Baylor, FDA
Michael Gerber, NIH
Linda Lambert, NIAID
Cheryl Lee, HHS

Others Present
Kaia Agarwal, SmithKline Beecham
Maureen Alt, national Partnership for Immunization
B.F. Anthony, Biologics Consulting Group
Lynn Bahta, Immunization Action Coalition
Michele Bailey, CDC National Immunization Hotline
Greg Ball, Aventis Pasteur
Sharraine L. Banks, ASTHO
Joseph Beaver, TN Department of Public Health
Karen Biscardi, Aventis Pasteur
John Bletz, Aviron
Elizabeth Blowers, Merck
Dewayne Brumlow, WLV
Phil Brunell, Stock, Inc.
Jillian Caneton, Cohn & Wolfe Healthcare
Dan Casto, Merck
Jill Chamberlain, Vaccine Bulletin
Dave Cobb, Aventis
Janelle Conlin, Wyoming Immunization Program
Brie Coughlin, OraVax, Inc.
Mike Cooper, Reuters
Dack Dalrymple, Bailey and Dalrymple
Richard Dinovitz, Wyeth Ayerst Labs
Craig Engesser, Wyeth Lederle
Darrell Ferguson, Wyeth Lederle
Joan Fusco, Baxter
Mary Gadek, Aventis Pasteur
Madeleine Gardberg, Wyeth Lederle Vaccines
Bruce Gellen, Vanderbilt University
Jayne Gilbert, Chiron Corp.
Velarie Gillispie, IAC
Ruth Gilmore, Georgia Immunization Program
Jesse Greene, SC Department of Health
Neal Halsey, Johns Hopkins Univ.
Emma Patten-Hitt, ICAN Inc.
Sandra Holmes, SmithKline Beecham
Philip Hosbach, Aventis Pasteur
Muriel A. Hoyt, Private Citizen
Sue Hubbard, Pedrerni Associates of Dallas
Sharon Humiston, University of Rochester
Dominick A. Iacuzio, Roche Labs, Inc.
Maggie Keane, Merck Vaccine Division

Rne Keilhauer, Merck
Matthew Kempf, Baxter Highland
Michelle Kirsche, Slack Inc.
Myron Levin, University of Colorado Health Sciences
Scott Litherland, Parallax Communications
Harold Lupton, Aventis Pasteur
Michael Massare, Novavax
Gary Melinkovich, Wyoming Department of Health
Paul Mendleman, Aviron
Fernando Norriega, Aventis Pasteur
Paul Paradiso, Wyeth Lederle
Stanley Plotkin, Aventis Pasteur
Kelly Plott, JMP/DVPD
Jill Pulley, Aviron
Scott Ratzan
Michele Ritan, Reuters Health Online
Roland Rodriguez, Wyeth Lederle
Mark Reed, Wyeth Ayerst
Anne Roger, Parallax Communications
Fred Ruben, Aventis Pasteur
Zeil Rosenberg, Becton Dickinson
Gail Rosselot, American Liver Foundation
Jerald Sadoff, Merck
David Salisbury, Department of Health
Kristine Severyn, Vaccine Policy Institute
Judith Shindman, Aventis Pasteur
Alan J. Sievert, Cobb County Board of Health
Natalie Smith, California DHS
Mary Staat, CHMC
Stacy Stuerke, Merck
John Talarico, NYSDOH
Richard Thompson, Cammo Medical Group
Miriam Tucker, Pediatric News
Theresa Turski, DHR, GDPH
Thomas M. Vernon, Merck
Peter Vigliarolo, Cooney Waters
Deborah Wexler, Immunization Action Coalition
Matt Wilcox, Aventis Pasteur
Paul Willems, SmithKline Beecham
Luana Wojcik, Aventis
Laura J. Yoric, WLV

Advisory Committee on Immunization Practices

Wednesday, October 18, 2000

OPENING COMMENTS

The Centers for Disease Control and Prevention convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on October18-19, 2000 at the Marriott Century Center in Atlanta, Georgia. ACIP Chair Dr. John Modlin called the meeting to order at 8:30 a.m. He introduced Dr. John Livengood, the Deputy Associate Director for Science, who will be the Executive Secretary for Dr. Dixie Snider during this meeting. Dr. Livengood welcomed the following newly-appointed ex-officio members: Dr. Karen Midthun, Center for Biologics Evaluation and Research, FDA; and Dr. Dana Bradshaw, Department of Defense, ex-officio member replacing Dr. David Trump. Amy Groom is serving today as the ex-officio representative from the Indian Health Service. Dr. Martin Mahoney is the new liaison representative from the American Association of Family Physicians and replaces Dr. William Phillips.

Dr. Livengood noted that nine appointed committee members are present. He reminded the Committee that seven members constitute a quorum. He stressed the importance of the voting members attending through the end of the meeting and asked that they return from breaks/lunches promptly. Dr. Livengood addressed other housekeeping duties including a review of the e-mail address, telephone and FAX numbers for the ACIP.

The next ACIP meeting will be held February 21-22, 2001 at the Marriott Century Center. The dates for subsequent meetings in 2001 will be June 20-21 and October 17-18.

Dr. Livengood stated that the ACIP charter gives the Executive Secretary or designee, the authority to temporarily designate ex-officio members as voting members when fewer than seven appointed members are qualified to vote because of a financial conflict of interest. Ex-officio members will be formally requested to vote when necessary. ACIP has always held open discussions and has reserved meeting time for official public comment. As the committee has a restricted time period for conducting business, formal comment periods are scheduled. Comments are received as time permits. Time for individual comments on specific agenda items must be arranged in advance.

Dr. Livengood described the operating logistics of the committee and where voting members, ex-officio members, and liaison members sit at the tables. Audience participants were asked to identify themselves when addressing the committee and were asked to use the microphones placed at each end of the tables so their comments can be recorded.

Dr. Modlin asked the voting members of the committee to introduce themselves and to disclose any potential financial conflicts of interest. ACIP members may participate in discussions of all issues provided any potential conflict has been fully disclosed; however, persons with a direct

conflict of interest may not vote on any issue related to the conflict. Only voting members are required to disclose conflicts; ex-officio and liaison members with significant conflicts are encouraged to disclose them but are not required to do so. ACIP has adopted a policy that prohibits members with financial conflict of interests from introducing, seconding or voting on Vaccines for Children (VFC) resolutions.

ACIP members:

- Dr. Dennis Brooks, Johns Hopkins University; no conflicts of interest
- Dr. Margaret Rennels, University of Maryland; she performs vaccine trials sponsored by Wyeth, Aventis Pasteur, and Merck and chairs a safety monitoring board of a trial sponsored by Aventis Pasteur
- Dr. David Johnson, State Health Department of Michigan; no conflicts of interest
- Dr. Lucy Tompkins, Stanford University; no conflicts of interest
- Dr. Richard Clover, University of Louisville; he and his department have received funding from SmithKline Beecham, Merck, Wyeth, Astra Zeneca, and Bayer
- Dr. Charles Helms, University of Iowa; no conflicts of interest
- Dr. Bonnie Word, pediatric infectious disease physician in New Jersey; no conflicts of interest
- Dr. Paul Offit, Children's Hospital of Philadelphia, the University of Pennsylvania School of Medicine; he consults with Merck on the development of a bovine human rotavirus vaccine
- Dr. John Modlin, Dartmouth Medical School; he has no conflicts of interest but has received travel expenses for participation in advisory board meetings for SmithKline Beecham and Aventis Pasteur

CDC representatives:

- Allison Mawle, Vaccine Coordinator for National Center for Infectious Diseases, NCID
- Dr. Ben Schwartz, Epidemiology and Surveillance Division, National Immunization Program, NIP
- Dr. Walter Orenstein, NIP Director

Ex officio and liaison members:

- Dr. Jon Abramson, Chair, Committee on Infectious Disease, American Academy of Pediatrics (AAP); no conflicts of interest
- Dr. Larry Pickering, Editor Red Book, 2000 edition; no conflicts of interest
- Dr. Georges Peter, liaison National Vaccine Advisory Committee (NVAC)
- Jane Siegel, UT Southwestern, Healthcare and Infection Control Practices Advisory Committee (HICPAC)
- Dr. Barbara Howe, SmithKline Beecham, liaison representative for Pharmaceutical Research and Manufacturers of America (PRMA)
- Dr. Stanley Gall, American College of Obstetricians and Gynecologists (ACOG)
- Dr. Sam Katz, Duke University and the National Network for Immunization Information, representing the Infectious Disease Society of America (IDSA)
- Dr. Bill Schaffner, Vanderbilt University, American Hospital Association (AHA)

- Dr. Eric France, Kaiser Permanente Colorado; he receives funds from Merck and Wyeth for vaccine trials
- Dr. Victor Marchessault, National Advisory Committee of Immunization in Canada; no conflicts of interest (NACIC)
- Dr. Rudolph Jackson, Morehouse School of Medicine and the National Medical Association (NMA); no conflicts of interest
- Dr. Rick Zimmerman, University of Pittsburgh, American Academy of Family Physicians (AAFP)
- Dr. Martin Mahoney, State University of New York at Buffalo, American Academy of Family Physicians (AAFP); no conflicts of interest
- Dr. Kristin Nichol, Department of Veterans Affairs; she has received funding from Wyeth, Merck, and Aventis Pasteur
- Dr. Martin Myers, National Vaccine Program Office (NVPO); no conflicts of interest
- Randy Graydon, Healthcare Financing Administration (HCFA); no conflicts of interest
- Amy Groom, Indian Health Service
- Dr. Dana Bradshaw, Chair of the Joint Preventive Medicine Policy Group for the Department of Defense (DOD)
- Dr. Carole Heilman, National Institutes of Health (NIH); no conflicts of interest
- Dr. Karen Midthun, Office of Vaccines Research and Review, Center for Biologics, Food and Drug Administration (FDA)
- Dr. Geoffrey Evans, National Vaccine Injury Compensation Program (NVIC); no conflicts of interest

Dr. Modlin noted that several ACIP updates and statements have been published since the June meeting as well as a CDC press release. Copies of these can be found in the committee members notebooks. Dr. Fernando Guerra will remain a member of the Committee until a replacement is appointed.

Dr. Modlin announced that on September 28, the ACIP held a meeting by conference call to discuss the influenza vaccine supply for the current season. A statement resulting from that meeting was published in MMWR on October 6. Dr. Keiji Fukuda will review the issues that were covered in the conference call as well as other topics relating to influenza vaccine.

INFLUENZA VACCINE

Overview of Seasonal Activity

Dr. Keiji Fukuda (NCID) presented an update of influenza activity given the existing vaccine supply situation. In the current year, the following influenza viruses have been isolated in the southern hemisphere: influenza A H1N1, influenza A H3N2 and influenza B. Traditionally, influenza A viruses have predominated over B viruses worldwide. Although an increase occurred in influenza A H1N1 activity earlier this year, Dr. Fukuda characterized overall activity worldwide as mild to moderate. CDC received several H1N1 isolates this summer from an outbreak that occurred at a children's camp in Texas as well as B isolates from Alaska,

California, Washington, and Nevada. However, as of week 40, none of the 426 specimens tested at the WHO laboratory in the U.S. have yielded influenza virus.

During the last influenza season, CDC detected a considerably higher rate (11.2%) for influenza mortality compared with recent years. Dr. Bill Thompson and Eric Weintraub analyzed the data collected over the past five seasons for each city in the 122-city surveillance system and compared this information with NCHS data. They determined that the baseline for the 1999 season was elevated about 1% over past seasons. They concluded that this baseline increase likely reflects several methodological issues that may have affected the way pneumonia and influenza (P and I) deaths were measured, particularly an evaluation of the surveillance system that caused a change in the case definition of P and I death. The baseline will be adjusted upward for the upcoming season.

Estimates of Vaccine Effectiveness

Dr. Marika Iwane presented the results of a CDC-sponsored collaborative project that determined the effectiveness of the 1999 influenza vaccine. Information was collected through the American Association of Health Plans (AAHP) regarding 127,000 non-institutionalized persons 65 years and older residing in the following regions in the U.S.: Oregon, Washington, Minnesota, and the New York City area. Two outcomes were used to evaluate vaccine effectiveness: hospitalization for pneumonia or influenza and death from any cause. Those undergoing vaccination represented 59% of the total; they tended to be older and have a high-risk condition.

The estimates resulting from this study show an overall reduction of 35% in hospitalizations for pneumonia and influenza (95% CI= 24-44%) among vaccinees and a 44% reduction in death (95% CI=38-50%) from all causes. Even though such estimates likely underestimate true vaccine effectiveness, efficacy is consistent over time as corroborated by data from 1997. In that year, the vaccine strain was not well matched with the predominant circulating strain, yet efficacy results for 1997 were similar to those for 1999.

Vaccine Supply Issues

Dr. Baylor addressed the current vaccine supply situation. In June, the ACIP was made aware of the potential for delays and possible shortages of vaccine for this influenza season. Two manufacturing issues were expected to have an effect on the supply: compliance with good manufacturing practices and an inability to get sufficient yield of growth of the Panama strain (this problem has been resolved). Of the four companies that manufacture influenza vaccine, three are currently producing product. Approximately 50% of the trivalent lots of vaccine distributed last year have been released this season. Dr. Baylor expects that more vaccine will be released and in distribution soon. Approximately 75 million doses of vaccine will be produced for distribution this year.

ACIP Response to the Delay

Dr. Ben Schwartz presented the recommendations that ACIP voted on and adopted in a recent meeting which took place by conference call. This information was published in the MMWR on

October 6. The basis for the recommendations concerned the expected delay in vaccine distribution this year, an awareness that many high-risk persons do not receive influenza vaccine, and the understanding that many who are vaccinated for influenza are not in a high-risk category. Although the ACIP recently expanded its recommendations to increase high-risk coverage for specific age groups, the focus of those recommendations was on original vaccination of high-risk persons and the health care workers who minister to them. High-risk persons should be immunized first; this effort should be addressed at the local level.

As long as vaccine is available, vaccination for influenza should continue through December 2000 or even later. The media can be employed to advertise the effort to increase immunization of high-risk persons and the elderly. Other strategies such as forming liaisons with community groups and corporations to disseminate this message are helpful. Although the task has been delayed this year, special efforts should continue to ensure that persons between the ages of 50 and 64 years are vaccinated. As vaccine will become available from time to time, providers who have high-risk patients should place a second order after December.

The Task Force on Community Preventive Services has summarized other proven strategies for increasing the rate of immunization among high risk groups. They include reminder recall systems, standing orders, and vaccination of persons discharged from the hospital. State and local health departments are urged to form coalitions with provider organizations and community groups to disseminate information and promote vaccination of nursing home residents. The Task Force also recommends that children be vaccinated first because they require two doses in the first year they receive vaccine. Current vaccine availability is published on the CDC website and can also be accessed on the CDC hotline.

As an introduction to his presentation, Dr. Schwartz showed an advertisement circulated by a local supermarket chain (Publix) in which pregnant women are not advised to get vaccinated. This information contradicts ACIP recommendations, which advocate vaccinating pregnant women in the second and third trimester as they considered high risk. Although mass immunizers such as supermarkets are scheduled to begin vaccination campaigns on October 14, many private practitioners who ordered vaccine have not yet received their shipment.

PRO Survey

Anecdotal information suggests that private practitioners are more likely to experience shipment delays than those conducting mass vaccination campaigns. As price-gouging has also been reported anecdotally, particularly when immediate shipment is requested, CDC organized a cooperate effort with Peer-Reviewed Organizations (PROs) to survey providers regarding their personal experience with vaccine delay this season.

Unpublished data collected in a telephone survey revealed that of 53 PROs contacted, 93.4% had ordered vaccine but only 15 % had received it as of the last week of September. Sixty-four percent received a complete shipment, yet others received only a partial shipment. The majority expected a vaccine shipment in October, but other providers had no idea when their shipment

would arrive. Mass immunizers were more likely to have been promised a shipment in October. Roughly half of the respondents represented an internal medicine practice, and the other half represented a family practice.

As for the vaccine policy of individual practices, solo and group practitioners most commonly provide vaccination on request, whereas mass immunizers and clinics vaccinate everyone regardless of their risk. Only 9-14% do not vaccinate people not at high risk. The majority have targeted high risk persons for vaccination in the past. Factors that would likely increase targeting of certain groups include receipt of a half-shipment, a national shortage of vaccine, or if CDC advocated targeting practices. Most respondents would be willing to defer vaccination of individuals not at high risk if a vaccine shortage occurred and would be willing to order additional vaccine in December. They considered the CDC and local health departments the best sources of vaccine information.

Program Response to the Delay

Dr. Lance Rodewald summarized CDC programmatic activities begun in response to the vaccine delay. A Federal contract was initiated for nine million doses of influenza vaccine that otherwise would not have been made available. Delivery of this vaccine is expected in mid-December with distribution in late December. The approximate price will be $3.00 for the public sector and $5.00 for the private sector. The public health priority associated with this purchase is implementation of the ACIP initiative to target high-risk persons. Vaccine will be distributed through Aventis to those who have applied for the product. CDC and Aventis personnel are currently developing an algorithm for ranking and prioritizing the applications. An article discussing the priority groups identified for this vaccine will be published in MMWR on November 3.

CDC has established an Internet site that comprises three parts. The vaccine availability section is an information-only site that can link providers who have no vaccine to providers with unused vaccine. The second part has information regarding ACIP recommendations, surveillance progress, and other news. The third part offers providers strategies for raising coverage, postcard prototypes for a reminder recall system, and brochures and flyers. As physicians have expressed a preference for using flyers to discuss vaccination with their patients, CDC has developed flyers that address vaccination barriers and motivators.

The final vaccine-related activity will be an immediate two-part advertising campaign targeted to African-Americans, Hispanic-Americans, and the general population conducted by the Office of Communications. Television, radio, and outdoor transit ads will be used. In mid-November, the main message to people will be to get vaccinated if in a high-risk group. In December and January that message will change to “it’s not too late to get vaccinated.”

Discussion

Dr. Marchessault commented that in Ontario, the biggest province in Canada, vaccine is provided free to anyone who wants it, regardless of their age. According to Dr. Nichol, mass immunizers

in Minnesota placed their orders very early, yet many long-term care facilities had not placed orders until September. She noted that some clinics have cancelled immunization programs on short notice because their vaccine had not arrived. Dr. Baylor stated that the international supply is not monitored at present. Dr. Pickering advocated continuing the vaccination program into December as influenza has peaked in January, February, and March several times in recent years.

Although standing orders for vaccination in hospitals and nursing homes are being used more frequently, Dr. Schwartz indicated there is no data to reflect the incidence of that activity. Drs. Peter and Zimmerman advocated gathering that data providing a distinction is made between a true standing order and a mere prompt to the physician. State regulations in Rhode Island were recently changed so that nurses can administer vaccines to hospital patients although physicians still have the right to refuse vaccination for their patient. Randy Graydon stated that he is sending a letter to all state Medicaid directors asking them to implement standing orders for influenza vaccine. Dean Mason, NIP, believes that given the current situation, it is more important who vaccine was ordered from than any priorities manufacturers might have. As an example, he noted that providers who had ordered vaccine from Medeva had received it quickly.

According to Dr. Baylor, the yields of particular strains cannot be predicted beforehand, which is a factor that has greatly affected this season's production. At least three, perhaps four, companies will manufacture influenza vaccine next year. Fred Rubin, Aventis Pasteur, indicated that identification of the strain selection even a week or two earlier in the year would aid the overall manufacturing process. He requested that ACIP use its influence to encourage earlier strain selection next season. Manufacturers want to increase production to comply with the expanded ACIP recommendations, and early strain selection would facilitate that process.

Dr. Nancy Cox urged the ACIP to take note of all the issues related to vaccine delay this year so as to be better prepared in coming years. Dr. Helms suggested that the present situation offers ACIP an opportunity to take proactive measures to address vaccine shortage and delays before they occur. Dr. Abramson indicated that pandemic preparedness should be addressed as well. Dr. Fukada added that the Working Group will discuss the vaccine delay that has occurred in terms of lessons learned. Dr. Kristine Severyn, of the Vaccine Policy Institute, requested the number of vaccines that were returned last year and the names of the manufacturers who had difficulties with good manufacturing practices. Dr. Baylor responded that 3-5 million doses were returned last year and indicated that Wyeth Lederle and Park Davis experienced manufacturing problems.

NIH Half-Dose Influenza Vaccine Study

Dr. Linda Lambert presented the preliminary results of an NIH study regarding the usefulness of giving healthy young adults a half dose of influenza vaccine. The study was initiated in response to the impending shortage/delay in vaccine. NIAID was notified in June of the possible vaccine delay/shortage, which gave CDC a narrow window for launching this study over the summer. The goal was to present study data to the ACIP at this meeting. Development and FDA approval of the protocol were expedited to facilitate this goal.

Vaccine was made available by Evans Vaccine, formerly Medeva, on August 7. A total of 1009 subjects were enrolled at six clinical sites around the U.S. The study was designed as a randomized, blinded, open-labeled study of healthy adults between the ages of 18 and 49 years. The subjects were stratified into two groups: those who self-reported receipt of vaccine within the last three years and those who did not. After a pre-vaccination blood draw, the subjects were randomly assigned to receive a single intramuscular (IM) dose of either 0.5 ml or 0.25 ml (half dose) trivalent inactivated vaccine. A post-vaccination blood draw took place approximately three weeks later. Sera were sent to CDC and FDA for testing. The laboratory data shown are from CDC laboratories.

The immune response was evaluated using two primary measures (a 1:40 or greater increase in HI titers and geometric mean titer [GMT]) and one secondary measure (percentage of subjects with a fourfold or greater rise in antibody response). Acceptable responses to a half dose of the vaccination were established: for the 1:40 titer, a difference no greater than 20% between the full and half dose; for GMT, a difference no greater than 1.5; and for the fourfold rise, a difference no greater than 20%.

Four hundred seventy-eight subjects received a full dose of vaccine, and 481 received a half dose. The percentage of subjects who demonstrated a 1:40 or greater increase in HI titers for H1N1 was 71% for half-dose recipients and 75 % for full-dose recipients for an observed difference (4.2%) that is not statistically significant (95% confidence limits). The observed difference between the whole dose GMT and the half dose GMT was 22%. As for the percentage of subjects who experienced a fourfold or greater rise, 70% half-dose recipients and 77% full-dose recipients demonstrated this response, for an observed difference of ~7%. Similar results were observed with the H3N2 and B antigens.

These results are preliminary and results from the FDA laboratories are anticipated next week. These data show by most measures that the immune response to a whole dose is better than to a half dose. However, the immune response to a half dose vaccine met, even exceeded, all the preset acceptability criteria for each of the three antigens. Even though preliminary, these data support use of a half dose of vaccine as a viable strategy when there is a reduced supply of vaccine.

Discussion

Dr. Modlin asked ACIP members for their input regarding the public policy implications of this new data. Dr. Offit suggested that future studies should involve younger subjects. Dr. Helms inquired whether and how well adults 65 years of age and older and those with underlying illnesses might respond to a half dose. Dr. Stan Plotkin addressed the importance of evaluating adjuvants such as the adjuvant used in Italy that produces high titers.

Jet Injector Study

At Dr. Modlin's request, Dr. Bob Chen presented results of a study conducted by the Group Health Cooperative at Puget Sound and the University of Washington. This study determined

whether the pain of injection with needles or jet injectors could be reduced by reducing the volume of the vaccine dose administered. Two jet injectors were compared: the Vitajet ® injector, which delivers vaccine subcutaneously and the Biojector ® injector, which delivers the dose IM. Both injectors were also compared with subcutaneous needle and syringe injection. Subjects in the study cohort were healthy adults 18-45 years of age; their mean age was 27 years. They were divided randomly into three groups: one group got a needle and syringe injection; another received a Vitajet ® injection; the third received an injection with the Biojector ®. Three dosage levels of Aventis 1998 vaccine were administered.

The results show the proportion of subjects demonstrating $\geq$ fourfold rise in HI titer for H1N1 28 days after the dose was administered. The full-dose results show that 87% of subjects achieved a fourfold rise in titer compared with 69% of those receiving smaller doses. Similar results were obtained for H3N2 and B antigens. The two needle-free injectors elicited equivalent responses. For the H1N1 antigen, 68% full-dose recipients demonstrated a titer $\geq$1:64 on day 28; 69% intermediate- and 59 % low-dose recipients demonstrated the same titer on the same day. For H3N2, the results were 94%, 88%, and 94%, respectively. For the B antigen, the results were 94%, 78%, and 81%, respectively.

Discussion
Dr. Modlin stated that this evidence supports other data indicating that doses less than 0.5 mg are immunogenic for healthy young adults. Dr. Tom Vernon, Merck Vaccine Division, noted that setting limits of acceptability for vaccines has implications for the future, and Dr.Modlin suggested that the Dose Reduction Working Group might indeed consider those implications.

Manufacturers are currently investigating the use of cell culture for the influenza vaccine virus. Grants were recently awarded to encourage research in this area. The award grantees are examining multiple cell lines to determine which provides the best growth. The cell lines under consideration include MDCK and varocells. Dr. Cox cautioned that although cell culture appears to have advantages over the traditional egg-based system, similar problems such as poor replication that affect production can also occur in cell culture.

Cost Effectiveness Study in Healthy Adults.
Dr. Carolyn Bridges presented results of a study of the effectiveness and cost-benefit of influenza vaccination of healthy working adults, which was published on October 4 in *JAMA*. One study objective was to replicate earlier study results (Nichol et al.) that were published in the *New England Journal of Medicine* in 1995. The earlier study reported a societal cost saving of $47/person associated with vaccinating healthy working adults younger than 65 years of age. Another purpose was to estimate the societal cost benefit of influenza vaccination in a double-blinded, randomized, placebo-controlled trial.

The subjects were healthy persons 18-64 years of age who were salaried workers at Ford Motor Company. Vaccination took place in October 1997. The subjects were followed for two influenza seasons (1997-1998 and 1998-1999) from November through March. Serological testing was

performed on the first 300 subjects; virologic surveillance was also conducted to determine the timing of the influenza season. Influenza-like illness (ILI) was defined as an illness with a temperature ≥ 100° F, plus a cough or sore throat. For those undergoing serological testing, influenza illness was defined as an ILI with laboratory evidence of infection. An economic analysis was conducted from the societal perspective. The cost of vaccination was estimated at ~$10/person. The vaccination procedure took approximately 30 minutes away from work.

For participants undergoing serological testing in the first year of the study (A/Sydney virus not included), the rates of illness were 2% for vaccine recipients and 4% for placebo recipients. Vaccine efficacy that year was 50%. In the second year, when A/Sydney virus predominated, influenza illness occurred at a rate of 1% for vaccine recipients and 10% for placebo recipients. Vaccine efficacy was 86% for the second year. Fewer illnesses, physician visits, and lost work days occurred, but only in the second year.

The cost of ILI for the second year averaged $26.73/person for vaccine recipients and $40.26/person for placebo recipients. Adding in the estimated cost of vaccination ($24.70) produced a societal net cost of $11.17/person vaccinated. Sensitivity analysis of the second year data revealed no cost savings. A cost savings of $2.36/person was determined only when the ILI rates were doubled.

The limitations of this study were several: intangible costs and benefits of reduced transmission to co-workers and family members were not factored into the analysis; the population was specific; and the ratios of lost work days/ILI were similar to those in other U.S. studies. No overall cost savings were associated with vaccination of healthy working adults although the vaccine provided health benefits. Therefore, the decision to vaccinate should be based on considerations other than cost benefit.

Discussion

Dr. Nichol maintained that demographics might have influenced the work loss rate in this study. She stated that the Cochran Review on Influenza in Healthy Adults estimated an average reduction in work loss of 0.4 working days/person vaccinated (~3 hours). A cost utility analysis estimated that vaccination of persons 25-44 years of age would cost $64/year of healthy life saved, which is ~$250 in 1999 dollars. Dr. Bridges commented that it is difficult to compare U.S. data with European data such as that derived from the Cochran study because some effects are due to cultural differences.

According to Dr. Orenstein, work immunization programs vaccinate all working adults not only healthy adults as in this study. Clear health benefits related to vaccination are evident regardless of a good vaccine match, and the ACIP recommendation to vaccinate adults 50-64 years of age should not be revoked. Dr. Abramson added that the true efficacy of vaccination will not be known until it can be determined how many work days parents miss because their children, not the parents, are sick. An evaluation of true efficacy must involve vaccination of entire households. Dr. Rubin indicated that the conclusions of this study might damage institutional

employee health programs. The conclusions reflect the one year in ten when the vaccine did not match the infecting strain rather than the nine in which a good match occurred. Keeping working adults healthy offers cost-savings to industry and benefits society. The impact of vaccination on worker productivity is another factor that requires consideration.

Update on LAIV and Pediatric Issues

The ACIP has long considered expanding the influenza vaccine recommendations to include other groups such as the pediatric population. This issue is linked to the development of a live attenuated influenza vaccine (LAIV). The question before the ACIP is whether it should recommend that young children receive this vaccine annually.

Dr. Fukuda stated that two factors have a significant impact on this decision. Information from the 70s and 80s suggests that children face an increased risk of hospitalization during periods when influenza viruses are circulating, an increase that is not associated with other viruses. In addition, in the fourth quarter of this year Aviron will submit its LAIV formulated as an intranasal spray for FDA approval. Licensing of this product may take place early next year. Dr. Fukada urged ACIP members to consider the safety of vaccinating young children, the logistics and feasibility of this practice, and the implications for the current vaccine schedule when making this important decision.

Studies to Evaluate LAIV in Children

Dr. Marika Iwane showed an illustration of the burden of widespread influenza immunization to a pediatrician with a practice of 2000 patients. Factors such as the number of visits/practice and the already-crowded immunization schedule were examined. To address the feasibility of widespread vaccination of children, CDC is collaborating with the University of Rochester in studies that represent a range of practice types. These studies are comprised of focus groups consisting of providers and their staff, time-motion and database studies, and a component designed to elicit the perspective of parents regarding additional immunization. A provider survey will assess barriers to implementation, current influenza vaccination practices, reminder and recall methods, and acceptability of alternate vaccination sites. Data from this and other trials regarding the amount of time needed to administer the intranasal spray vaccine will be collected. Office-based billing data and insurance billing data will be analyzed as well.

Dr. Fukuda expects that new safety data regarding LAIV will be available early in 2001. He proposed that CDC schedule a meeting in May to review the safety of routinely vaccinating young children with LAIV and that an additional meeting of the Influenza Working Group be arranged next summer to address feasibility data and other related issues. He proposed that this topic be updated at the June ACIP meeting and discussed further in October so the recommendations regarding this issue can be in place for the February 2002 meeting of the ACIP.

Discussion
Dr.Modlin asked for the committee's response to the time line Dr. Fukuda presented. Dr. Midthun responded that the FDA will not have the results of ongoing safety studies when the license application is submitted later this year, and the FDA will focus on the specific application that is submitted. Dr. Paul Mendleman, Aviron, stated that Dr.Gleason's first-year experience with vaccinating 4298 children has been presented and analysis of the second-year findings is ongoing. A historical written document of findings will be submitted with the license application.

Input from the Influenza Working Group will be critical to future ACIP discussions and a decision regarding this matter. Dr. Katz cautioned the ACIP to remember the problems encountered when the pneumococcal vaccine was added to the immunization schedule so similar problems can be avoided in this context. He added that the ACIP should be proactive rather than reactive regarding this vaccine and that special consideration be given to the perspective of parents.

IMMUNIZATION OF FOREIGN ADOPTEES

The General Recommendations Workgroup presented the final topic to be included in the general recommendations statement. Dr. Bill Atkinson stated that the acceptability of immunization received outside the U.S. is the third major policy issue the ACIP has addressed. The other major policy issues, those relating to the spacing and timing of vaccines, have been resolved.

Focus of the Workgroup

Dr. Lucy Tompkins, Chairman of the General Recommendations Workgroup, explained that the focus of this discussion concerns immunization only of foreign adoptees. Although this issue was brought before the ACIP at both the February and June meetings, progress was stalled because more data was needed. The Workgroup relied on data provided by consultants Drs. M. Hostetter of Yale and Mary Statt of Children's Hospital as well as input from Dr. Jon Abramson of the AAP and WHO.

Dr. Hostetter's Study

Dr. Hostetter shared her data with the ACIP by speaker phone. In her review of immunization certificates of orphanage adoptees from China, Russia and countries in eastern Europe, she noted irregularities such as immunizations that had all been administered on the same day of the month, multiple vaccinations that were inconsistent with a child's age, and immunizations that had been given before a child's birth date. These findings led to a prospective study begun in 1996 of all foreign adoptees with written immunization certificates showing three or more DTP vaccinations.

Serum samples from these children were sent to the Association of Regional and University Pathologists for determination of diphtheria and neutralizing antibody titers. The following were considered valid reasons for exclusion from the study: no written certificate, evidence of fewer

than three DTPs, receipt of any immunization in the U.S., and evidence of any immunization within the preceding six months.

Fifty-five children from China, Russia and eastern Europe formed the original cohort studied in 1996-1998. No control titers were run. Children considered immune demonstrated a titer ≥1:80 for diphtheria and tetanus: 43% of children from eastern Europe, 12.5% from China, and 52% from Russia met this criteria. The overall percentage of immunity was 38%. Only 18% of children who had resided exclusively in an orphanage before their adoption were immune. Approximately 68% who had spent some time in the community in Russia or eastern Europe were immune.

As a result of expansion of the study through 2000, the number of children in the cohort grew to 154 and represented additional countries including India, the Phillippines, and Korea. As the Association of Regional and University Pathologists no longer performed the needed testing, subsequent testing was performed at Fairview University Hospital, University of Minnesota. The net result, 39% immunity, was the same. The overall protective immunity for the expanded group was 42%. Older children were more likely to be protected in general. For eastern European adoptees, the r^2 was .8, for Chinese .027, and .07 for Russian children. This correlation applies only to the 55 children in the original group.

Discussion

Seroconversion data in English children indicate good protection for ~1 year after vaccination. Russian orphanages are of two types: government-sponsored and those that specialize in adoption. However, Dr. Hostetter was unable to determine the specific type of orphanage for the children studied.

Dr. Statt's Findings

Dr. Mary Statt, Cincinnati Children's Hospital International Adoption Center, addressed antibody protection to diphtheria, tetanus, and hepatitis B in internationally adopted children. The majority of internationally adopted children are < 5 years of age, ~45% are <1 year of age, and 43% are between 1 and 5 years. Russia children are adopted most often (28%), followed by children from China (27%), Korea, Guatemala, Viet Nam, India, Romania, and other countries.

She examined antibody levels to diphtheria and tetanus in children who had written documentation of two or more doses of DTP in their birth country. Fifty-one children who arrived in the U.S. in 1998-2000 met the criteria. Laboratory testing for diphtheria and/or tetanus antibody was performed before any immunization took place. Specimens were sent to MRL in Cypress, CA; this laboratory uses a diphtheria antibody ELISA and tetanus IgG ELISA. Standard cut-off values for diphtheria protection (protective ≥0.01 IU/ml) were used. Conservative cut-off values (≥0.50 IU/ml) were applied for tetanus. Positive controls were not used.

The majority (39%) of children studied came from Russia, followed by eastern European countries (18%), and China (19.6%). The remainder were from several other countries. The

children ranged in age from 6-81 months. Overall, 78% received their immunizations while living in an orphanage, and most had received three DTPs. Mean age in months at time of testing for children from Russia was 24 months, mean age at last vaccine, 17 months; for eastern Europe, 21 and 11 months, respectively; for China, 12 and 7 months; for Viet Nam, 8 and 5 months; for India, 9.7 and 6 months; and for Korea, 14 and 7.5 months. The one child from Guatemala had received vaccine the same month he arrived, and the child from Bolivia was tested at 12 months and received the last vaccine at 9 months of age. All children (100%) had protective levels for diphtheria antibody, but only 82% were protected for tetanus. Of those lacking protective antibody for tetanus, 8 of 9 children had indeterminate levels.

A qualitative test was performed for hepatitis B as part of the evaluation of international adoptees. Those who were evaluated (71%) were negative for surface antigen and core antibody. For those receiving two doses, 56% were positive for surface antibody; for three doses, 90%, and for four doses, 100%. A wide range of positive levels was observed by country. Environment, i.e., foster care versus an orphanage, did not affect immunity.

The observed differences between Dr. Statt's results and Dr. Hostetter's might be due to differences in the study design, the age of the children, the time period the studies were conducted, and the laboratory methods used. Small sample size and potential bias of the samples limit both studies.

Discussion

The timing of immunization, i.e., vaccine given over a short interval and at a young age, may affect the antibody level. Dr. Beth Bell added that as antibody levels such as anti-HBs wane over time, the child's age when testing is performed is an important consideration. Regarding laboratory testing, Dr. Orenstein explained that toxin neutralization for tetanus antibody has been the gold standard, and passive protection correlates best with clinical protection. Some investigators have explored the use of passive hemagglutination assays, but enzyme immunoassay correlates best with toxin neutralization to a point (usually 0.15 - 0.2 IU /ml). Although the cut-off for enzyme immunoassay seems higher than for other tests, at lower levels antibodies do not have the same affinity for toxin and do not perform as well in neutralization. He added that priming can be determined by measuring detectable tetanus antitoxin 7 days after vaccination.

Progress Towards Recommending Immunization of Foreign Adoptees

Dr. Schwartz presented the data the Working Group has used as the basis for discussions regarding adoptee vaccination. The Working Group incorporated input from the AAP Committee on Infectious Diseases obtained in conference calls as well as data from Drs.Statt and Hostetter. The Working Group considered several options:

- Make no changes in the current policy
- Accept records from specific countries with caution
- Accept records with caution generally

- Never accept records; perform revaccination in all cases
- Never accept records; perform selective testing and revaccination in all cases

The Working Group agreed that the best option was to *accept records with caution generally*. Several limitations to formulating recommendations were recognized:

- Data from many countries and regions are limited or lacking (*should children from all developing countries be grouped together? should children from developed countries be included*?)
- The reliability of the results of laboratory testing is unclear (*what standards were used and how were they interpreted? would clinicians be able to act appropriately on the basis of the tests?)*
- Providers might have varying access to laboratory testing and should be given options and alternatives; parents may choose not to have their child revaccinated

For the purpose of comparison, Dr. Schwartz cited a review article authored by Kathy Edwards (*Pediatrics* 1995) in which several trials established the degree of protection children derive from DTaP vaccination in the U.S. One month after receiving the third dose, 100% of children were protected against tetanus and a substantial proportion were protected against diphtheria. In a study conducted in the United Kingdom (U.K.) by Ramsey et al. (*BMJ* 1991), more than 88% of children evaluated at the age of 4 years had protective antibody levels.

<u>General Principles</u>

The general principles included in the introduction to the recommendations follow:

- Despite limited data, records of children adopted from developing countries may not be accurate and more data need to be collected.
- Although records with appropriate dates and intervals may be more likely to be accurate, protection of a child cannot be predicted only by country of origin and quality of records.
- Lack of protection may not only be due to falsified records but to other causes such as improper storage or handling of vaccines or to immune defects such as those caused by severe malnutrition.
- Alternatives could be provided to clinicians stating that revaccination is generally safe with the only caveat being DTP or DTaP and that judicious serological testing may decrease the number of additional doses of vaccine that need to be administered.

Vaccine-specific recommendations:

- For MMR: *Because reimmunization would require only two injections and adverse events following MMR are rare, reimmunization is a reasonable option. Serological testing is widely available for measles IgG antibody. A child whose records indicate receipt of a monovalent measles or rubella vaccine at >1year old and who has protective antibody to measles should receive a single dose of MMR as age appropriate to assure protection against mumps and rubella. If a child whose records indicate receipt of MMR has a protective level of antibody to measles, no additional vaccination would be needed.*
- For *Haemophilus influenza* type B (Hib): *Serological correlates for protection for children vaccinated >1 month previously may be difficult to interpret. Because the*

number of immunizations needed for protection decreases with age and adverse events are rare, age-appropriate immunization should be provided. For children ≥5 years old, immunization is not needed.

- For Hepatitis B: *Serological testing for hepatitis surface antigen and antibody (anti-HBs) (quantitative) and for core antibody (anti-HBc) are routinely recommended for international adoptees. Guidelines for the interpretation of serological testing are provided in -----. Presence of hepatitis B surface antigen may indicate chronic infection and household members should be vaccinated. A child whose records indicate receipt of ≥3 doses of vaccine and who has a protective level of anti-HBs (≥10 IU/ml) can be considered protected and additional doses are not needed if at least one dose was administered at ≥6 months. Children with protective anti-HBs levels who received ≥3 doses at <6 months of age should receive an additional dose at ≥6 months, as recommended in the U. S. schedule; adverse events are rare. Children with protective anti-HBs levels who have received fewer than 3 doses should complete the vaccination series with the last dose at >6 months of age. Presence of anti-HBc indicates past hepatitis B infection in a child who has lost passively transferred maternal antibody or current infection in conjunction with a positive test for surface antigen; vaccination of the child is not needed in either circumstance.*

Dr. Abramson proposed keeping the recommendation as it stands. Dr. Zimmerman suggested the ACIP identify the points in the recommendations that are based on strong science and those that are judgement-based.

- For Polio: *The simplest approach is to reimmunize children with IPV according to the U.S. schedule. Children appropriately vaccinated with three doses of OPV in developing countries, however, may have suboptimal seroconversion, especially to type 3. Adverse events following IPV are extremely rare. Alternatively, serological testing for neutralizing antibody to polio types 1, 2, and 3 can be obtained commercially and at several State health department laboratories. Children with protective titers against all three types do not need reimmunization and should complete the schedule as age appropriate.*

Dr. Modlin questioned whether to include serologic testing for polio because of the added cost and the fact that there is no downside to reimmunization. Dr. Tompkins added that a major drawback for parents is the need to comply with an excessive number of vaccines. As for the best choice of language, Dr. Rennels suggested emphasizing *the simplest, least expensive approach* and Dr. Modlin preferred *recommended approach*. Dr. Peter suggested rephrasing as follows: *the simplest approach that does not add additional cost and possible delay in immunization*.

- For DTaP: *Two alternatives are available. Providers can reimmunize a child, ignoring any recorded doses. The major concern with this approach is that excessive doses of tetanus toxoid have, in adults, occasionally been associated with severe local reactions although these arthus type reactions are not life-threatening. Recent data raise the possibility of increased rates of whole limb swelling with increasing numbers of pertussis vaccinations. If a reimmunization approach is adopted and a severe local reaction occurs, antibody to tetanus toxin should be measured before administering another dose. A high level indicates that further doses are unnecessary and subsequent vaccination*

should occur as age appropriate. There are no established correlates for protection against pertussis.
For a child whose records indicate receipt of ≥3 doses, serological testing for specific IgG antibody to both and tetanus toxin is reasonable; if protective levels are obtained, the vaccination series should be completed as age-appropriate. Indeterminate antibody levels in a child vaccinated months previously may indicate waning of immunity; serology could be repeated following a booster dose if a provider wishes to avoid reimmunization with a complete series.*

- For Varicella: *Varicella vaccine is not administered in most countries. A child who lacks a reliable history of prior varicella disease should be immunized as age-appropriate.*
- For Pneumococcal conjugate: *Pneumococcal conjugate vaccine is not administered in most countries and should be administered as age-appropriate.*

*ELISA tests are most readily available; results of toxin neutralization and passive hemaglutination are also acceptable. Providers should contact the laboratory performing the test for interpretive standards.

Discussion
The proposed additions to the recommendations for diphtheria and tetanus were discussed. Dr. Rennels advocated eliminating any references to adults. Dr.Abramson indicated that although the AAP would likely accept these recommendations, it is important to measure the levels of both antibodies, not just one, to determine whether a child is adequately protected. Dr. Schwartz stated that draft recommendations not yet published in MMWR advise administering the next dose of DTaP vaccine to a child who had experienced entire limb swelling. Dr. Abramson declared he would hesitate to make that suggestion. As an alternative, Dr. Abramson proposed that a child who had experienced entire limb swelling undergo immunization one more time, followed by a measurement of the antibody level.

As no data exist regarding local reactions in children, discussion concerned whether adult data can be extrapolated to children. Dr. Orenstein said that extrapolation was made initially when the rule of six was devised: a child should have no more than six DTP immunizations by the time of school entry. Dr. Modlin expressed concern that the statement overemphasizes the possibility of immunization reactions, which might unintentionally create a barrier to immunization. Drs. Peter and Modlin advocated emphasizing "*when in doubt, revaccinate*" to strengthen the statement.

Other Changes
After additional wordsmithing of the recommendations, Dr. Schwartz reviewed the proposed changes. The second paragraph under Recommendations has been modified to read:

> *In situations where there is a desire to avoid extra injections, judicious serological testing may be helpful for the health care provider in determining which immunizations may be needed. Administration of extra doses of vaccines is generally safe; however, the frequencies of local reactions and fever increase with increasing number of doses of DTP/DTaP.*

The Hepatitis B section now reads

> *Guidelines for the interpretation of serological testing are provided in the Red Book. Presence of hepatitis B surface antigen indicates acute or chronic infection and household members should be vaccinated.*

Minor changes in this section include insertion of "mili"(≥10 *mili* IU/ml) and deletion of core antibody from the last sentence. A brief introductory section will be added to underscore the message that "the best course is to repeat immunization for any international adoptee." This information will also be added as a bolded footnote to Table 1. *The simplest approach is to revaccinate* was added to the Polio and MMR recommendations. The DTaP section has been modified to read:

> *The major concern with this approach is that excessive doses of DTP/DTaP have occasionally been associated with severe local reactions. These local reactions are not life-threatening. If a reimmunization approach is adopted and a severe local reaction occurs, antibody to diphtheria and tetanus toxins should be measured before administering another dose. A high level is changed to a protective level.*

Decision

Dr.Modlin reminded the committee that this recommendation is an addition to the general recommendations and is not a stand-alone statement. Dr. Tompkins made a motion that the ACIP adopt the language that has been proposed and Dr. Schwartz's future revision without further review of the document. Her motion was seconded. There were no conflicts of interest.

> **In Favor:** Brooks, Rennels, Johnson, Tompkins, Clover, Helms, Word, Offit, Modlin
> **Opposed:** None
> **Abstaining:** None

Decision: Motion passed

RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE

Proposed Changes

Dr. J. Cono, NIP, reviewed the proposed changes to the 2001 Harmonized Schedule. *Inactivated Polio* and *Pneumococcal Conjugate* (PCV7) were added to the list of vaccines. The recommended ages for administration of PCV7 (2, 4, 6 and 12-15 months) have been added. The bar for Hepatitis A was extended to include children *14-18 years of age,* an age group added to the schedule. Dose numbers (Hep B-1, etc.) were added to Hepatitis B and MMR (MMR-1) vaccines. Footnote #5 was added:

> *The heptavalent conjugate pneumococcal vaccine (PCV7) is recommended for all children 2-23 months of age. It is also recommended for children 24-59 months of age.* (See MMWR Oct.6, 2000/49 (RR9); 1-38, also at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4909a1.htm).

The following footnotes have also been updated:

> Footnote #1: *This schedule indicates the recommended ages for routine administration of currently licensed vaccines through age 18 years as of 11/1/00.*
> Footnote #2: *All children and adolescents who have not been immunized against hepatitis*

B should begin the series during any visit.
Footnote #6: *An all-IPV schedule is recommended for routine childhood polio vaccination in the United States. All children should receive four doses of IPV at 2 months, 4 months, 6-18 months, and 4-6 years. Oral polio vaccine (OPV) should be used only in selected circumstances*. (See MMWR May 19,2000/49(RR5);1-22).
Footnote #9: *Hepatitis A (hep A) is shaded to indicate its recommended use in selected states and/or regions, and for certain high risk groups; consult your local public health authority.* (See MMWR Oct.1, 1999/48(RR12);1-37).

Discussion

Representatives of the AAP and the AAFP approve of the recommended changes to the language. Dr. Johnson suggested that the Internet website reference be added to all footnotes; Dr. Cono offered a method for doing this in a concise manner. Dr.Orenstein suggested removing the reference to OPV from footnote #6 as it is no longer available in the U.S.

The use of identification numbers for various vaccines was discussed as length. Tom Vernon pointed out that codifying vaccines in this manner raises the risk of confusion in the field. The consensus recommendation is to drop numbering for MMR and PCV, leaving 1, 2, and 3 with the # sign for Hepatitis B. Dr. Modlin stated that the designated abbreviation on the harmonized schedule is the most broadly accepted at the moment and is a point that has been fervently discussed recently. Further discussion yielded these changes to the graphic:

- Addition of #1, #2, #3 to the bars for Hepatitis B
- Removal of the 7 from every use of Pneumococcal conjugate (PCV)
- Removal of 1 and 2 from MMR
- Relocation of the Internet reference to the bottom of the footnotes page and rephrasing: *For additional information regarding the vaccines listed above, please log on to . . .* (the general ACIP Recommendations page).

Decision

Dr. Helms made a motion, seconded by Dr. Offit, to approve these changes to the ACIP Harmonized Schedule for 2001.
In Favor: Brooks, Rennels, Johnson, Tompkins, Helms, Clover, Word, Offit, Modlin
Opposed: None
Abstaining: None
Decision: Motion passed

Dr. Modlin announced that discussions will begin early next year regarding the format of the Harmonized Schedule. It may be revised to resemble the schedule currently used by the Minnesota Department of Health. Dr. Atkinson suggested adding the 800 hotline phone number and NIP/ to the Harmonized Schedule, and Dr. Peter advised adding a list of contraindications and safety precautions to the schedule as well.

SMALLPOX VACCINE RECOMMENDATIONS

Dr. Helms and the working group will present their draft of recommendations regarding the smallpox vaccine at the next ACIP meeting in February, 2001. The recommendations currently in development will address the following points:

- Non-emergency use of the vaccine
- Vaccine side effects and adverse effects
- Vaccine contraindications and precautions
- Recommendations for prevention of contact, transmission, and treatment of vaccine adverse events
- Recommendations for alternatives for treatment of adverse events
- Recommendations for the role of smallpox vaccine in civilian populations in bioterrorism preparedness

Dr. Lisa Rotz presented an overview of the changes the Working Group is considering. The non-bioterrorism-related information was separated from that addressing bioterrorism-related events. New sections that have been added to the 1991 version address how to vaccinate and interpret responses, recommendations concerning new antiviral compounds, and specific recommendations for smallpox vaccination for bioterrorism preparedness.

Smallpox Vaccination for Laboratory Workers

The 1991 ACIP statement recommended that researchers and laboratory workers who handle recombinant vaccinia viruses be vaccinated every 10 years. New data suggest that laboratory workers handling specific strains (MVA, NYVAC, ALVAC, and TROVAC only) no longer require routine vaccination as there have been no reports of transmission of disease to health care personnel. Workers who handle strains other than the four mentioned should continue to get vaccinations for their own protection. Health care workers in contact with patients in vaccine trials using recombinant vaccines should also undergo revaccination. For personnel working with virulent orthopox viruses such as monkey pox, more frequent revaccination should be considered.

The recommendations for sections addressing side effects, adverse events, and contraindications are essentially the same as the 1991 recommendations. The exception is that administration of Vaccinia Immune Globulin (VIG) is no longer advised for the treatment of vaccinial keratitis. Insufficient information is available to make a decision regarding the safety and efficacy of antivirals for treating orthopoxvirus infections. New wording regarding prevention of contact transmission and care of the vaccination site has been suggested:

> *Recently vaccinated health care workers should avoid contact with patients, particularly those who are immunocompromised until the scab has separated from the skin. However, if continued contact with patients is essential and unavoidable, they may continue to have contact with patients including those with immunodeficiencies, as long as the vaccination site is well covered and good hand-washing technique is maintained.*

Smallpox Vaccine for Bioterrorism Preparedness

A section addressing surveillance has been added. Because use of the variola virus as a bioterrorist weapon is a low-risk possibility, pre-exposure vaccination is currently not recommended for any group other than persons who face a significant calculable risk. Certain groups might benefit from post-release vaccination, however.

- Persons exposed to the initial release of the virus
- Persons who had a face-to-face contact with a confirmed smallpox patient
- Laboratory personnel involved in collecting or processing specimens from patients with confirmed or suspected smallpox
- Personnel involved in direct medical care of confirmed or suspected smallpox patients
- Persons with a high likelihood of contact with infectious materials from a smallpox patient

Once an outbreak has occurred, only those who have been successfully vaccinated should minister to patients with confirmed smallpox. Children and pregnant women with a definite exposure to smallpox should be vaccinated as well as those whose function is considered essential but who are not in contact with smallpox patients or infectious material. A new section addresses the possibility of aerosol transmission versus the more common droplet transmission in a hospital setting:

> *Because of the high rates of transmission that were seen in previous outbreaks involving hospital settings, the need for vaccination of non-direct hospital contacts should be evaluated by public health officials. The ultimate decision to vaccinate non-direct hospital contacts with no contraindications to vaccination should occur only after careful evaluation of the hospital setting for determination of the exposure potential from the less common aerosol transmission.*

In accordance with previous statements and policies, the Working Group determined there are no absolute contraindications to vaccination of an individual with a definite high risk exposure to smallpox. Additional infection control measures will be needed to control an outbreak of smallpox. They include hospital and non-hospital isolation of infectious patients and surveillance of patient contacts during their potential incubation period. Isolation is recommended for all suspected cases of smallpox in an outbreak if these persons are isolated together to prevent transmission. Current supplies of VIG are not sufficient to allow for its prophylactic use with vaccination or treatment of non-life threatening complications in a smallpox outbreak.

The Working Group also identified research activities that should be given high priority. These include the development, evaluation, and production of additional vaccine using FDA-approved cell culture techniques as well as the development and evaluation of alternatives to VIG.

Discussion

Currently, 15.4 million doses of smallpox vaccine are available but they can only be obtained through CDC. A contract was recently awarded for development of a cell culture vaccine, but the steps leading to licensure will take about 4 years. Dr. Heilman is currently involved in a dose-reduction study of the smallpox vaccine. A secondary backup to VIG, Cidofovir, for

disseminated vaccinia is available. Application for its compassionate use may be made on the basis of its evaluation in an animal (monkeypox in Rhesus monkeys) model.

Mike Massare of Novavax suggested that persons with HIV should be among the group vaccinated in a bioterrorism situation. Dr. Rotz replied that in that situation, risk versus benefit will be determined on a case-by-case basis. If a large vaccination campaign were needed, some modification may be necessary to address the current recommendation to examine the site 6-8 days after vaccination. Lance Gordon, Orovax, stated that as the new cell culture vaccine will be accompanied by brochures, descriptive comparison cards could easily be included with the brochures. Dr. Modlin suggested that the recommendations clarify the issue of revaccination as vaccine efficacy persists for at least 5 years.

Dr. Modlin thanked the Working Group for their progress on this complicated statement. The goal is to complete and vote on this recommendation at the February 2001 meeting.

SUBCOMMITTEE ON OVERSIGHT OF THE VACCINE HEALTH CARE NETWORK

Dr. M. McNeil, NIP, announced that Congress has charged CDC with specific activities relating to the licensed anthrax vaccine. They involve determining the risk factors for adverse events (including the differences in adverse events for men and women), determining immunological correlates of protection and documenting vaccine efficacy, optimizing the vaccine schedule, and minimizing the number of dosage requirements.

CDC's efforts and Congressional funds for these activities are distributed between NCID and NIP. A large collaborative human trial involving NCID, NIP and the Department of Defense (DOD) is now underway. NIP activities will be addressed as a combined effort with the DOD through implementation of the Vaccine Healthcare (VHC) Network. Improved reporting of adverse events to VAERS will be facilitated through an electronic system linking the centers within the Network. The VHC Network will enhance anthrax vaccine safety and acceptability and promote public trust and confidence in the ability of the DOD to practice quality vaccine health care. The lead VHC and a National Atlantic Regional VHC will be established at Walter Reed Army Medical Center (WRAMC). When the currently low vaccine supply has been replenished, additional regional sites will be established in the Atlantic coast region and Seoul, South Korea.

A Clinical Advisory Board, with input from the ACIP and the Armed Forces Epidemiological Board (AFEB), will provide oversight of this Network This Clinical Advisory Board, a combination of civilian and military experts, will comprise subcommittees established under the ACIP and AFEB meeting jointly. The Chair of the ACIP subcommittee is Dr. Charles Helms, the Executive Secretary is Dr. McNeil, and Dr. David Johnson and Dr. Lucy Tompkins are members. Dr. Modlin stated that this will be a standing subcommittee of the ACIP for the foreseeable future.

Dr. Katz announced that the Institute of Medicine has established two other groups for the study of anthrax. An alternative vaccine, RPA, is in development and testing is about ready to begin.

FDA UPDATE ON USE OF BOVINE DERIVED MATERIALS IN THE MANUFACTURER OF VACCINES

Dr. Karen Midthun presented the recommendations suggested by members of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) and the Transmissible Spongiform Encephalopathy Advisory Committee (TSEAC) who attended a combined meeting in July. These committees addressed the perceived risk of prion and prion-like agents in certain constituents used in the manufacture of vaccines.

Background

Bovine-derived materials are used in the manufacture of many biological products including vaccines. The Center for Biologics (CBER) has been concerned about minimizing potential contamination of vaccines with the agent of bovine spongiform encephalopathy (BSE). BSE was recognized in the U.K. in the 1980s and human transmissible spongiform encephalopathy (New Variant CJD) appeared in 1996.

Although no case of CJD has resulted from vaccination, the FDA issued recommendations to U.S. manufacturers in 1993 and 1996 that materials derived from cattle from countries where BSE is known to exist, or where surveillance was inadequate to determine if it existed, should not be used. These recommendations did not take the form of regulations or rules. A list of these countries, which was expanded in 1998 to include all European countries, has been maintained by the U.S. Department of Agriculture.

It became clear to CBER that these recommendations in at least one instance had not been followed. U.S. vaccine manufacturers were therefore required to review their source(s) of bovine-derived materials. This review revealed that some manufacturers had received supplies from countries on the list. CBER conducted a risk assessment and convened a joint meeting of two FDA advisory committees that was held on July 27.

Recommendations of the FDA joint TSEAC and VRBPAC Meeting

The risks posed by use of the bovine materials were considered theoretical and negligible. However, as these issues are of public interest, the committee advocated public disclosure. The joint committee also recommended that materials from countries on the FDA list be replaced as soon as possible, and that working seeds be replaced, but there is no need to re-derive master bacterial and viral seed banks as the risk of transmission is negligible. Many manufacturers have already made changes and other changes are in progress. The FDA is currently drafting a disclosure document.

UPDATE ON VACCINE SAFETY INITIATIVES

Dr. Bob Chen showed data illustrating the nearly 100% reduction in the incidence of pre-vaccination rates of vaccine-preventable diseases (VPDs) compared with post-vaccination rates. At the same time, vaccine adverse events have gone from zero in the pre-vaccine era to ~11,000 annual reports, which is about double the sum of routine childhood vaccine-preventable diseases. Immunization against diseases such as smallpox and polio have totally or almost totally eradicated those diseases. Unfortunately, as most diseases worth eradicating could be used for bioterrorist purposes, the historical paradigm of stopping vaccination once widespread coverage has eradicated the illness may no longer be feasible. This situation places most mature immunization programs like that of the U. S. and other developed countries in the uncomfortable position of having relatively high rates of vaccine adverse events compared to VPDs. Another media crisis may result in loss of confidence in vaccines and a resurgence in the number of VPDs.

The need to sustain such mature immunization programs is a new chapter in human history, and it remains to be seen whether this can be done successfully. Possible steps to sustain these programs in an unprecedented era of little disease and successful routine vaccination include the following:

- Changing the focus to reduction of all diseases, both vaccine-preventable and vaccine-induced
- Institution of immunization registries
- Continued education regarding the benefits of immunization
- Continued assessment and reduction of immunization risk
- Establishment of an immunization safety systems approach

According to Dr. Chen, an improved vaccine safety system includes both pre-licensure and post-licensure issues. Pre-licensure needs include the presence of persons experienced in rare disease epidemiology or vaccine safety skills on Data Safety Monitoring Boards; institution of a large, simple trial to evaluate vaccine safety issues in addition to efficacy trials; and involvement with the Brighton Collaboration to standardize case definitions for adverse events. Post-licensure surveillance needs involve the Brighton Collaboration, expanding VAERS and the Vaccine Safety Datalink (VSD) as well as the following initiatives.

Vaccine Safety Initiatives

Dr. Chen explained that the life cycle of vaccine safety concern involves a scientific process that usually takes many years to complete. In the meantime, however, the concern may already be published. CDC and NIH recently initiated a project with the Institute of Medicine (IOM) to review emerging safety concerns. Its goals are to assess the proper level of societal concern regarding allegations of injury, identify alternative plausible explanations regarding allegations, and evaluate the biological plausibility of allegations. This new committee will meet three times a year.

Clinical Immunization Safety Assessment Centers (CISA), the civilian equivalent of Vaccine Health Care centers for the military, are now being developed and funded to collect and interpret safety data. They will function to increase scientific knowledge and maximize utilization of VAERS. The following list represents other activities CISA will perform.

- Conduct intensive studies of persons with true reactions
- Perform standard assessment of potential Syndrome X
- Monitor the next dose in patients who have experienced a severe adverse event
- Become a consultation center to answer provider safety questions and track compliance and outcome

The current method of detecting new safety concern relies on VAERS signals. VAERS is more complex than typical CDC surveillance systems since it receives data on multiple exposures and outcomes. As the number of permutations has increased for childhood immunization schedules, the ability to pick up safety signals has been lost because the number of children receiving these specific immunization schedules has not been tracked. With the aid of new data mining/artificial intelligence software, the ability to detect unusual and complex occurrences will be upgraded and the approach to evaluating patterns of adverse events will be improved. Adding to the problem is that vaccine identifier information has been miscoded. The Vaccine Identification Standards Initiatives (VISI) will help develop standards for vaccine identifiers, abbreviations, and bar codes to permit accurate and efficient transfer of vaccine identity.

Integration of vaccine monitoring into Safety Immunization Registries will achieve timely and accurate VAERS reporting and help restore the ability to detect VAERS signals. This integration may also deliver earlier notice of potential contraindications to providers and identify potential problems through complete capture of vaccine files and linkages to other databases used to screen possible associations and aid hypothesis testing and generation. With these schemes, the various arms of the vaccine safety program, VAERS-CISA-IOM, can work in tandem to *immunize smarter not just more*.

Discussion

The severity and prevalence of a number of factors associated with allegations of injury are needed to establish priorities for the IOM review. Discussion of the workings of the IOM committee revealed the concern of several ACIP members whether this group can successfully evaluate complex questions of safety and arrive at a seasoned judgement within 60 days. Past committees have called scientific meetings to provide documentation for review. The IOM has the capacity to request input from consultants. A major problem involves study of allegations of injury that are temporally remote from vaccination.

Dr. Modlin asked for public comments. There were no comments. He adjourned the meeting at 5:09 p.m.

Thursday, October 19, 2000

UPDATES

National Center for Infectious Diseases (NCID*)*

Dr. A. Mawle proudly displayed slides of the 100,000 square feet of new NCID laboratory space currently in Phase II of construction. Congress approved the expansion more than 10 years ago. The facilities provide space for the study of polio, influenza and tuberculosis.

Two studies that will assess Anthrax vaccine (RFA) in human trials will begin soon. One study will evaluate reduction of the number of doses from six to five or even three doses. The other will investigate changing the present route of subcutaneous administration to IM injection. Three sites for the studies have been selected. Immune correlates will be investigated in a monkey model for inhalation of anthrax. Data from this project will be used to help evaluate the new anthrax vaccine.

The GAVI Task Force on Research and Development has announced projects to develop three conjugate vaccines: *Streptococcus pneumoniae*, Group A *Neisseria meningitidis*, and rotavirus. WHO has begun standardizing serological assays against *Streptococcus pneumoniae* and Group A *Neisseria meningitidis*.

National Immunization Program (NIP)

Dr. W. Orenstein updated immunization coverage data for children 19-35 months of age during calendar year 1999. The 1999 levels are similar to those for 1998: > 90% for DTP, Hib, and MMR; 90% for polio vaccine; 88% for Hepatitis B; and 83% for DTP 4. Varicella coverage has increased to 59% in just 2 years.

The national coverage estimate using the 4:3:1:3 (DTP, Polio, MMR, and Hib, respectively) series is 78% although there is considerable variation in coverage by state and region. Even though the confidence limits are approximately $\pm$ 5-6%, the general patterns of higher coverage rates in New England and lower coverage rates in southwestern states hold true. Measles cases numbered 100 in 1999, down from 28,000 cases 10 years ago.

ACIP approval of the VFC resolution in June 2000 was key to finalizing the contract for the pneumococcal conjugate vaccine PCV7 (Prevnar). The contract price is $44.25 until the end of this calendar year; next year the price will increase to $45.99 (both include a $0.75 excise tax). Since the contract went into effect, 43 states have placed orders for a total of 1.6 million doses. Dr. Orenstein indicated that more vaccine should have been ordered. One estimate of the number of doses that should have been ordered is 12 million rather than the 1.6 million doses ordered to date. Barriers to implementation of this vaccine program include lack of 317 vaccine funding (317 faces a possible $45 million shortfall)and a lack of state funds. In addition, many health insurers do not cover PCV7 vaccination.

Discussion
It is difficult to compare states that rely only on VFC with those that are universal purchase states. Dr. Orenstein stated his concern that children in the VFC program will get pneumococcal vaccine at local health departments, but children not in the VFC will not be vaccinated, particularly in non-universal purchase states. Dr. Abramson pointed out that the AAP considers the Prevnar introduction an example of a vaccine program that doesn't work. The AAP hopes to achieve an even rollout of vaccines across the country as they become approved by various committees and the FDA. Dr. Peter responded that the NVAC intends to discuss this issue.

Food and Drug Administration (FDA)
Dr. Midthun announced that Tripedia, the DTaP vaccine produced by Aventis Pasteur, was recently approved for a fifth consecutive dose. The license application for a five-component acellular DTaP vaccine filed by Aventis Pasteur will be reviewed at an Advisory Committee meeting November 3.

Vaccine Injury Compensation Program (VICP)
Dr. Geoffrey Evans informed the ACIP that 161 claims have been filed this year, which averages approximately 13 per month. Nearly all the pre-1988 claims for adjudication have been completed. A little over $1 billion has been paid in claims to date, and there is $1.4 billion is in the trust fund.

An excise tax enacted by Congress became effective the day after Prevnar was licensed in February. When vaccines are added to the VICP, they must be recommended by the ACIP for routine administration to children. Whenever a vaccine is added, there are eight years of retroactive coverage and a 2-year window to file claims. As CDC recommendations regarding Prevnar were published last week, this vaccine has now been officially added to the list of vaccines covered by the VICP.

Rotavirus vaccine was licensed in 1998. The ACIP recommendations regarding this vaccine were withdrawn at the October 1999 meeting after epidemiological evidence suggested an association between rotavirus vaccine and intussusception. Five claims that injury was caused by this vaccine have been filed. As intussusception is a non-tabled injury at present, causation must be proved and > 6 months of continued effects must be demonstrated. However, few cases will meet the latter requirement as intussusception resolves on its own or with surgical intervention. Legislation might permit surgical intervention and inpatient hospitalization to fulfill the 6 month requirement. Excise tax legislation seeks to reduce the excise tax from $0.75 to $0.25.

A Criminal Justice, Drug Policy, and Human Resources House Subcommittee met with program representatives in 1999 to address what can be done to change the possibly adversarial nature of the program, to evaluate whether the evidentiary and adjudicative standards are too strict for determining compensation, and to determine whether enough funds have been allocated to satisfy claims and ensure preservation of the program. A bipartisan report just released, which was unanimously voted upon, offered the following recommendations to the VICP: review the

Vaccine Injury Table to ensure that it reflects current science and epidemiology; continue developing and implementing speedy and fair informal dispute resolution options and practices; and determine a reasonable alternative standard for non-tabled cases. No specific guidance was given regarding who will carry out this advice.

An alternative dispute resolution plan was implemented for Department of Justice attorneys to address the adversarial nature of the process. Newly licensed vaccines are often in widespread use long before sufficient scientific data regarding adverse events is generated and collected; as a result, most alleged cases of injury currently are for vaccines not on the table. Dr. Evans suggested that because of this problem, some changes to compensation standards need to be addressed.

Discussion
Two bills have been introduced before Congress that would dramatically change the burden of proof for vaccine injury. Of the five claims made thus far, no surgical complications occurred. More than 1500 families have been awarded compensation.

For pre-FY88 claims, several years may have elapsed between the time a claim was filed and adjudication; post-FY88 claims average two years from filing to adjudication. Dr. Severyn asked whether short gut syndrome is a long-term result of an intussusception that was corrected surgically. Dr. Modlin answered that at surgery for intussusception, nonviable bowel is resected; usually only a small portion of bowel is affected. In most cases, short gut syndrome is an uncommon event resulting from surgery for intussusception.

National Vaccine Program Office (NVPO)
Dr. Marty Myers explained that the NVPO functions across multiple agencies to coordinate vaccine policy. WHO has established an initiative to contain wild-type poliovirus that is still kept in laboratories throughout the world. An interagency National Vaccine Advisory Committee (NVAC)Working Group has been formed to address polio eradication through inventory and destruction of poliovirus stored in laboratories.

The NVAC subcommittee has taken on the issue of intussusception as a challenge in the development of new rotavirus and other oral vaccines. A workshop in May 2001 will address the issue of how a rare serious adverse event such as intussusception poses a barrier to the development of important new vaccines. Dr. John Modlin will be the ACIP representative at that meeting.

The NVPO has been developing adult immunization standards and is revising the pediatric standards as well. A Vaccine Risk/Benefit Communication workshop was held recently in which a multidisciplinary approach was used to address issues related to improving vaccine communication. An upcoming workshop that will apply a similar multidisciplinary approach will address barriers to development of a perinatal cytomegalovirus vaccine. As a result of the influenza vaccine delay this year, the NVAC Pandemic Influenza Working Group had an

opportunity to prepare as a "dry run" its response to an early pandemic in which a shortage of vaccine occurs.

Dr. Myers announced that the Chairman of NVAC, Dr. Georges Peter, has been nominated as one of two candidates for President of the AAP.

Discussion
Dr. Peter added that NVAC reports to the Assistant Secretary for Health, Dr. David Satcher at HHS and is responsible for programmatic issues, whereas the ACIP deals with technical issues. The impetus for the upcoming rotavirus vaccine workshop is the impact of the ACIP decision on worldwide development of a new rotavirus vaccine. ACIP members will be invited to participate in this multidisciplinary meeting and the resulting report to HHS. Dr. Modlin added that the ACIP will have the opportunity to review data from case-controlled and other intussusception studies as well as the Committee's decision regarding the rotavirus vaccine made last October. Dr. Katz noted that the India-U.S. Vaccine Program, which is jointly sponsored by NIH and AID, is currently developing a rotavirus vaccine based on strains of rotavirus from India.

ADULT IMMUNIZATION WORKING GROUP

Pertussis Among Adolescents and Adults
Dr. Clover announced that the Working Group continues its review of pneumococcal data and will present this information to the ACIP in the future. Review of the general adult immunization guidelines will begin soon.

Dr. Kris Bisgard asked the ACIP membership to consider the following questions when making a decision about this vaccine:

- Is the burden of disease sufficient among adolescents sufficient to warrant vaccination?
- Is the burden of disease sufficient among adults and/or selected risk groups sufficient to warrant vaccination?
- What impact would vaccination of adolescents and/or adults have on the epidemiology of pertussis especially among infants?
- Is there a role for a monovalent acellular pertussis vaccine, especially for those given a tetanus and diphtheria toxoids (Td) booster in the last five years?
- Is safety an issue for children who have received five or more prior DTaP doses?
- What is the cost and the benefit of a pertussis vaccination program for adolescents and/or adults?

The Working Group considers the following types of studies beneficial: cost-benefit analysis; burden of disease study; usefulness of a dTpa vaccine for outbreak control; study on the source of infant pertussis.

Disease Burden of Pertussis
Although reported pertussis cases among adults and adolescents increased during the 1990s, most cases of pertussis in the U.S. occur among children <1 year of age and those 10-14 years of age.

An increase in incidence has occurred among unvaccinated infants ≤ 3 months of age in the last decade, but no change in incidence was evident in those case-patients aged 4-11 months. According to enhanced surveillance data from Georgia, Illinois, Massachusetts, and Minnesota for 1999-2000, 30% of 312 infant cases had a known or suspected source. By age in months, 32% of 255 infants aged 0-3 months had a known/suspected source and 21% of 57 infants aged 4-11 months had a known/suspected source. For infants aged ≤ 3 months, the source of pertussis illness is mainly parents and siblings, and for infants 4-11 months the source is mainly "other" or "friend." No increase in vaccine failures occurred during the period from1990 to 1999.

Dr. Paul Willems, SmithKline Beecham, presented the clinical profile of Boostrix™ (dTpa) vaccine for adolescents and adults. Boostrix™ was derived from Infanrix®, the DTPa vaccine for infant use and has one-third the antigen content of Infanrix® for *B. pertussis* components. Boostrix™ was not used in the APERT trial; only a monovalent acellular pertussis (pa) vaccine without the d and T components was used.

The safety and acceptability of Boostrix™ was compared to a Td vaccine. The intention was to achieve an immunologic response to Boostrix™ similar to that in infants. Two clinical trials in Europe were performed in adolescents and two in adults. Boostrix™ vaccine was compared to the Td Lederle vaccine in one trial.

SmithKline Beecham Data on Boostrix™ Study

No differences for reactogenicity in terms of solicited adverse events during the first 48 hours after vaccination were observed. Only five severe adverse events were reported for more than 1,000 vaccinees in the four studies included in the European registration file; none of these events were considered related to the vaccination. Special attention was also paid to recurrent and late onset reactions previously described for acellular pertussis vaccines in older age groups. Both recurrent and late onset reactions occurred with similar frequency, intensity, and timing for both Boostrix™ and all comparator vaccines (ie., Td, Pa and pa). The acellular pertussis vaccine Infanrix® containing the same antigens had been proven efficacious in infants in two efficacy trials. Antibody titers induced by Boostrix™ in the present studies are higher than those following Infanrix® after primary vaccination in the efficacy trials, which has been accepted as predictive for efficacy of Boostrix™ in these older age groups. For diphtheria and tetanus, the seroprotection rates following Boostrix™ were similar to those following Td. The observed differences in geometric mean titers (GMTs) for these antibodies are without clinical relevance. No differences in anti-*B. pertussis* antibody titers were found between subjects primed with DTPw vaccine (< 40 years of age) and subjects not previously vaccinated (≥ 40 years), which suggest that natural priming through contact with wild bacteria had previously occurred.

It was concluded that Boostrix™ is tolerated at least as well as the licensed Td vaccine. It has similar immunogenicity as the licensed Td vaccine in terms of protection against diphtheria and tetanus, and it produces high antibody responses to all three pertussis antigens.

Question and Answer
Q: Dr. Pickering: How well does the pertussis response of this vaccine compare to control responses after the fifth dose of the acellular pertussis vaccine in children 4-6 years of age? What countries use this vaccine? What type of assays were used to measure diphtheria and tetanus titers?
A: Dr. Willems: The GMTs were higher in the children 4-6 years of age than those for adults in the Boostrix™ studies shown. Nevertheless, the results are variable; the conclusion in the European submission was that the results were similar.
Q: Dr. Modlin: Who is getting this vaccine in Germany and how well has it been accepted?
A: Dr. Willems: The vaccine is indicated for persons older than 10 years of age. An official recommendation was made by the immunization advisory body in Germany
Q: Dr. Modlin: Did the recommendation specify how often to give the vaccine after age 10?
A: Dr.Willems: The recommendation is to give the booster every 10 years.
Q: Dr. Myers: Why is there an aluminum salt in this vaccine?
A: Dr.Willems: The product was derived from Infanrix®, which contains aluminum. The aluminum was left in the vaccine because removing it would have an unknown effect on efficacy.
Q: Dr. Zimmerman: What is the rate of seroconversion for tetanus and diphtheria antibodies 2 years after vaccination?
A: Dr.Willems: For Td, it is 75.6% and for dTpa, 73.8%.
Q: Dr. Gall: Has there been any experience with use in pregnancy?
A: Dr.Willems: No data has been collected thus far.
Q: Dr. Philip Renon: Is the contribution of adult contacts to disease in children inflated because of the use of serology? Has the increase in adult cases over the last decade been observed in other countries?
A: Dr. Bisgard: Serology is widely used only in Massachusetts where there are many culture-confirmed cases in adults and adolescents. Serology is used when more than two weeks have elapsed from cough onset.
A: Dr.Willems: Some data from France and the U.K. suggest that adults play a role in transmission of pertussis to very young children.

Criteria for Making Recommendations for the Pertussis Booster
Background
Dr. Joel Ward addressed the diagnosis of pertussis, the incidence of the disease, the true public health burden, and the impact of immunization. Immunity to pertussis wanes over a 5 to10-year period. Current vaccine recommendations state that the vaccine should not be used in children over 7 years of age. Pertussis culture and serology are rarely performed in adults with a cough illness.

He stated his belief that in adults, cough illness is the equivalent of otitis media in children in terms of doctor visits, cost, and antibiotic use. Pertussis is a potentially preventable cause of cough illness in adults. However, diagnosing this illness in adolescents and adults is difficult because everyone has partial immunity, it requires early culture, serological parameters have not been standardized, and diagnostic criteria have not been developed.

Suggested Criteria for Making a Recommendation

Dr.Ward suggested that the ACIP consider use of the following criteria to guide the decision concerning a pertussis booster for adults and adolescents.

- Information about the clinical spectrum of the illness and how the diagnosis is made (what endpoints were selected in trials?)
- Information about the epidemiology, transmission patterns and incidence of infection and clinical disease
- Vaccine safety, immunogenicity and effectiveness data (efficacy data, protective correlates)
- Potential for reduction of the burden of cough illness due to proven pertussis (reduced transmission to children, public acceptance, practicality of added immunization)

The APERT Trial

The overall objective of the APERT trial was to characterize the spectrum of pertussis in adolescents and adults; ascertain the rates of *B. pertussis* illness and infection; and evaluate the safety, immunogenicity and protective efficacy of an acellular pertussis vaccine in this population. This trial was supported by NIH and SmithKline Beecham.

The APERT trial was a prospective, multicenter study of 2,781 subjects and was conducted over a 2-year period beginning in 1997. Subjects were recruited into two groups: one group received a three-component monovalent acellular pertussis vaccine and the other group was given a hepatitis A vaccine, which was the control vaccine. All study subjects were telephoned every two weeks for two years. Specimens for culture, PCR, and serological testing were collected from anyone with a cough illness lasting longer than 5 days. Convalescent sera was collected approximately 42 days after the acute serum specimen was collected. Many persons had more than one cough episode/year. Blood was obtained prior to immunization, 1 month later, and 6, 12 and 18 months after immunization. Recruited subjects were 15-65 years of age, and approximately two-thirds were female.

Four severe adverse events occurred within 14 days of vaccination, but none was judged by the safety committee to be related to immunization. From day 14 through the end of the study (2 years) there were 60 pregnancies within 2 months of vaccination; no adverse event was recognized in mother or newborn. The primary case definition of pertussis included a cough illness of $\geq$5 days and laboratory confirmation by one of the following: 1) a positive culture, 2) a positive PCR test at time of illness, or 3) meeting specified serologic criteria for a “full response” between the acute and convalescent sera. Serologic criteria were standardized to optimize sensitivity and specificity.

Results

The overall incidence of cough illness lasting 5 days or longer was 0.65 episodes/year/subject. Some cough illnesses lasted weeks to months in duration. An absence of systemic symptoms was noted. Most cough illnesses occurred during the winter months, and more frequent episodes occurred in smokers. No clear pattern emerged for the onset of a cough illness and immunization.

As the codes have not been broken, the efficacy of the trial has not yet been determined. Preliminary data suggest that the prevalence of primary cases of pertussis proven by serology or culture will be between ten and 30 cases. The number of secondary cases in persons with a rise in antibody to a single antigen is estimated to be between 12 and 22 cases. The number of tertiary cases in persons with a single high titer cannot be estimated until the codes are broken. On the basis of preliminary information, the minimum estimate of the incidence of primary disease is between two and 12 cases/1,000 person/years; for primary and secondary cases, the estimate is between four and 20 cases/1,000 person/years.

Dr. Ward indicated that until all of the data from the APERT trial can be analyzed completely, no recommendations can be made to the ACIP. The spectrum of disease is still not understood completely.

Discussion

No interim analysis of the data was made. The known cases were spread throughout the age range, and no clustering occurred. Risk factors will be evaluated once all the data is analyzed. None of the reactions observed in this study were significant for pain or debilitation or required medical attention.

Dr. Severyn asked Dr.Ward to explain the rationale for using a second vaccine as a control rather than a placebo control. He explained that it offers study subjects some extra benefits. The hepatitis A vaccine is licensed, is recommended for travelers, and is expensive to obtain. In fact, this vaccine will be offered to study subjects who did not receive it after unblinding occurs.
Dr. Severyn maintained that the public does not agree with this practice and that use of an additional vaccine is poor science. Dr. Ward answered that, on the contrary, the hepatitis A vaccine was a major reason many people chose to participate in the study.

MENINGOCOCCAL CONJUGATE VACCINATION IN THE UNITED KINGDOM

Update

Dr. D. Salisbury, Department of Health, presented an update of the meningococcal vaccination program begun in the U.K. one year ago. Group B disease accounts for 60-65% and Group C 35-40% of the total number of cases of *Neisseria meningitidis* septicemia and meningitis. The U.K. is the first country in the world to use Group C conjugate vaccine in a routine vaccination program.

Meningococcal disease in the U.K. peaks in two age groups: in children approximately 1 year and those 16 years of age. The case fatality rate for Group B disease is ~7%; for Group C, the case fatality rate is similar to Group B disease for young children, but it is much higher in teenagers 15-18 years of age. The Department of Health estimated the total burden of Group C meningococcal disease at more than 1530 cases with 150 deaths each year.

The program, which sought to reduce the greatest number of cases and deaths, was driven by vaccine availability. The three companies that supplied vaccine, Wyeth, Chiron Biocine, and

North American Vaccines, each bid for a share of 18 months supply of vaccine. As vaccine was distributed from central supply quickly, 24 hours after being batch-tested, it has never been stockpiled. Every child under age 18 has been invited to be immunized at a specific time and place. The program was implemented as a school-based service to accommodate children >5 years of age and as a primary care-based service to reach children <5 years of age.

To determine the quantity of vaccine needed, the amount of DTP and Hib each general practitioner ordered and the number of patients receiving them was tracked for 2 years before the program began. Each physician is notified one month ahead of time as to the amount of vaccine that has been allocated for delivery. Children are called for immunization on the basis of vaccine supplies according to a national timetable. Vaccine manufacturers are obligated to deliver their product on a specific date.

In order to manage the demand for vaccine with limited supplies, an extensive ad campaign was begun. Between November and December 1999, all persons 15-17 years of age were immunized. Beginning in December, routine immunization of infants 2-4 months of age and those undergoing MMR vaccination was started. The remaining children under 2 years of age and the cohort 11-14 years of age have all been vaccinated as of early 2000. The remaining cohorts of children age 5-10 years have been vaccinated in school programs starting this Fall.

Results of the Immunization Program

Immunization of persons 15-17 years old has significantly reduced Group C meningococcal disease in this cohort; since July 2000, no disease has occurred in this age group. Low levels of disease have occurred in the group aged 11-14 years even though they were immunized much later. Disease in children less than 1 year has virtually stopped since vaccination began. Overall, 225 cases of Group C meningococcal disease and 23 deaths have been prevented in persons 15-17 years of age and <1 year. The total reduction is about 75% across immunized groups and 85% since last year. Dr. Salisbury considers this effort a huge public health success for the National Health Service.

As for serious adverse events, 237 (1.3/100,000 doses) episodes of convulsions/seizures occurred. This ill-defined category included febrile seizures, syncopal episodes, and seizures that occurred many weeks post-vaccination. Forty-four (0.24/100,000 doses) cases of anaphylaxis and 14 deaths (0.13/100,000 doses), irrespective of cause and interval after vaccination, were reported. Seven deaths were due to SIDS. Two children succumbed to Group B meningococcal septicemia, one to pneumococcal septicemia, one to bronchiolitis, one to pneumonia, and one to infantile spasm. One death was unexplained. No clustering of SIDS deaths occurred.

Discussion

The school-based programs have achieved approximately 90% coverage of persons 15-17 years of age. Coverage is also very high in children < 1 year. No evidence of herd immunity exists. Three vaccine failures have occurred. No plan is in place to implement booster doses once the program is mature. Private practitioners pay $7.50 per dose and the cost to school services is $1.50 per

dose. Although he could not reveal the actual cost of the vaccine, Dr. Salisbury stated that its value is good relative to the amount of money spent. The Y strain has not emerged as a problem in European countries. A phase 3 efficacy trial would be enormous in size, very costly to implement, and would have questionable value.

Vaccine Manufacturers Update

Dr. Joan Fusco, representative of Baxter (formerly North American Vaccine), stated that her company has a large development program and participated in the meningococcal conjugate vaccine program in the U.K. Baxter is interested in clinical studies of meningococcal C conjugate vaccine as well as their meningococcal B polysaccharide conjugate vaccine and a B-C combination in the U.S. Jane Gilbert, Chiron Vaccines, U.S., announced that Chiron is evaluating an A - C conjugate, one of three meningococcal-C vaccines used in the U.K. They have approached the FDA with plans to evaluate this vaccine in the U.S. Fred Rubin, Aventis Pasteur, stated that his company is developing a quadrivalent meningococcal conjugate vaccine. Laura Yoric of Wyeth-Lederle, stated that Wyeth provided meningococcal C vaccine for the U.K. program. Wyeth is currently developing a tetravalent vaccine to cover meningococcus Y. Other research is investigating development of a meningococcal B vaccine.

UPDATE ON MEASLES VACCINE AND OUTBREAKS OF DISEASE IN THE UNITED KINGDOM

Dr. Salisbury said that all practitioners in the U.K. are required to notify the Department of Health of suspected cases of measles. No case definition is used and all reported suspected cases are investigated thoroughly. A saliva sample is collected and sent to a central Public Health laboratory for IgM analysis. Sensitive and specific surveillance strategies include age-specific serological testing, RT-PCR for the measles genotype on saliva samples, and mathematical modeling of different immunization schemes.

MMR was introduced in the U.K. in 1988. When MMR was implicated as a cause of autism, there was a drop in parent confidence and a concomitant drop in vaccine coverage among children 16 months of age. This drop in coverage is being taken very seriously. Coverage is routinely measured quarterly in all locations in the country. At present, first-dose coverage of children 2 years of age is 88.3%, which increases to 93% at age 5. Second dose coverage in children who have received the first dose is 75%.

Measles notifications in the U.K. have fallen consistently since 1995 largely due to physician education regarding clinical signs and symptoms and testing of notified cases. The proportion of positive cases among the tested cases has risen. The small focal outbreaks of measles that have occurred are compatible with importation of the virus from other countries. Significant measles epidemics have occurred in The Netherlands and southern Ireland. The three biggest countries in Europe, France, Italy and Germany, do not have the same level of protective coverage for measles as the U.K., which presents a constant threat to the country of measles importation.

Discussion

The size of localized pockets where coverage has dropped are easy to determine from coverage data. The loss in confidence regarding the safety of the MMR vaccine occurred among parents who read the newspaper, not tabloid readers. Media-related information addressing the safety issue was carried out but not on the same scale as that used for the meningococcal vaccine. Licensed rubella vaccine is available in the U.K., but there is no licensed mumps or measles vaccine. Imported unlicensed versions of these vaccines demonstrated very low protective efficacy. No data suggests benefit from giving individual vaccines one year apart.

PERSISTENT POLIO VIRUS EXCRETION IN PATIENTS WITH B CELL IMMUNE DEFICIENCY DISORDERS

Overview of Polio Eradication

Dr. Roland Sutter, NIP, stated that as recently as12 years ago, polio was still widespread despite effective vaccines. As a result, the World Health Assembly, the governing body of WHO, resolved to eradicate polio by the year 2000. However, new goals have been formulated because the initial goal was not achieved. It is now hoped that poliovirus transmission will be stopped by 2002 and the world can be certified as free of poliovirus by 2005. In addition, WHO has prepared a global plan of action to contain poliovirus in laboratories around the world.

Strategies for reaching these goals include high routine immunization coverage in the first year of life followed by National Immunization Days. Poliovirus transmission occurs now in only a few areas of the world, and approximately 7,000 cases were reported worldwide last year. Polio surveillance has improved rapidly, but much is left to be done in certain countries, particularly those situated in Africa. As of 1999, virus transmission continues only in Northern India.

Data indicate that some patients with B cell immune deficiency disorder may continue to excrete poliovirus for long periods. They may therefore become a source of introducing the virus in a post-eradication world in which vaccination has ended. Dr. Sutter suggested consideration of a recommendation requiring testing of these patients for poliovirus excretion and treatment if they excrete poliovirus.

Poliovirus Excretion and B Cell Immune Deficiencies

According to Dr. Olen Kew, virus excretion occurs most often in common variable immune deficiency (CVID) and X-linked agammaglobulinemia (XLA). Although no documentation exists of chronic excretion of wild-type polioviruses, vaccine-derived viral excretion of types 2 and 1 has been documented (type 3 has also been reported). He presented several case studies of patients with B cell immune deficiency and characterized their excretion in terms of their illness and the virus type excreted. Oral immunoglobulin and an antiviral agent, Pleconaril, have been used experimentally to treat these patients, but the effectiveness of these agents has not yet been determined.

Identification of Patients with Poliovirus Excretion

Dr. Neal Halsey, Johns Hopkins University, reviewed studies performed to identify patients with prolonged excretion of poliovirus. Two surrogate markers, acute flaccid paralysis (AFP) and recurrent infections, were used to identify children in developing countries at high risk for B cell immune deficiency disorders. Children 2-15 years of age were cultured one year after AFP onset and blood was drawn for IgG and IgA determinations. Of 158 children with AFP in Ethiopia and 150 in Pakistan, no IgG deficiency disorders were identified. One IgA deficiency was found in each country, for a total of two cases. For children with radiographically-confirmed pneumonia or persistent diarrhea or sinusitis, three Sabin-type viruses were cultured; however, none of the children studied have IgG deficiency. Similarly, no IgG deficiencies have been found in Haitian children with recurrent pneumonia. It therefore appears that these immune deficiencies are not a significant problem in children over 2 years of age and that persistent poliovirus excretion appears to be uncommon.

In the U.S., CVID, XLA, and severe combined immune deficiency (SCID) are associated with prolonged, persistent excretion of enteroviruses. Children with SCID are not considered a serious source of reintroduction of the virus. In a small study, stool samples were collected for culture from children ages 3-15 years of age with CVID, XLA, and IgA deficiency. Of the 83 children evaluated, none were culture-positive for poliovirus. This study was hampered in that some discrimination exists for these patients and some of their primary care physicians resented the study's intrusion upon their practice.

Dr. Halsey estimates that the prevalence of persistent excretion of poliovirus by individuals with B cell immune deficiencies is likely between 0.01% and 1%. Larger numbers of patients must be evaluated to determine the exact incidence. It is hoped that a study in the planning stage can be expanded to at least 500 patients in the U.S. and that patients in Mexico and Brazil can be added. Of the 40 children with HIV infection who have been studied, none of them had poliovirus in their stool. Immunologists who are caring for patients with these disorders have been notified so their patients can also be enrolled in the study.

In closing, Dr. Halsey proposed that patients with B cell deficiency disorders undergo at least one stool culture for poliovirus because they are at risk of paralysis. He would like to convene a workshop so that immunologists from various perspectives and members of several advisory groups can discuss this issue.

Discussion

Dr. Offit commented that the challenge of ridding laboratories of revertant virus and wild-type virus is a daunting one. The extent of the public health threat as a consequence of revertant virus is unknown. Dr. Orenstein noted that although revertant viruses can cause paralytic disease, they are rare and they do not cause disease of the same virulence as wild-type virus. Dr. Katz pointed out that in countries where polio persists, up to 30-40% of adults may be HIV-positive. However, no evidence exists that HIV infection predisposes persistent excretion or is a significant risk factor for vaccine-associated paralytic polio. Children with HIV have a slightly longer duration of

excretion, but that rate is not on the same scale as children with B cell deficiencies. Dr. Kew added that when persistent excreters stop excreting virus, it is long-term cessation.

The risk that persistent excreters can transmit disease is markedly reduced compared with persons infected with wild-type virus. Two of three viruses are susceptible in vitro to Pleconaril, and there is hope that it can be used successfully as a treatment.

ANAPHYLAXIS DUE TO GELATIN AFTER MMR VACCINATION

Background

Gelatin is used in vaccines to stabilize the product. According to Dr. V. Pool, NIP, published reports from Japan have indicated a link between immediate hypersensitivity reactions to vaccine and the presence of IgE antibodies to gelatin. Japanese investigators showed that children with anaphylaxis and systemic urticaria following vaccination for measles are more likely to have received a gelatin-containing DTaP series and suggested that there may be a causal relationship. Persons with severe, generalized urticaria reactions following Varivax vaccination had a positive skin test for gelatin used in the vaccine. Although these findings may be due to a recent change in Japan's immunization schedule, a case-controlled study was initiated to determine the role of gelatin in anaphylaxis after MMR vaccination.

Case-Controlled Study

The source of cases studied was VAERS. All reports of anaphylactic shock, allergic reaction or a combination of dermatological, respiratory and/or gastrointestinal symptoms on the day of MMR were coded as probable, possible, non-anaphylaxis, or as cases with insufficient information. Two groups of controls were used: cases of non-anaphylactic reactions reported to VAERS and healthy persons from the Mayo Clinic who had received MMR vaccination without incident.

Both cases and controls were administered a questionnaire eliciting their history of allergy, noting their symptoms and the timing of those symptoms. Blood samples were drawn for IgE testing of antibodies to whole egg, gelatin, and individual viral antigens using solid-phase radioimmunoassay. Results were expressed as radioactive counts per minute.

One hundred fifty-two probable/possible cases of anaphylaxis were contacted by telephone. Of these, 57 agreed to participate and 22 donated blood for IgE testing. Recruitment of VAERS controls was abandoned due to a lack of response, and new convenience controls were recruited from the Mayo Clinic. Of these, 27 agreed to donate a blood sample, and 21 provided an allergy history.

The 22 cases were predominately female (13) and ranged in age from 15 months to 33 years. Eleven had received MMR alone, nine received MMR in combination with other non-gelatin containing vaccine, and two received a single-antigen measles vaccine. Five had received one prior dose of MMR, and none had received DTaP or other gelatin-containing vaccine. The mean level of anti-gelatin IgE antibodies was significantly higher in cases than in controls. None of the

controls or cases had elevated mumps or rubella anti-IgE antibodies. Only cases (28%) reported allergies to food, a difference that was statistically significant.

Results of the Study

The following observations were made.

- Persons with reported anaphylaxis following administration of MMR have significantly higher levels of anti-gelatin IgE compared with matched controls.

- Up to 50% of cases of anaphylaxis following MMR are associated with elevated levels of anti-gelatin IgE.
- Food allergies were more common among cases than controls.
- Neither cases nor controls reported a food allergy to gelatin.

This study was limited in several respects. There was a low rate of participation; the controls were not matched for history of atopic disease; there was recall bias; the ethnic origin of cases is unknown; and it is unknown whether food allergy occurred before or after immunization.

Note: In 1998 and 1999, the rate of hypersensitivity reactions in Japan decreased markedly. This change may be related to two factors. Since February 1999, all DTaP vaccines in Japan became gelatin-free, and vaccine manufacturers switched from a bovine to a hydrolyzed porcine gelatin stabilizer. In the U.S., no significant increase of anaphylaxis to MMR has occurred.

Dr. Pool proposed some additions to the current ACIP immunization recommendations regarding gelatin in vaccines (MMR, varicella, influenza, etc.). Option 1 would provide background, results, and recommendations and Option 2 would be a brief statement of caution.

Dr. Vernon showed evidence that contraindications are clearly presented in the package circular for MMR-2 and Varivax vaccine. A previous hypersensitivity to agents, including gelatin, is specifically mentioned as a contraindication. Hypersensitivity reactions cannot always be predicted from a patient's history. A negative test does not rule out the possibility of an anaphylactic reaction, and a screening test will not alter the precautions that should be taken for all persons.

Merck uses a very tight definition of anaphylaxis for its Worldwide Adverse Events Surveillance System. According to this passive, voluntary, likely underreported system, there were 3.3 reports of anaphylaxis/10 million MMR doses distributed. For Varivax, ten adverse events were reported for 22.1 million doses distributed. A highly hydrolyzed porcine gelatin of low molecular weight is used in MMR-2 and Varivax; it does not produce a detectable antibody response with repeated dosing in rabbits.

Dr. Modlin requested that the ACIP members review the proposed additions to the general recommendations and send their comments to Dr. Pool so that the general recommendations statement can be completed at the February meeting. He specifically asked the members to review the options proposed by Dr. Pool and the data he presented on risk of anaphylaxis in persons with

anti-gelatin antibodies. A third document, the Summary of Current ACIP Statements on Anaphylaxis Due to Vaccines and Gelatin in Vaccines, should be reviewed as well.

Discussion
Dr. Chen stated that these changes have been proposed is to alert people to be cautious as anaphylaxis may be due to the gelatin content, not the vaccine itself. These findings may present an opportunity for the ACIP to address low risk adverse events.

UPDATE FROM MANUFACTURERS ON THIMEROSOL-FREE VACCINE

Roger Bernier referred to the joint statement from the Public Health Service, AAFP, and the AAP that was endorsed by the ACIP in July 2000, which indicates that the U.S. will complete its transition to a secure routine pediatric vaccine supply free of thimerosol by the first quarter of 2001. Until thimerosol-free vaccine is acceptable, use of vaccine containing thimerosol is acceptable.

Aventis Pasteur has filed its license supplement with the FDA. Aventis has a second thimerosol-free DTaP vaccine, which has five components. Aventis intends to apply knowledge gained from its experience with Tripedia to its Pediatric DT supplement. Matthew Kemp, Baxter Highland ImmunoVaccines, announced that Baxter completed its acquisition of North American Vaccine. Thimerosol-free Sortiba, their DTaP vaccine, is expected in 2002 or 2003. Wyeth Lederle reports that it has eliminated thimerosol from its Hib vaccine. Work to remove thimerosol from its DTaP vaccine is ongoing, but the company will not file with the FDA by the end of the year.
Dr. Midthun commented that the FDA will consider Aventis Pasteur's license supplement application a priority.

Td VACCINE SHORTAGE

Dr. Zanardi alerted the ACIP to a shortage of tetanus toxoid (Td) vaccine. Wyeth Lederle has stopped shipping Td while they are addressing manufacturing practices with the FDA. Aventis Pasteur has also temporarily decreased the amount of Td vaccine they are shipping. However, Aventis Pasteur predicts full availability of the vaccine by February, 2001.

The following priorities have been drafted for use of this vaccine while the shortage persists. They are in descending order.

- For prophylaxis in wound management
- Persons traveling to diphtheria-endemic countries
- Persons who have received less than three tetanus or diphtheria vaccinations
- Pregnant women and persons at occupational risk who are due their 10-year booster
- Adults who are due for their 10-year booster
- Adolescents who are due for their first Td vaccination

Comments
Dr. Orenstein suggested that people traveling to endemic areas should be given first priority and that the last two priorities in the list be reversed. Dr. Gardner remarked that a substantial price increase for Td recently took place. According to a company representative, Aventis Pasteur did increase the price for this vaccine at the beginning of this year, but at that time, the company did not anticipate any production difficulties. Aventis has stopped shipping Td because of production issues, not because there is a shortage of the vaccine. This issue will be addressed as a CDC update in MMWR.

Dr. Modlin opened the meeting for public comments. There were no comments. The meeting was adjourned at 1:40.

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

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John F. Modlin, M.D. Date