CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICE

Records of the Meeting Held on

February 21-22, 2001

Atlanta Mariott Century Center Hotel
Atlanta, Georgia

CENTERS FOR DISEASE CONTROL AND PREVENTION
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
February 21-22, 2001

Agenda Item	Purpose/Action	Presider/Presenter(s)
February 21		
8:30 Welcome		Dr. J. Modlin (Chair, ACIP)
Disclosure by Committee Members		Dr. D. Snider (CDC, OD)
9:00 Influenza vaccine	Information	Dr. Carolyn Bridges (NCID,DVRD)
U.S. influenza surveillance summary	Discussion	Dr. N. Cox (NCID, DVRD)
International update and vaccine selection for 2001-2002 influenza season	Decision	Dr. K. Fukuda (NCID,DVRD)
2001-2002 Control and Prevention of Influenza Recommendations		
10:00 BREAK		
10:30 Influenza vaccine supply and delay	Information	Dr. K. Midthun (FDA,CBER)
Vaccine distribution for the 2000-2001 season	Discussion	Dr. M. Myers (NVPO)
		Dr. G. Peter (NVAC)
		Dr. L. Rodewald (NIP, ISD)
11:15 Update on live attenuated influenza vaccine	Information Discussion	Dr. Keiji Fukuda (NCID,DVRD)
12:00 Smallpox Vaccine Recommendations	Discussion	Dr. C. Helms (Univ. of Iowa)
Recommended use of vaccine for laboratorians working with highly-attenuated and non-attenuated strains of vaccinia virus or other orthopoxviruses	Draft Statement Decision	Dr. L. Rotz (NCID, DVRD)
Recommended use of vaccine in a bioterrorism event involving smallpox virus		
Recommendations regarding antiviral alternatives to VIG for treating vaccine adverse reactions		
1:00 LUNCH		
2:00 Update on Td and DTaP Vaccine Supply	Information	Dr. K. Bisgard (NIP, ESD)
Update from manufacturers	Discussion	Dr. P. Hosbach (Aventis Pasteur)
Recommendations for use of DTaP if a shortage develops	Decision	Dr. B. Howe(SmithKline Beecham)
		Dr. M. Kempf (Baxter Hyland Immuno)
		Mr. D. Mason (NIP, ISD)
		Dr. L. Zanardi (NIP, ESD)
3:30 Update on thimerosal-related research	Information	Dr. R. Bernier (NIP, OD)
		Dr. C. Heilman (NIH)
		Dr. G. Mootrey (NIP,ESD)

February 21 - continued

Agenda Item	Purpose/Action	Presider/Presenter(s)
4:00 BREAK		
4:30 Polio outbreak in the Dominican Republic Status of outbreak and control measures Virology data Policy implication to polio eradication in the U.S. Immunization coverage data	Information Discussion	Dr. O. Kew (NCID,DVRD) Dr. C. de Quadros (PAHO) Dr. R. Sutter (NIP,OD)
5:30 Dose reduction of IPV U.S. polio immunization policy Stock pile of polio vaccine	Information	Dr. J. Cono (NIP, ESD) Dr. T. Murphy (NIP, ESD) Dr. P. Offit (Children's Hosp. of Phili.)
6:15 Dose-Reduction Working Group Update Haemophilus vaccine doses	Information	Dr. D. Brooks (Johnson Med Cntr.)
6:30 Public Comment		
6:45 ADJOURN		

FEBRUARY 22

Agenda Item	Purpose/Action	Presider/Presenter(s)
8:00 Unfinished Business from Previous Day		Dr. J. Modlin (Chair, ACIP)
8:30 Updates National Center for Infectious Diseases National Immunization Program Food and Drug Administration National Institutes of Health Vaccine Injury Compensation Program National Vaccine Program	Information	 Dr. A. Mawle (NCID, OD) Dr. W. Orenstein (NIP, OD) Dr. K. Midthun (FDA, CBER) Dr. C. Heilman (NIH,NIAID) Dr. G. Evans (HRSA) Dr. M. Myers (NVPO)
9:45 BREAK		
10:15 Review of the new hepatitis B safety studies	Discussion Decision	Dr. H. Margolis (NCID,DVRD)
10:45 General Recommendations Outstanding Issues	Discussion	Dr. B. Atkinson (NIP,ISD)
11:15 Institute of Medicine Report on the Immunization Safety Review Committee	Information	Dr. M. McCormick (IOM)

February 22 - continued

Agenda Item		Purpose/Action	Presider/Presenter(s)
11:45	Discontinuation of manufacture and marketing of the only licensed cholera vaccine in the U.S. and the only licensed typhoid fever vaccine for children age 6 months - 2 years in the U.S.	Information Discussion	Dr. E. Mintz (NCID,DBMD)
12:00	**LUNCH**		
1:00	Adult Immunization Working Group Pertussis among adolescents and adults in the US: Data from the APERT trial	Information Discussion	Dr. K. Bisgard (NIP, ESD) Dr. R. Clover (Univ of Louisville) Dr. T. Murphy (NIP, ESD) Dr. J. Ward (UCLA)
2:15	Update: Hepatitis A Vaccination Activities	Information	Dr. B. Bell (NCID, DVRD)
2:45	Cost effectiveness of universal childhood vaccination against hepatitis A in states covered by ACIP recommendations	Information	Dr. B. Bell (NCID,DVRD) Dr. J. Jacobs (Capitol Outcomes Research)
3:15	StaphVAX Phase 3 efficacy trial in end-stage renal Disease patients on hemodialysis	Information	Mr. G. Horwith (NABI) Dr. J. Jernigan (NCID,HIP)
3:30	Public Comment		
3:45	**ADJOURN**		

ATTENDEES:

Committee Members
Dr. John Modlin, (Chair)
Dr. Dennis Brooks
Dr. Richard Clover
Dr. Jaime Deseda-Tous
Dr. Charles Helms
Dr. David Johnson
Dr. Myron Levin
Dr. Paul Offit
Dr. Margaret Rennels
Dr. Natalie Smith
Dr. Lucy Tompkins
Dr. Bonnie Word

Ex Officio Members and Liaison Representatives
Dr. Jon Abramson (AAP)
Dr. James E. Cheek, IHS
Dr. Benedict Diniega (DOD)
Dr. Geoffrey Evans (NVICP)
Dr. Eric France (AAHP)
Mr. Randolph Graydon (HCFA)
Dr. Carol Heilman, (NIH)
Dr. Barbara Howe (PhARMA)
Dr. Randolph Jackson (NMA)
Dr. Samuel Katz (IDSA)
Dr. Victor Marchessault (NACI)
Dr. Martin Mahoney (AAFP)
Dr. Karen Midthun, FDA
Dr. Martin Myers, NVPO
Dr. Margarite Nava (NIC, Mexico)
Dr. Kathy Neuzil (ACP)
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
Dr. Dixie E. Snider, Jr.

Office of the Director
Dr. David Fleming

Office of General Counsel
Kevin Malone

National Center for Infectious Diseases
Christopher Allen
Miriam Alter
Michael Bailey
John Becher
Beth Bell
Lynn Brammer
Carolyn Bridges
Jay Butler
Nicole Coffin
Nancy J. Cox
Cindy Dougherty
Andrea Drull
Henrietta Hall
John Jernigan
Olen Kew
Rima Khabbar
Alexander Klimor
Janice Knight
Matt Kuehnert
Yu Li
Allison Mawle
Linda McKibben
Martin Metzer
Eric Mintz
Ann Moen
Erin Murray
Joann Patton
Gary Sanden
Kanta Subbrao
Eric Weintraub
Tim Wyeki

National Immunization Program
Yancris Aboeu
William Atkinson
Roger Bernier
Kris Bisgard
Ed Brink
Sharon Butler
Scott Campbell
Lynn Carroll
Bob Chen
Susan Chu
Gary Coil
Joanne Cono
Karin Galil
Joyce Geoff
Debbie Gust
Sara Foster
Stephen Hadler
Beth Hibbs
Penina Haber
Anne Huang
Janet Kelly
John Iskander
Alison Johnson
Laurie Johnson
Sharon Katz
Duane Kilgus
Karin Kohl
Randy Louchart
Tasneem Malik
Dean Mason
Mary McCauley
Mike McNeil
Elaine Miller
Gina Mootrey
Trudy V. Murphy
Bill Nichols
Glen Nowak
Joseph Olan
Dennis O'Mara
Walter Orenstein
Brian Pascual
Jeri Pickett
Robert Pless
Kelly Plots
Bette Pollard
Vitali Pool
Kristen Poydence
Susan Reef
Lance Rodewald
Susan Scheinman
Ben Schwartz
Jane Seward
Kristine Sheedy
Jim Singleton
Ray Strikas
Bob Snyder
Charlis Tompson
Kim Waggoner
Fran Walker
Donna L. Weaver
Bruce Weninger
Craig Wilkins
Skip Wolfe
Lynn Zanardi

CDC Health Clinic
Patricia Blackwell

CDC-OHS
Tammy Gorny

Epidemiology Program Office
Janey Kelly

National Center for Environmental Health
Marvin Bailey
Susan Gorman

National Center for HIV, STD, and TB Prevention
Timothy Mastro

NVPO
Alicia Postema
Greg Wallace

Food and Drug Administration
Leslie Ball
Norman Baylor

Others Present
Kaia Agarwal, SmithKline Beecham
Bascom F. Anthony, Biologics Consulting Group
Deborah Amndell, Roche Labs Inc.
Lynn Bahta, Immunization Action Coalition
Greg Ball, Aventis Pasteur
Joseph Beaver, TN Department of Public Health
Phil Brunell, Stock, Inc.
Anton Cangelosi, New Orleans, LA
Pat Carron, Newnan, GA
Dan Casto, Merck
Timothy Cleary,
Leonore Cooney, Cooney-Waters
Dack Dalrymple, Bailey and Dalrymple
Michael Decker, Aventis Pasteur
Dominique Delearups
Dan DeNoon, WebMD
Ciro de Quadros, PAHO
Carmen Deseda, San Juan, PR
Ingram Douglas-Hall, GIV
Frank Dzvonik, Philadelphia, PA
Craig Engesser, Wyeth
Ali Fattom
David Fedson, Aventis Pasteur, France
Alicia Gable, Institute of Medicine
Beverly Gaines, National Medical Association
Jonathan Gal, Cambridge, MA
Madeleine Gardberg, Wyeth Lederle
Bruce Gellin, Vanderbilt University
Jayne Gilbert, Chiron Corp.
Ruth Gilmore, Georgia Immunization Program
Cynthia Good, Atlanta, GA
Jesse Greene, SC Department of Health
K.P. Guito, Aventis Pasteur
Jeff Hackman, Aventis Pasteur
Neal Halsey, Johns Hopkins Univ.
Claire Hannan, ASTHO
Michael Hogue, American Pharmaceuticals Association
Gary Horwith, NABI
Philip Hosbach, Aventis Pasteur
Melonie Jackson, Atlanta, GA
R. Jake Jacobs, Capitol Outcomes Research
Matthew Kempf, Baxter Hyland
Michelle Kirsche, Slack Inc.
Edgar Ledbetter, San Antonio, TX

Others Present - continued
Len Lavenda, Aventis Pasteur
Walter Lee, Vienna, Austria
Pam Lennard, Nancy Lee & Associates
Scott Litherland, Parallax Communications
Harold Lupton, Aventis Pasteur
Michael Massare, Novavax
Marie McCormick, Harvard School of Public Health
M.A.J. McKenna, Atlanta Journal-Constitution
Shawn McMahon
Paul Mendleman, Aviron
Sheila Moorth, Merck
Tuwanna Morris, Austell, GA
Barbara Mulach, Bethesda, MD
Marie Murray, Atlanta, GA
Gwendolyn Myers, Acambis Inc.
Angeline Nanni, Columbia, MD
David Neumann, Bethesda, MD
Regina Ofiara, Deerfield, IL
Laszlo Palkonyay, Canada
Peter Paradiso, Wyeth Lederle
Emma Patten-Hitt
Stanley Plotkin, Aventis Pasteur
Lyn Redwood, Safe Minds
Anne Rogers, Parallax Communications
Zeil Rosenberg, Becton Dickenson
Fred Ruben, Aventis Pasteur
Judith Schmidt, Decatur, GA
Dr. Kristine Severyn, Vaccine Policy Institute
Patti Skuder
Judith Shindman, Aventis Pasteur
Alan J. Sievert, Cobb County Board of Health
Don Sinisi, Roswell, GA
Gary Siskowski
Parker Smith
Ron Stern, North Wales, PA
Stacy Stuerke, Merck
Lonnie Thomas, Bastian, VA
Eric Tischler, Aventis Pasteur
Ted Tsai, Wyeth Pharmaceuticals
Miriam Tucker, Pediatric News
Theresa Turski, DHR, GDPH
Brian Vastag, Bethesda, MD
Thomas M. Vernon, Merck
Peter Vigliarolo, Cooney Waters

Others Present - continued
Alun Vontillius, Atlanta, GA
Joel Ward, UCLA Medical Center
Barbara Watson, Philadelphia Department of Public Health
Diane Watson, Waycross, GA
Deborah Wexler, Immunization Action Coalition
Walter Woods, Aventis
Lvana Wotcik, Aventis Pasteur
Laura J. York, WLV
John Zahradnik, Aventis Pasteur

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Centers for Disease Control and Prevention
Advisory Committee on Immunization Practice
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FEBRUARY 21, 2001

The Centers for Disease Control and Prevention convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on February 21-22, 2001, at the Atlanta Maraud North Central Hotel in Atlanta, Georgia. Chair Dr. John Modlin called the meeting to order at 8:29 a.m.

Opening Comments

ACIP Executive Secretary Dr. Dixie Snider welcomed three new members, Dr. Jaime Deseda-Tous, of the San Jorge Children's Hospital, San Juan, Puerto Rico; Dr. Myron Levin, University of Colorado School of Medicine in Denver, Colorado; and Dr. Natalie Smith, California Department of Health Services. He also welcomed a new Ex-Officio representative, Col. Benedict Diniega of the Department of Defense; and two new liaisons, Dr. Cathy Neuzil of the American College of Physicians and Dr. David Salisbury, London Department of Health. Dr. Margarita Nava, of the National Immunization Council and Ministry of Child Health of Mexico, attended for Dr. Ignacio Santos.

Dr. Snider announced that last December, Dr. Koplan had amended the ACIP charter to add three new members. Although they were not yet appointed, that addition had changed the ACIP quorum to eight attending members. Dr. Snider asked the members present be sure to maintain a quorum at all times. The Charter allows the Executive Secretary to designate Ex-Officios as voting members when necessary (<8 members present who have no conflict of interest and are qualified to vote).

He announced the Web address for the committee, <ACIP@cdc.gov>, and the home page site at <www.cdc.gov/nip/acip>. The home page has the committee charter; membership roster; ACIP resolutions; and meeting dates, locations, and agendas. When the revisions to the ACIP Policies and Procedures Document are done, that will be added as well. The revisions demanding considerable discussion relate to the nomination of future ACIP candidates. Current consideration is being given to not nominating individuals before they resign certain relationships, or alternatively, not providing waivers for them. Waivers would be required for such matters as stock ownership in vaccine companies, membership on vaccine manufacturer advisory boards that address business rather than simply technical matters, or serving as an expert witness for vaccine manufacturers while an ACIP member.

Dr. Snider welcomed public comment at the scheduled times and requested that those wishing to comment sign up to do so. Comments at other times would also be entertained as long as the meeting agenda was not delayed. Finally, he announced the 2001 meeting dates (June 20-21 at this same hotel, and October 17-18); the 2002 meeting dates will be set at the next meeting.

Dr. Modlin also welcomed the new members, liaisons, and ex-officios, and Dr. Wharton, to the table. He noted the distribution in the meeting books of three *MMWR* publications: the 2001 Childhood Immunization Schedule, the AAP/PHS joint Statement on Thimerosal in Vaccines, and the ACIP Anthrax Vaccine Statement.

Financial Disclosure

Dr. Modlin stated that all may participate in discussion as long as any conflicts of interest are disclosed. However, those with such conflicts may not: a) vote on any related issue, b) vote on the Vaccines for Children resolutions; or c) introduce or second a vote for a VFC resolution. Ex-Officios and liaisons, who do not vote anyway, were asked to disclose conflicts as well.

The ACIP members, Ex-Officio representatives, and liaison members introduced themselves and stated any potential conflicts of interest. This is compulsory for ACIP members and voluntary for others. Conflicts were stated by:

Dr. Clover reported funding provided to him and his department at the University of Louisville from Wyeth, Merck, SmithKline, Bayer, and Astra Zeneca.
Dr. Word reported recent participation in a Merck advisory committee.
Dr. Helms reported no conflict of interest; he received no honorarium for his participation in Merck's Vaccine Division's National Immunization Advisory Board in November 2000.
Dr. Rennels reported her conduct of vaccine trials for Wyeth Lederle, Aventis Pasteur, Glaxo SmithKline and Merck, and her chairing of a Safety Monitoring Board of Aventis Pasteur.
Dr. Offit is the co-holder of a patent on a bovine human reassortant rotavirus vaccine and serves as an unpaid consultant to Merck on its development.
Dr. Levin reported clinical research conducted with Merck, Glaxo SmithKline, and Medimmune; and he holds stock in Glaxo SmithKline and Baxter.

Workgroup Formation

Dr. Modlin requested volunteers for the two new workgroups. The Rotashield/Rotavirus Vaccine Workgroup will examine the related CDC/NIH data soon to be released and advise the committee of its findings for full discussion at the October meeting. An NVPO science meeting in September (5-7) also will examine all the science related to rotavirus vaccine and intussusception. Volunteers were Drs. Deseda, Levin, Offit, Reynolds, Peter, Pickering, Katz, France, Evans, and Jackson.

The 2002 Harmonized Schedule Workgroup will develop the harmonized schedule with the AAP and AAFP for the next year and consider the option of publishing this electronically for continuous updates. Volunteers were Drs. Smith, Brooks, Clover, Peter, Zimmerman, and Siegel. Also nominated was Dr. Charles Prober to represent the AAP. Dr. Modlin requested volunteers for an informal workgroup to help Dr. Hal Margolis develop the hepatitis B statement for ACIP approval in June.

Influenza Vaccine

U.S. Influenza Surveillance Summary. Ms. Lynette Brammer summarized this season's influenza activity and updated the committee on the vaccine selection for the Northern Hemisphere's 2001-02 influenza season. The collaborating laboratories of the WHO and the National Respiratory and Enteric Virus Surveillance System reported that 68% of the respiratory specimens testing positive for influenza were Type A, and most of the influenza-type viruses subtyped are H1N1. The season appears to have peaked in week four and is now in decline. Compared to last year, this season was relatively mild with a peak four weeks later. Data of patient visits to sentinel physicians this year versus last parallels those patterns.

The mortality data for 122 cities showed no excess mortality for this season. The majority of the WHO collaborating labs' A (H1N1) viruses sent to CDC for antigenic characterization were similar to the A/New Caledonia/20/99 vaccine strain, which also cross-reacted well with the few that were similar to the older A/Bayern/95 strains. The few influenza A (H3N2) virus strains seen in the U.S. were similar to the A/Moscow/10/99 and A/Panama/2007/99, which is in this year's vaccine. Most of the influenza B viruses seen this year are similar to the B/Sichuan/379/99, a drift variant of the B Beijing 184/93-type viruses which are in the vaccine. They cross-react even though they are antigenically distinguishable.

The international picture parallels that of the U.S., with influenza A (H1N1) predominating, although influenza B dominated in Canada, Portugal, and some other countries. No countries have reported widespread influenza A (H3N2) activity this season.

The FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) met in January, and WHO's Vaccine Selection Advisory Committee met in February. Both meetings retained the A/New Caledonia H1N1-like virus, and the A/Moscow H3N2-like strain for the 2001-2 seasons. Since most viruses worldwide are increasingly similar to the Sichuan virus rather than the Beijing-like virus, the B component should be updated to include the latter. The FDA advisory committee will meet March 9 and finalize their recommendations.

Changes to the 2001 Recommendations. Dr. Carolyn Bridges reported fewer changes in the recommendations than necessary last year, particularly in anticipation of the use of live attenuated influenza vaccine (LAIV) next year. The vaccine strains for next year will be updated after the FDA meeting. Additional references will be incorporated with those now in the draft. She summarized the current recommendation changes:

1. *Introduction.* Page 8; introduction information was shortened to eliminate redundancies from the introduction to specific sections. High risk target groups were expanded from two to three groups in response to confusion during the vaccine delivery delays: healthy 50-64 year-olds were a lower priority and were recommended to be vaccinated later in the season. Impact information on the 50-64 year-old age group will be incorporated to next year's draft. They are now delineated to: a) ≥65 years and <65 years with high risk conditions; b) people aged 50-64; and c) the contacts of high risk people, including health care workers. The inclusion of more information on health benefits for those aged 50-64 will be moved back into the rationale section. There was no committee discussion on the proposed language.

2. *Burden of disease*. On page 10, a table was suggested to describe hospitalization data by age group rather than in the text; as was adding information on page 12 regarding cost effectiveness and on the number weeks to develop antibody response after vaccination.
   - Committee comments were: 1) Dr. Siegel: Regarding health benefits, include some text about decreased use of antibiotics; 2) Dr. Abramson: Include some discussion of the possibility of influenza-associated encephalopathy, although lack of good data hampers this. Perhaps a line could be added that "more rare complications of influenza might include . . ."

3. A separate cost effectiveness section (pp 12-13) addresses: a) the economics of influenza in cost effectiveness and utility emphasized over cost benefit, since the latter implies that cost saving is necessary for benefit. More emphasis on cost utility allows more comparison to other interventions; b) adding additional references was suggested; c) Dr. Nichol suggested providing more information on vaccine cost savings related to prevented productivity losses among the healthy adult group.
   - Committee comments were: 1) Dr. Johnson: Expand on current text about reduced direct/indirect medical costs and absenteeism in healthy adult vaccine recipients, in order to further distinguish between cost savings and cost utility and the arguments favoring vaccine use despite no cost savings; 2) Dr. Snider: compare this section's data on the 18-64 year-olds' to data on other preventive interventions. The statement's information and data are adequate, but consider highlighting the cost issues by summarizing them in a table. Dr. Bridges noted that in response to other suggestions, the rationale section would also cite the benefits of immunization in health adults.

4. Vaccine coverage and racial disparities are further delineated by added data on coverage by race/ethnicity, as well as NIP data showing a plateau in vaccine rates among those aged ≥65 years. A paragraph on vaccine supply acknowledging the possibility of a shortage or delay was also added.

Manufacturer comments. Dr. Modlin asked for a comment on the next year's vaccine supply from the manufacturer representatives.

- Wyeth: Dr. Peter Paradiso reported initial production of Flushield® and bulk concentrates for next season, while they await the final strain selection. Current projections are of similar supply volume as last season (~24 million doses). Wyeth does not anticipate any issues since they have experience with the two A strains.
- Aventis Pasteur: Dr. Phil Hosbach reported their plan to produce 38 million doses. They can produce an additional 17 million upon early notification of strain selection on March 9, an immunization season extends at least to the end of November. They also have added three incubators, working closely with the FDA. Subject to all that, they can release 55 million doses by the end of November.
- Medeva; Dr. Fukuda reported Medeva's projection the previous day of producing slightly less or about the same amount of vaccine as last year, predicated on the strain selection process and the season length (to gauge demand).
- The manufacturers stated that the A strain selected for this year reduces supply interruption risk considerably. Only the B strain variables might challenge production.

Committee discussion included:

- Dr. Helms: If data are available, add text to the supply interruptions data to support the efficacy of the vaccine intervention (e.g., ability to respond, number of people vaccinated).
- Dr. Zimmerman noted that Aventis, who alone produced whole virus vaccine last year, is now producing the split preparation.
- Dr. Myers supported the added text urging providers to consider planning later (after mid-October) mass vaccination campaigns. Information about the timing of peak influenza activity should be placed on a table to ensure that it is noted.
- Dr. Orenstein: As well as the table, add such text as "However, vaccine is still likely to be beneficial if vaccination campaigns are conducted into late November and beyond." This could encourage Pasteur to produce those extra 17 million doses.

5. Approved age groups for the vaccine were added, as was information on the required needle length for intramuscular injection.

Committee comments included:

- Dr. Levin: There are no data on coverage during pregnancy (page 17). Add text to encourage obstetricians to keep vaccination in mind during influenza season, and note that this may affect the high neonatal infection cited. The data are insufficient to be any more specific. Dr. Modlin: Incorporate the *MMWR* update into the statement on safety regarding vaccine/thimerosal issues of pregnancy and immunization.

- Dr. Smith: On page 19's General Population paragraph, add a caveat about vaccine availability.

- Dr. Zimmerman: Many vaccinations are given by private providers. Extending the immunization season gives them extra time to schedule this. The text also advises starting vaccination of those at high risk in September.

6. Antiviral medication section updates the references and notes approval of Zanamivir for those aged ≥7 years and Oseltamivir for those aged ≥ 13 years. Table 1 notes that Parkdale's non-production leaves only three manufacturers. Table 2 was updated to reflect the recommended ages for use of antivirals for prophylaxis.

Committee comments included:

- Dr. France: Replace the page 10 text on hospitalization of groups and the page 22 paragraph on GBS risk with the new table on page 10.

- Dr. Levin: On page 18, give more information on CD4 and viral load; note the need for caution in vaccinating HIV-infected people when a new medication's effect on viral load must be assessed; reword the GBS text on page 22. He suggested text advising prophylactic management during influenza season if vaccination seems ill-advised.

- Dr. Abramson: Consider being more encouraging of the use of trivalent vaccine for children. Dr. Modlin asked him to work with Drs. Bridges and Fukuda on possible language, since the pediatric issues will be examined in detail in the next 12-18 months. Dr. Neuzil thought that putting the hospitalization rates in a table would make it clear that children's rates are as high as in other groups. Dr. Fedson encouraged the ACIP to begin addressing child immunization, noting the imminent publication of Japanese data[1] showing greatly lowered mortality with early immunization (that rose again when stopped) among six million person-years of observation.

Dr. Fukuda responded that the rationale for vaccinating children has been discussed by ACIP for two years. The general philosophy has been to reduce mortality in the group of vaccinated people; there is debate whether vaccinating children will boost herd immunity. The Reichert analysis has been anticipated, but will involve a big paradigm shift; Paul Gleason is testing that hypothesis in Texas. Before ACIP considers changing its recommendation, those data should be examined in depth.

[1] Thomas Reichert et al; study demonstrating that Japanese immunization of school children over 20 years prevented 37-40,000 deaths.

He asked for clarification of the committee's position on expanding the immunization season. In past, this has been presented in terms of the optimal time to consistently vaccinate those at high risk. He asked if this would encourage immunization well past the season for those at high risk. Dr. Zimmerman responded that this would depend on the epidemiology of the seasonal peak. If early in December, the optimal vaccination period would be through mid-November. He thought that different wording could be used to encourage expanded use. Dr. Bridges noted that specific communities or geographic areas may differ from the national season temporal trends.

Dr. Modlin suggested that the current language be retained, and that any suggestions for change be provided to Drs. Fukuda and Bridges. He also asked Dr. Abramson to work with them as well, if the pediatric issues can be addressed without a major shift.

Dr. Levin raised the potentially greater risk with RSV co-infection with influenza (page 25). He also advised taking the opportunity to teach that specificity and sensitivity vary greatly by laboratory and by test; that the published data vary year to year without a viral change (page 26-27); and that some tests are not licensed for all specimens (swabs, nasal swabs in children, or not). And, since some tests are actually bad, a table should be done of the different kinds of lab diagnoses of influenza. At least one and maybe two tests are marketed to be used in the physician's office, with no approved regulations. He also raised the vagueness of the page 35 text on Zanamivir, but neither Drs. Bridges nor Midthun could provide any specific rate information to clarify that. Dr. Levin then asked for the addition of any available information on the drug interactions with P450 in the liver system, because up- or downward regulation would affect the recommendations for persons with HIV. Finally, note should be inserted on the page 53 table of formulations that Tamiflu® is now in a suspension formulation

Dr. Modlin confirmed the committee's comfort that Drs. Fukuda and Bridges could address any rewording questions about pediatric issues or change emphasis regarding seasonality with the interested ACIP members. Finally, Dr. Deseda suggested that the text note that other respiratory illness influences the influenza vaccination; the patient should not be sure a subsequent illness is from a vaccine failure.

VOTE: Dr. Helms **moved to approve the influenza statement as presented and amended.** Dr. Word seconded the motion. Conflicts related to Wyeth, Aventis Pasteur, and Medeva. Drs. Reynolds and Clover abstained. Those in favor were Drs. Deseda, Johnson, Levin, Smith, Offit, Tompkins, Helms, Word, Modlin, and Brooks. None were opposed. **The vote passed.**

Influenza Vaccine Supply and Delay

Dr. Myers reported discussion in NVAC's previous meeting of the issues of vaccine supply and vulnerability. Influenza and tetanus toxoid-containing vaccines were used as the primary example, as well as menigococcal vaccine and the need for a poliovirus stockpile.

While the immunization programs may be the greatest achievement of the 20th century, they have vulnerabilities. These include the reduction of disease, which led to lessened parental motivation, challenges to vaccine safety credibility, disparities in coverage, and vaccine supply. Challenges to vaccine supply include: 1) the changing and often unpredictable demand (e.g., from OPV to IPV; changing composition of influenza vaccine; episodic outbreaks); 2) the limited number of manufacturers (with high development expense, limited profit motivation, and public skepticism about vaccine safety as factors influencing their entrance into these markets); 3) vaccines (or components) produced offshore; 4) regulatory imperatives; 5) complex vaccine production cycles; and 6) dependency on other industries for vaccine components.

Issues relating to the distribution and redistribution of vaccine in short supply include the difficulty of determining the doses available (involving proprietary information), tracking vaccine in the "pipeline" (i.e., leftover doses); pre-existing commitments for vaccine; creating and managing stockpiles; the difference of private and public distribution systems; the difference in infrastructure to deliver adult and pediatric vaccines; and cost.

***Vaccine Development/Distribution: FDA Perspective*.** Dr. Norman Baylor outlined the vulnerability of vaccine supply using the previous season's influenza vaccine experience. To be effective, the vaccines potentially must be changed every year to antigenically match their antibodies to the hemagglutinin (HA) and neuraminidase (NA) of the season's evolving dominant strain.

The number of doses of trivalent vaccine submitted for release in 2000 was similar to the 1998-99 season, but the time in which they were available was critical to a perception of a shortage. Dr. Baylor shared a slide demonstrating that, although almost 50% of the vaccine was prepared by August 1998 and 1999, it was unavailable until October 2000 and not fully distributed until the end of November/early December.

The delays were caused by: 1) the unprecedented production delay at three of the four manufacturers licensed to produce influenza vaccine in 2000; 2) correction of deviations from good manufacturing practice in two of the manufacturers (one, Wyeth, could correct in time for late production; Parkdale could not); and 3) a low yield of the A/Panama 2007/99 strain. By outlining the ongoing vaccine production cycle from January of one year to January of the next, he demonstrated how a breakdown in any component activity will delay the supply. Charts also were shared to demonstrate the time of distribution by influenza strain and reagents used in the vaccine; the time of seed virus submitted for release; and the time of trivalent vaccine lots submitted for release by month. Distribution begins in July; trivalent formulations start in May/June; and the monovalents begin in February after the strains are identified. Development of good yields for new seed viruses goes on all year, as does surveillance and identification of new reference strains. A breakdown in any component activity will delay the supply. Between 1990 and 2000, the amount of trivalent vaccines available doubled from 40 to 80 million doses.

He summarized that: 1) distribution delays can be expected if production is delayed at multiple manufacturing facilities, a situation that is hard to predict; 2) production of vaccine was delayed by temporary difficulties with a new vaccine strain and by the need to correct manufacturer practice. FDA hopes to minimize this by working with the manufacturers; 3) one manufacturer (Parkdale) did not complete corrections and withdrew from production. But in other ways, the experience in 2000 was typical of influenza vaccine production in most years (e.g., the reagents were available and the strain selection was on target). Some things can be controlled; some cannot.

CDC Influenza Vaccine Contracting and Program Operations process was presented by Mr. Dean Mason of NIP. CDC entered the influenza vaccine contracting process with the swine influenza program in 1976. With some interruptions, contracting has been fairly consistent for the last six years. The program has been stimulated by special initiatives (e.g., a 1986 pilot program with HCFA to evaluate cost effectiveness and Medicare payment for vaccines). Aventis Pasteur (AvP) has been the most consistent producer among the seven companies which contracted with CDC in the past 25 years.[2] Only three manufacturers intend to produce influenza vaccine for 2001-2002.

Charts of influenza vaccine distribution by month from August to December 1999 and 2000 were shared. While almost all vaccine was distributed by the end of October 1999, this was not true for 2000. Over 55% of the influenza vaccine was distributed between October and December, 2000. This did not match the customer's accustomed vaccination pattern or the demand of recent years. Forty-seven percent of the U.S. vaccine supply is purchased by private providers; 35% by distributors; 14% by the government, and 3% by nursing homes. If Schein/GIV is counted as a distributor and not a manufacturer, then distributors are responsible for 54% of all the influenza vaccine supply in the U.S.

Mr. Mason provided a time line (Attachment #1) of the key events in the public health response to the influenza vaccine supply problems, 2000-2001.

CDC contracted with Aventis-Pasteur to produce an additional 9 million doses of influenza vaccine on behalf of the states, at $2.99 per dose for the public sector and $5 per dose for the private sector. Of the extra nine million doses ordered, 1.3 million doses were stockpiled in bulk form and 7.7 million doses were shipped. However, 67% of the total 2709 orders were canceled, 1.8 million doses by one reseller. As it became clear that the supply would be adequate, orders were canceled. The public health sector was the most stable purchasing entity.

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[2] Merrell-National; Connaught, Pasteur Merieux Connaught, Aventis Pasteur; Evans Medical, E.R. Squibb, Warner Lambert, Wyeth, Parke-Davis, and Merck.

Manufacturers limited CDC's contracts to 2.0 million doses of influenza vaccine. Provisional data reflect the fact that CDC contracts for only a small portion (<5%) of the total influenza vaccine doses supplied, versus >53% of pediatric vaccine doses. The CDC/ACIP influence is much greater for the latter.

With respect to influenza vaccine, the lessons learned are: 1) there is potential for a supply problem every year because of new formulations, vaccine company uncertainties, and because contract obligations for private purchases are executed before ACIP recommendations are made. It must also be recognized that ACIP recommendations may have only limited impact due to the small federal purchase, and the potential of large industries to ignore distribution recommendations based on other motives such as preventing employee illness); 2) distributors play a major role in vaccine supply, and prices increase with each level of handling; 3) the market demand ends in November; and 4) there is a wide variance in state operations and infrastructure (from county- to more centralized state-levels).

The key steps in the vaccine supply for 2001-2002 include identification of the virus strains, vaccine production, FDA approval, and ACIP recommendations. The CDC contracts will be awarded on or around April 16 and vaccine distribution is expected to begin in August.

Dr. Myers summarized that, in this very complex process of producing 79-80 million doses of vaccine annually, it is surprising that no problems occurred before. Since it is distributed mostly in the private sector, the available responses to a short supply are limited. There is no infrastructure for adult immunizations similar to those for childhood immunizations. For all those reasons, the following issues are being reexamined: assuring supply, consideration of distribution and redistribution when vaccine is in short supply, and issues of adult immunization.

Discussion. Dr. Modlin thanked the NVAC for addressing this issue and opened discussion. The comments included the following:

- Dr. Peter: NVAC formed a workgroup to examine vaccine supply vulnerabilities and related challenges. They hoped for ACIP representation in this, and expected to begin work soon with a conference call.

- The contribution of the "gray market" to aggravating maldistribution of vaccine is only anecdotally known. The GAO is investigating.

- Dr. Tompkins volunteered for the workgroup, and asked what factors produced the ACIP's greater influence on pediatric immunizations. Dr. Peter identified the collaboration with the influential AAP, particularly its Red Book Committee, whose advice is followed by the pediatricians who deliver most of the vaccines. He welcomed her involvement to also supply the IDSA perspective.

- Dr. Snider added the school immunization requirements as a big contributor, and the inclusion of influenza vaccine coverage in the HEDIS measures. Dr. Zimmerman added the impact of the harmonized schedule on impacting routine pediatric immunizations. He asked if the harmonized adult schedule would be developed, and if so, by whom. Dr. Clover identified the Adult Immunizations Workgroup, which would begin discussion on this day.

- Dr. Marchessault recommended the effectiveness of the Canadian model, in which the production of influenza vaccine is a responsibility of public health. This controls the flow of influenza vaccine as well as the price.

- Dr. Orenstein reported that CDC will try to evaluate how much of the 1.5 million doses purchased (of the nine million doses ordered) were used. The committee supported that purchase as a wise "insurance policy" that would have been more utilized if the influenza season had been severe instead of light.

- Dr. Tompkins asked about ACIP's coordination with Medicare, which represents the high-risk vaccination group of the older population. Mr. Graydon reported HCFA's ten-state project with CDC to encourage the use of standing orders for influenza immunization, which makes it easier to bill Medicare for that work (i.e.., a single ledger bill for everyone in a nursing home).

- Dr. Word commented that there is no adult concept paralleling the routine childhood immunizations, which prevents the same buy-in from other parties. For example, the NMA has an immunization-supportive project called "A Family Affair" to encourage the whole family to be immunized together.

- Dr. Sam Katz noted that few ACIP members (Drs. Schaffner, Fedson, and Gardner) had ever promoted adult vaccinations, proposing a "Green Book" to parallel for adults the Red Book for children. But physicians' interest could never be gained. Dr. Fedson credited the influence of Medicare reimbursement in the rise of influenza vaccination since 1993, and noted that pneumococcal vaccination is also above 50%. The U.S. leads most of the world in those immunizations, but it could be better. The U.S. delay would never occur in Canada, where 90-95% of influenza vaccine is distributed to physicians by the provincial governments' Health departments.

- Dr. Lance Rodewald reported the National Committee for Quality Assurance's vote two weeks earlier to extend the HEDIS measures to vaccinate those aged 50-64 years. That will add millions of adults to the rolls and greatly impact adult vaccination. That should be supported when final. Public comment will extend to about March 3. They also reduced the length of participation required in a plan before a child is counted for an immunization benefit.

Live Attenuated Influenza Vaccine (LAIV) Update

Dr. Keiji Fukuda updated the committee on the status of the dynamics and timetable of Live Attenuated Influenza Vaccine (LAIV) development. The related recommendation issues include: 1) should healthy/young children routinely be vaccinated against influenza?; and 2) if an LAIV is approved by the FDA, how would ACIP recommend its use?

The two issues are somewhat intertwined but should be kept separate. The potential approval of LAIV will focus attention on whether children should be routinely vaccinated against influenza. Studies of the efficacy and effectiveness among children have produced generally favorable results, and there are other benefits (e.g., it can be administered without needles). Other studies affirm that influenza has a serious impact in young children ≤4 years of age. It is clear that Aviron and other companies intend to market LAIV for children.

The points offered by Dr. Fukuda for consideration included: 1) the issue of whether to recommend influenza vaccination in children is a separate issue from the ACIP's recommendations for use of LAIVs in general; 2) there already is an inactivated influenza vaccine used in the U.S. which is permitted for all children aged ≥6 months; and 3) ACIP already recommends vaccination of children age ≥6 months who have high-risk conditions. However, this has not been successfully implemented; for example, data indicate coverage of only ~10% among children with asthma.

Key events in the LAIV development time line include:

1. The October 31 submission of the biologics license application to FDA was accepted at the end of December. Most likely in summer/fall of 2001, FDA's VRBPAC will review the product. Subsequent timing of FDA actions is unknown.

2. However, possibly in time for the October ACIP meeting, an LAIV will be licensed and an ACIP decision will be needed then or in time for the 2002 recommendations.

3. The related schedules for this year include this ACIP meeting and the planned May 2001 Influenza Workgroup meeting in Atlanta to discuss:
    a. The safety/effectiveness of inactivated vaccine in children;
    b. Review of development /published studies on the effectiveness of LAIV vaccines;
    c. Subgroups will review topics, including (I) the potential for reversion of LAIV to more virulent strains; (ii) the potential of LAIV strains and wild virus to recombine; (iii) a review of mortality and morbidity data of the impact of influenza on children; (iv) the potential of adverse effects from repeat influenza vaccinations among children; and (v) the potential biologic issues regarding co-administration of influenza vaccines with other childhood vaccines.

4. In July or later, VRBPAC will review the Aviron product's efficacy and safety data, and approve or reject the product, or request more data.

5. A second Workgroup meeting is expected after May (perhaps in mid-September or October) to address such issues as the feasibility of implementing any potential pediatric recommendations; the economic considerations of such recommendations; and the impact of pediatric recommendations on existing childhood vaccine schedules and programs. Also at the second meeting in fall, if FDA/VRBPAC have completed work on Aviron's submission, the Workgroup will review unpublished data on any increases in adverse events among LAIV recipients, and on the risk if exposures to LAIV in certain high risk groups (e.g., those with chronic lung disease of immunosuppressed). They will continue to draft potential options for ACIP recommendation.

6. In October, the ACIP may need to address LAIV recommendations for the 2002 season. The VRBPAC/FDA process will determine when the ACIP addresses the LAIV. If not approved, a decision can be deferred; if approved before the October ACIP meeting, a decision to make or to defer a recommendation will be needed. An October recommendation for the 2001 season would have to be issued in a supplemental publication.

Dr. Fukuda summarized that the adult and pediatric issues clearly overlap, but need to be kept separate. The fundamental question is whether to recommend routine vaccine use in young children. Such a recommendation will impact children, parents, pediatric practitioners, pediatric programs and schedules, and potentially the vaccine supply. If approved and recommended by the ACIP, the LAIV provides another option for carrying out existing recommendations. In short, the ACIP needs to be prepared to act either in October 2001 or February 2002.

The committee's comments included the following:

- Dr. Abramson related the AAP's agreement that these are intertwined but separate issues. They will decide In March if the vaccine's use in young children should be encouraged, but he expected them to support it.
- Dr. Word supported expansion of the recommendations to include LAIV, and if so, the options, but also emphasized the need to keep the issues distinct.
- Dr. Snider reported CDC's close work with the FDA on this. ACIP needs to be ready, since much public sector activity rests on ACIP approval. They have discussed how FDA could share the necessary proprietary corporate information with the committee and workgroup members. One solution may be by appointing them as special government employees.
- Dr. Neuzil asked, if FDA approves LAIV for children and adults, how the recommendations will be linked, and how ACIP should address LAIV in an adult population. Dr. Snider reported discussions with FDA about off-label use, on which CDC does not wish to recommend in the absence of supporting data.

Dr. Paul Mendelman of Aviron reported that the indication submitted in the license application is for healthy children age ≥1 year and adults. They also included a small amount of data for certain populations that may be at high risk (e.g., showing it to be safe and tolerated in a subset of 50 adult HIV asymptomatic patients; in 48 children with asthma and another, larger subset of Texas children [18 months-18 years] with asthma); and an NIH study of mildly- or asymptomatic HIV-infected children and adults.

Smallpox Vaccination Recommendations

Dr. Helms introduced this topic for the Bioterrorism Workgroup. The group has worked for over a year on anthrax vaccinations and recommendations, which were approved and published. On this day, they presented the final draft of the vaccinia vaccine recommendation.

Dr. Lisa Rotz presented the changes to the 1991 recommendation, made since the last June/July 2000 draft.

Vaccine efficacy: Prevalence data suggest a high level of protection by smallpox vaccine for five years from primary vaccination. The protection remains substantial, although decreasing, for up to ten years, and more than one dose or a booster dose provides antibody protection for longer than 10 years. She outlined the relevant studies:

- A 1977 study showed >95% of those successfully vaccinated the first time have a neutralizing antibody of ≥1:10 for up to five years; 10 years with a booster; and to 30 years in those with ≥3 vaccinations.
- Since 1991, there is more information on poxviruses that are used as vaccine vectors. Some are not infectious to humans, and some are associated with specific species that are unaffected by the protection induced by vaccinia vaccine and therefore would receive no vaccine benefit.

The new recommendation for non-emergency or non-bioterrorism-related use of the vaccine advises: 1) vaccinations are required for laboratorians who handle cultures/animals contaminated/infected with the potent vaccinia or other orthopoxvirus strains that infect humans (the highly attenuated strains not requiring vaccination are listed); 2) vaccination is also offered but not required for health care workers handling dressings contaminated with the lesser-attenuated strains (a low infection risk); 3) vaccination is not required for workers who handle only four highly attenuated strains (MVA, TROVAC, NYVAC, ALVAC) that do not replicate in mammalian cells or cause clinical infections.

The statement for *routine, non-emergency use of vaccine* still calls for routine revaccination of affected laboratorians every ten years, but now specifies for which types of viruses, and recommends consideration of vaccination every three years or more for those working with more virulent strains such as monkey pox virus. 2) The precautions and contraindications for routine or non-emergency use of the vaccine are essentially the same as in 1991, but specify that it is not to be used in children and

includes two tables for emergency and non-emergency vaccination, as well as information on relevant immunosuppressive conditions.

Treatment of complications: 1) addresses the currently limited vaccinia immune globulin supply and recommends it be reserved for treatment of severe complications; 2) an added table of adverse effects advises whether vaccinia would be helpful; and 3) a statement was added on contraindication to VIG use in cases of vaccinial keratitis.

New text in the 2001 recommendations includes:

1. A section discussing other *treatment options for treatment complications* cites currently insufficient information and encourages the physician to call CDC for additional information.

2. *Prevention of contact transmission* (page 9): emphasizes careful handling to prevent autoinoculation. It provides procedures for careful hand washing/infection control if the vaccination site is covered or not covered, general guidance on keeping the site dry, and on disposal of contaminated materials.

3. *Restrictions on health care workers* advise avoidance of contact with unvaccinated or immunodeficient patients until the infectiousness of the vaccine site subsides. If contact is unavoidable, wearing a more occlusive dressing is advised. More specific recommendations that were previously dropped on site, method, and evaluation of vaccination site were also added back in to provide sufficient guidance for non-emergency and emergency situations.

4. *The use of smallpox vaccine in bioterrorism preparedness.* An introduction explains why this was included, as were surveillance guidelines for reporting suspected cases and quick reference by the clinician. Prevaccination is not recommended, but may be indicated in the future for those potentially at higher risk if the risk of smallpox release increases. Post-release vaccination is directed to those at higher risk of exposure, such as contacts and response teams to a public health emergency who are potentially at high risk of virus contact (e.g., police, EMTs, hospital workers) and who have no contraindications. Those with contraindications should be reassigned for duty elsewhere.

5. In an emergency release situation, those at high risk are listed, and specific text addresses those without contraindications whose “unhindered function is essential to response.” Evaluation is advised of the risk of aerosol spread in hospital settings, and when the level of exposure is unclear.

6. *Additional post-release guidance* is listed for a) personnel at risk and without contraindication to vaccination (those with contraindications are transferred); b) directing first selection for patient contact of those previously vaccinated (who are likely to have a quicker rise in antibody titers); c) that smallpox vaccine may

be effective even 2-3 days after vaccination and d) the advisability of taking respiratory precautions and using removable personal protective clothing.

7. A statement on the prophylactic use of VIG cites the currently insufficient sources of VIG and supports its reservation for complications that are considered severe and life threatening. The section on infection control measures outlines procedures on respiratory isolation, vaccination of all in/out of facility; ensuring public health input to prevent disease spread in hospital and non-hospital isolation, and stresses surveillance of contacts during the incubation period.

8. The research agenda is outlined: development of a new vaccinia vaccine (to augment the current supply) and its evaluation for safety and efficacy; and with the VIG shortage, research on alternative methods of treatment, including antivirals, animal models and immunoassays for evaluation.

In discussion, the committee offered the following comments:

- The Workgroup was thanked for a thorough, thoughtful review of an important document. Dr. Rotz confirmed upon question that additional vaccine is being manufactured.

- Dr. Tompkins: Include photographs of smallpox lesions to aid first care facilities such as emergency rooms to identify disease. Dr. Helms: explore connection of the CDC Bioterrorism Website's excellent slide collection to such sites for speedy access. Dr. Rotz reported CDC's development of a video on smallpox vaccination.

- Dr. Siegel: This document should be included in institutions' bioterrorism plan. It should address recommendations regarding respiratory precautions and hygiene products for handwashing.

- Dr. Zimmerman: on page 6, clarify "some history of eczema" to avoid over-interpretation, since most physicians will have some hydrotic eczema. But in the absence of severity data post-vaccination among those who previously had eczema, this may have to be left to a physician-patient risk-benefit discussion.

- Dr. Deseda asked about risk of prion contamination from bovine derivatives, but Dr. Midthun responded that this is of most concern from pre-1980 product.

- Dr. Diniega: Add in the anthrax statement's sentence on its use in pre-release situations, including military populations.

- Dr. Katz: Altered cellular immune deficiencies or immunodeficiencies should be cited, not agammaglobulinemia The latter text was drawn from the 1991 Red Book, but that text was partly based on work done before humoral or cellular immunity was distinguished to delineate cellular versus antibody response.

- Dr. Modlin: Since this is an educational document, provide more information on the data regarding the efficacy of VIG.

Dr. Tompkins moved to accept the smallpox document as presented by the Workgroup. The motion was seconded by Dr. Brooks. There were no conflicts of interest possible, since the vaccine is not yet manufactured.

Vote: In favor: Drs. Deseda, Johnson, Levin, Smith, Offit, Rennels, Tompkins, Helms, Word, Clover, Brooks, Modlin. None were opposed and none abstained. **The vote passed.**

Update on Tetanus/Diphtheria Vaccines

Dr. Melinda Wharton introduced the updates of the tetanus/diphtheria vaccine supply status to the committee. **Mr. Mason** began, discussing the present supply status, what caused it, and predicted future stores.

Wyeth-Lederle announced in December 2000 their decision to withdraw entirely from the DTaP, Td, tetanus toxoid, and DT pediatric markets. They were a major supplier of Td and tetanus toxoid, with a 32% market share in 1999 and 19% in 2000. Aside from Wyeth, the two largest contracts with CDC for DTaP vaccine in the last several years have been with Aventis Pasteur and Glaxo-SmithKline. Baxter Hyland contracted with CDC in 1998 to produce DTaP, but neither they nor Wyeth-Lederle (WL) have supplied vaccine since June 2000 due to production problems and thimerosal issues. That equates to about 20-24% of the total CDC market, not counting the private sector.

Historically, annual DTAP vaccine purchases through CDC's contracts have ranged from 8.3 million doses in 1997 to 11.1 million doses in 1999. Manufacturers are required to deliver within 15 days of order receipt. The DTAP shortage is intensifying. Currently, CDC has 30 projects with DTAP vaccine back orders that are >30 days overdue (345,000 doses); 19 projects with back orders >14 days (211,000 doses); and 15 projects with back orders <14 days (653,000). As of February 6, 2001, six projects had DTAP inventories of <7 days in central vaccine depots; 14 projects have <14 days of supply; 26 projects <30 days' supply; 15 have <60 days of supply; and 5 projects have <90 days' inventory. CDC will monitor vaccine distribution to ensure that it is equitable.

In 1997, 8.3 million doses of DTAP vaccine was purchased through CDC's contracts. With the addition of private purchasers' 6.8 million doses, the total market equaled 15-20 million doses. The 1999 market total of 20.4 million doses fell to 16.6 million doses in 2000, perhaps due to some under-reporting. The two vaccine manufacturers for 2001 (GK. and Av-P) estimate a production ability of 21-25 million doses. However, the need to catch up with low inventory means that the supply may not be adequate for several months. While the supply should be caught up by end of the year, there is a potential for spot shortages over the next several months.

Biological Surveillance System data on the national distribution of all diphtheria- and tetanus-containing products (except DTAP) between 1997-2000 showed a precipitous decline from 24.7 million to 15.7 million doses in the last four years. Td supply showed a steady decline from 15.3 million doses in 1997 to 12.7 million in 2000, reflecting the increasing pressure on the now sole-source national manufacturer.

Only Aventis Pasteur and Glaxo-SmithKline now produce DTAP vaccine. Av-P is now the sole manufacturer of DTAP-Hib, td, DT pediatric and tetanus toxoid. The University of Massachusetts Medical School produces some Td, mostly for state residents. CDC hopes they will expand production in response to the Td national shortage. CDC has not had a contract for Td for several years. Av-P has chosen not to offer a contract price for CDC because of the Vaccines for Children (VFC) program's price caps. For DTAP, only a few instances of supply disruption have been reported to date.

To address the TD shortage, Av-P is screening all Td orders and prioritizing shipments to hospitals, trauma centers, etc. The amounts shipped are limited to 50 doses, and Av-P maintains a 24-hour hotline. CDC recommended that all states instruct their health care providers to limit vaccine/toxoid inventory to a 30-day supply and to limit state depot inventories to a <45-day supply. CDC will continue to monitor state orders for DTAP and allocate vaccine if necessary. DTAP supply issues are expected to remain through most of 2001, but should improve in the latter part of the year. Over the next 10-14 months, the Td shortages will probably remain. The ACIP will consider recommendations that might reduce product demand.

The committee's discussion included the following:

- Dr. Offit asked if any manufacturer is likely to re-enter the market, and the effect on pricing. Mr. Mason reported that negotiations are underway on a new consolidated contract to begin on April 1, but only two manufacturers will be producing for 2001-2002.
- Dr. Smith asked about DTAP disposition in the private sector, specifically about stockpiling. Mr. Mason responded that it is the manufacturer's policy to try and apportion between the public and private sectors and to respond to individual circumstances.
- The manufacturers updated the committee:
  - *Glaxo SmithKline.* Dr. Howe reported that GSK's DTAP situation remains unchanged. They cannot supply the entire U.S. market with the 5-dose whole series, but they can provide the primary three-dose series. They are committed to the DTAP supply in U.S.; that will be the cornerstone of their pediatric combinations in the U.S. GSK also has adult reduced-antigen Td and DT products licensed outside the U.S. and are actively developing the reduced-antigen DT pertussis-containing vaccine for adult use. It parallels the product studied in the NIH-sponsored efficacy trial,
  - *Aventis Pasteur.* Dr. Phil Hosbach clarified that Aventis Pasteur is working with FDA to release vaccine lots as quickly as possible to compensate for the marketplace shortfalls. Among the issues and

remedies, he advised: 1) not underestimating the thimerosal factor in eliminating one manufacturer; 2) decisions are needed about where to focus the limited supply of tetanus toxoid, a major component of Tripedia® and Td. They hope to resolve this and concentrate on one version of Tripedia.® In addition, 3) they are adjusting production to move to the single-dose DTAP; and 4) in the longer term, FDA is now considering Av-P's request to introduce a five-component vaccine now marketed in Canada. Since the T and D components are produced in Canada, that will relieve the supply demand here and free it for adolescent and adult Td vaccines. AvP is also working with CDC to identify areas of need in public health, and are trying to maintain a 60/40 split of DTAP vaccine between the public and private sector, respectively. If Aventis Pasteur cannot fill the order, they will refer inquiries to their competitors.

They plan to produce 13.9 million doses of Td. They are managing the supply, limiting customer supply, and drop-shipping to keep control of the product due to the shortage. By year's end, they will have implemented production plans to have 20 million doses available to meet the pipeline and stockpile needs. In the meantime, they have sent a letter to all hospitals with a toll-free vaccine number for emergency requests that will be addressed 24 hours a day/7 days a week.

- *Baxter-Hyland:* Dr. Walter Lee reported that he was present to understand the implications and ACIP's considerations in planning their production of DTAP products. Baxter-Hyland will not be supplying the DTAP combination vaccines. When asked, he stated that thimerosal was not the main issue that led to this business decision. They are considering several factors to re-enter the market for a DTAP combination, including what the American market will require in terms of recommendations and other technical factors. They will update ACIP in future about their plans.

Update on the Td Shortage/Potential DTAP Shortage

Td Shortage. Dr. Lynn Zanardi reviewed the priorities for use of Td in case of a shortage which were published in the November 2000 *MMWR:* 1) use in travelers to countries where the risk of diphtheria is high; 2) use as prophylaxis and in wound management; 3) completion of the primary series for adults who had no full primary series; 4) a booster dose for pregnant women and persons with occupational risks of tetanus; 5) the adolescent booster; and finally, 6) the adult booster.

Wyeth-Lederle's removal from the market leaves Aventis Pasteur as the sole producer and leaves the shortage unresolved. Due to the length of time required to make tetanus toxoid, the shortage is expected to remain through 2001. Surveillance indicates no evidence of increased disease, particularly of tetanus, but there are reporting delays.

The actions taken have been to continue prioritization. Av-P is directing doses to Emergency Rooms and Trauma Units, and the calls to CDC for tetanus vaccine are

forwarded to the Av-P number. This seems sufficient, as they have not called back. CDC will continue review of reported diphtheria and tetanus cases.

DTaP Shortage. Subsequently, Dr. Kris Bisgard requested ACIP guidance on prioritization should the shortage continue: 1) should doses 1-3 be prioritized for the optimal protection of infants; 2) should DTAP dose #4 be suspended or deferred; and 3) should DTAP dose #5 be suspected or deferred? The recommendations issued for the DTP shortage of 1985 were to prioritize the infant's primary three-dose and to defer doses #4 and #5 until supplies were adequate. They also recommended not administering partial doses of DTP; not substituting DT for DTP among children aged 18-months and 4-6 years; and recalling children for normal doses when supplies were replenished. Provisional enrollment for school attendance was recommended.

A level of 0.1 international units per ml (IU/ml) of diphtheria antitoxin is needed for protection against diphtheria. The data from a multi-center acellular pertussis vaccine trial show differences in GMT and the proportion of children reaching a protective level; but about 85% of children obtained a protective level after dose #3. Another study examined two different diphtheria toxoid-containing vaccines with different schedules (2,4,6, and 15 months; 3,5, and 12 months). A booster dose (at 12 or 15 months) was needed to ensure that children obtain a protective antibody level. The level dropped again by age four. The U.S. has had few diphtheria cases since the early 1980s, but the boosters at age two and for preschool appear necessary to maintain protective levels.

From 1983-1999, pertussis incidence increased in infants <3 months, but it was stable among infants 4-11 months of age. Incidence is highest among infants, and that among children aged 1-4 years is slightly higher than that among children aged 5-9 years. Because of waning immunity, incidence in adolescents aged 12-14 years is as high as for children aged 1-4 years.

Dr. Bisgard then reviewed the efficacy of the four U.S.-licensed vaccines. Because of differences in trial design, efficacy results cannot be compared between trials. The efficacy of Infanrix® given at 2,4,6 months and followed up after 17-months was 84%, which persisted to age four. The efficacy of Certiva® (administered at 3, 5, and 12 months and followed up at 17½ months) was 71%, which rose to 77% after another 6 months of unblinded observation. The efficacy shown in the German ACEL-Immune® trials, administered in four doses at 3,5,7, and 12 months, and followed up for 25½ months (i.e., age 3½) was 85% (estimated to be 73% after dose #3). In a case-control study design, Tripedia® administered at 3,5,7 months showed an efficacy of 80%. These data suggest that the primary series is needed for protection of infants, and this protection may last for several years after the primary series.

The two options, then, are to defer or suspend dose #4 or #5. Dr. Bisgard presented the advantages and disadvantages of each:

- *Defer/Suspend Dose #4:* Pro: Doses 1-3 provide protection against pertussis and tetanus, and the youth of these children should make catch-up vaccination easier. Con: Protection is probably inadequate against diphtheria, especially for children who travel to endemic areas.
- *Defer/Suspend Dose #5:* Pro: doses 1-4 would ensure the greatest protection for young children and adequate protection against diphtheria and tetanus. Con: waning immunity to pertussis could lead to more elementary school outbreaks and catch-up vaccination may be more difficult.

Committee discussion included:

- Mr. Mason noted that suspending one of the last two doses could save about 4 million doses.

- Dr. Natalie Smith commented that changing the doses required for school entry would require a massive implementation effort. Great concern was expressed the prior week at a meeting with the state and territorial program managers. Their main message to CDC was to just decide on a course of action and to stick with it. However, the programs would implement that effort upon confirmation that the five-dose supply is inadequate.

- Dr. Abramson asked if data on the pertussis mortality and morbidity in the second year might support suspending the 18-month dose. Dr. Bisgard reported that most pertussis hospitalizations occurred in children <6 months of age and among children who received <3 doses of a pertussis-containing vaccine.

- Dr. Peter commented on the difference that in 1985 shortage, a whole-cell vaccine was used. The current acellular vaccine seems to have a longer duration of immunity.

- Dr. Orenstein observed that one vaccine's protection extends well into the second year of life, although there are issues in part of the first year. The issues of morbidity are considerably less than they were in 1985, but the first three doses are still paramount.

- Dr. Zimmerman saw this as a policy issue: suspension or deferral of dose #4 involves waiver of daycare requirements, while dose #5 involves waiver of school entry vaccination requirements. He was reluctant to remove both from the schedule.

- Dr. Peter observed that issuing guidelines now would alert the physician of what to do if a DTAP shortage were to occur, as was done in 1985. The data are also unclear of what percentage of children receive dose #4 at 12,15, and 18 months; he suspected that most do so between 15-18 months. The initial schedule of 18 months was changed only to allow doses to be administered concurrently with other vaccines, so a slight delay might be all right.

- Dr. Modlin though that deferring dose #4 to 18 months of age could be a good short-term solution for a short-term problem, and noted that schools would be called upon to help recall those children not receiving the fifth dose anyway. If a short-term DTAP shortage occurred, an *MMWR* update could be adequate; a footnote on the harmonized schedule might be needed if a lengthy DTAP shortage occurred.

- Clearly, being able to predict the length of the shortfall is critical, but the manufacturers will have an uncertain supply. A sensitive surveillance system would be needed to prompt a quick response if the shortage lasted longer. Dr. Hosbach also could not be 100% reassuring; the likely 3-6 months to substantial improvement could be delayed by production problems, which in turn seem to follow Murphy's Law in such difficult situations. The length of time to completely transfer Tripedia® to a thimerosal-free formula is also a factor.

- Given a choice, Dr. Johnson preferred to defer/delay the fourth dose since the number of health care interactions at age 2 or 3 would allow a dose catch up. Perhaps children not in daycare could also be deferred. Drs. Smith and Rennels agreed; the fourth dose still can be caught up at kindergarten. It is more unrealistic to expect schools to be able to monitor a catch-up of dose #5, and school pertussis outbreaks are of concern.
- Dr. Deseda asked, if the shortage continues, if the FDA could extend a dispensation to use a foreign vaccine. Dr. Midthun said that this could only be done if it were assigned an IND drug certification, if the vaccine was not already licensed in the U.S.

Dr. Modlin summarized the committee's consensus, if there is a need to delay vaccination, to do so at the fourth dose. He asked Dr. Wharton to provide appropriate language for the committee's consideration and vote on the next day. Dr. Orenstein added, to further consensus, that **if the shortage is more severe, dose #5 would be the next to delay, and doses 1-3 would be kept intact.** The committee will re-review the situation at its next meeting in four months.

Dr. Word asked what definition would indicate the shortage's resolution. Dr. Modlin said that the NIP would make that decision, and with ACIP and AAP/private sector advice, publish advisories for distributors/programs to act accordingly. Drs. Orenstein and Snider added that there is no hard and fast rule; CDC would consult with the FDA, manufacturers, the states, and the CDC Director, if not the DHHS Secretary. A conference call would be convened, if this occurred between regular meetings for the ACIP, to discuss and effect any changes to the policies and procedures.

Update on Thimerosal Issues

Dr. Roger Bernier, of the NIP, reported that a second thimerosal-free DTAP vaccine is expected to be approved by the first part of 2001. Since only two manufacturers make thimerosal-free vaccine and the supply is tight, the ACIP need not address whether or

not it wishes to express a vaccine preference at this time. Instead, an update on research related to thimerosal will be given. This research is motivated primarily by issues facing the compensation program and by policy makers in other countries still using thimerosal-containing vaccines in the routine pediatric schedule. Dr. Bernier asked for mention of further research known by anyone, to allow NIP to track it. He introduced two informational presentations on thimerosal-related research: an NIH study presented by Dr. Carole Heilman, and a CDC epidemiologic study presented by Dr. Gina Mootrey.

NIH Study. Dr. Carol Heilman, of the NIH/NIAID Division of Microbiology and Infectious Disease, outlined NIH's role in vaccine research and discovery. The agency's infrastructure is capable of supporting multiple Phase 1 through 4 trials and can at any time have dozens underway.

The unanswered questions related to thimerosal include: 1) whether the guidelines for methyl mercury, which are based on chronic dietary exposure, are appropriate for application to thimerosal/ethyl mercury injected intramuscularly, and 2) whether exposure to methyl mercury and ethyl mercury results in the same levels of mercury in the brain, which is the primary concern about thimerosal.

To answer those, an NIH Vaccine Testing and Evaluation Unit (VTEU) conducted a study of two populations, human and then animal. The study collaborators were outlined. The studies compared mercury levels in the serum and urine of children receiving routine immunizations, one group with vaccines containing thimerosal and the other receiving thimerosal-free vaccine. The cohort included 63 full-term infants, 40 of whom had routine immunizations with thimerosal-containing vaccines, and 23 at two other sites that used thimerosal-free vaccine.

Serum mercury in nanograms per milliliter (ng/ml) was measured and charted according to days post-vaccination, with the children delineated by >50 ng/ml or <50 ng/ml of total mercury. None had anywhere near the EPA or ATSDR levels of toxic effects from mercury; all were within permissible levels. A graph of the two cohorts showed no trends and no relationship between thimerosal-containing vaccine and serum mercury.

However, there were three outliers, all three months of age and all receiving 30µg of thimerosal-containing vaccine. No temporal relationship was shown relating to when the vaccine was received; the only potential relationship was that two of the three had maternal hair levels at 2 parts per billion (ppb). The average person has 4 ppm in hair. The child of another mother with >1 ppb of mercury in hair, had <1.5 ppb.

This led back to the first question of whether there is any relationship between methyl mercury toxicity and thimerosal. Dr. Heilman outlined five animal model studies of thimerosal in macaques and mice which will be conducted in partnership with the NIEHS.

The macaque study seeks to: 1) determine the peak blood and brain levels of mercury in juvenile macaques after weekly exposure to injections of 50 µg/kg/day of thimerosal plus infant vaccines, versus 50 µg/kg orally of methyl mercury. Then, the 2,4,6-month scheduled will be followed in infant macaques. The mouse study will compare tissue distribution levels of mercury after escalated doses of thimerosal, ethyl mercury, or methyl mercury.

In discussion, it was noted that aside from 63 infants with no toxic levels, the maximum levels in controls receiving no thimerosal were ≤1.5 ng/ml, and there were no patterns in the urine measurements. All the mothers' hair levels were measured down to about 0.1 ppb. However, this was not a definitive study; the small cohort size was only to demonstrate what to look for in animal studies.

CDC Epidemiologic Thimerosal Cohort Study. Dr. Gina Mootrey reported the development of the protocol for CDC's epidemiologic thimerosal cohort study. In June 2000, the NIP convened a panel of external consultants to review NIP's data analysis results from the Vaccine Safety Datalink (VSD) project. The VSD analysis examined the potential association between infant exposure to thimerosal-containing vaccines and selected neurodevelopmental disorders and renal effects. The analysis found an association between cumulative exposure at different months during infancy with unspecified developmental delay, tics, speech and language delay, and ADHD. They also explored several other conditions, including autism, and found no association.

However, the limitations of the analysis include: 1) a potential ascertainment bias or confounding related to health care-seeking behavior (those more likely to have been vaccinated could also have been those more likely to seek health care); 2) a limited meaning or significance of exposure (due to little data from which to extrapolate methyl- to ethyl mercury exposure effects); 3) concerns about the inexactness of neurodevelopmental diagnoses (ICD-9, and inconsistent diagnoses across clinicians, clinics, and HMO sites); 4) lack of data on familial/genetic predisposition to neurodevelopmental outcomes; and 5) a limited ability to distinguish between risks attributed to thimerosal versus those from other vaccines or vaccine components.

The consultants found that the statistical association was weak. The VSD results offer inadequate evidence to either support or refute a causal relationship. However, they also felt that this study posed broad implications that warrant further investigation (analysis of similar datasets at a third HMO site, Harvard Pilgrim, was done and presented to ACIP), as well as the conduct of epidemiologic studies designed to control *a priori* for potential biases, to better define and ensure quality of diagnosis, and to collect data on other factors.

A new study was designed to attempt to validate the previous VSD results, to overcome the potential health care-seeking bias, and to measure specific neuropsychological functions and status by testing individual children. The previous study evaluated the automated diagnostic data. The challenges to this study include: 1) defining accurate

and appropriate exposure groups; 2) defining sensitive, specific, and consistent outcome measures; and 3) identifying feasible study sites.

The exposure considerations include identifying the critical timing of exposure, exposure levels, and identifying and controlling for confounders (e.g., child/family medical history, birth weight, SES, home environment, maternal IQ and maternal prenatal behaviors such as alcohol consumption and tobacco use). The neuropsychological outcomes considered will be psychological disorders (ADHD), language/speech delays; other unspecified developmental delays; intelligence; achievement; child behavior; memory; visual motor functioning and motor skills.

The selected study site(s) will need to provide a sufficiently large cohort of eligible children who have good records of vaccine lot/manufacturer and vaccine administration. Similar vaccination policies and health care services will be offered. The selection criteria call for a random sample stratified by age, sex, health care site and thimerosal exposure, and for children aged 6-8 years. That age was selected because it is the critical period when school placement and the need for special age services are decided. There are suitable neuropsychological tests which can be done by most children this age.

The time line for protocol development was outlined, from literature review and expert consultation by mid-March 2001, to identification of the study contractor, protocol submission to IRBs, development of standardized data collection tools, and commencement of the study after April 15, 2001.

Committee discussion included:

1. Dr. France: Few children born within an HMO will still be a member 6-8 years later, challenging information on vaccine lot numbers, etc. Dr. Mootrey agreed, but a younger cohort makes test administration harder. This is one reason the study is considering different populations to seek available data.

2. Ms. Redwood: Also include a question of whether the mother was exposed to RhoGam as well as thimerosal in pregnancy. That could be important, related to the Rh-negative status of 7% of the population.

3. Dr. Halsey commended the effort, but noted that neither approach considers the background level of exposure among women, which varies considerably geographically. EPA estimates that 7% of women exceed the EPA's recommended background level of methyl mercury. Dr. Heilman's presentation also did not address the additive effect of ethyl mercury exposure above that exceeded level of methyl mercury. Dr. Mootrey reported a questionnaire component on fish consumption of methyl mercury to attempt to address that. Dr. Heilman added that such considerations could be included in the as-yet incomplete protocols for the second and third studies.

4. Dr. Paradiso noted that the Harvard Pilgrim data did not confirm the VSD data, and in some aspects were quite divergent. Dr. Mootrey responded that as the third VSD site, Harvard Pilgrim could be part of the study.

5. Dr. Modlin encouraged going beyond the obvious HMO databases to find stable populations and good records, such contacting the PROs' practitioners.

6. Dr. Mahoney suggested a military population as a possible cohort to control for the potential medical care-seeking bias raised by peer reviewers.

Polio Outbreak in Hispaniola

Dr. Roland Sutter (NIP) introduced the topic; and the Director of PAHO's Division of Vaccines and Immunizations, Dr. Ciro deQuadros, presented data on a vaccine-derived (Sabin) poliomyelitis outbreak in Haiti and the Dominican Republic (Hispaniola). The last polio case documented in the Dominican Republic occurred in 1985, and that in Haiti was in 1989. The last case in the Americas was in Peru in 1991, and in 1995 the Americas were certified by the WHO as an area of no indigenous polio.

Between 1983-1993 in the Dominican Republic, 16.1 million oral polio vaccine doses were distributed, for a coverage of about 80%, but that dropped in 1991-92 and 1998-99. The last reported case was in 1985. Haiti, however, is different, with very low coverage (<50%) in most of its districts. Surveillance has deteriorated in the two countries. However, some surveillance indicators collected from notification sites reporting weekly showed a 10-20% rise in the detection of enterovirus isolates (except from 1995 to 1997).

An intensive national immunization campaign in the Dominican Republic last December vaccinated >1 million children aged 1-5 years. The present outbreak there began in July 2000 and extended to the end of January 2001. They now have found 17 isolates of the derived virus but only 12 confirmed cases of acute flaccid paralysis. Nine of these were presented by the case patient and three cases were confirmed from virus isolated from close contacts. About 18-19 cases are pending investigation. The rates were charted by age group, showing most occurring in children aged 4 years, most of whom were unvaccinated.

In Haiti, with coverage now at <30%, an immunization campaign is underway. So far, only one polio isolate has been found (in August 2000, in the only child in a village who was not vaccinated), but determination of three other cases is still pending. After the single case was discovered, an intensive search was done for others. Although AFP cases were found, most had negative specimens, and no additional case so far has been documented in Haiti.

Response activities include an active search for cases in both countries, and environmental sampling done with CDC in both countries that is now in lab analysis. The Dominican Republic conducted a second mass campaign in February 2001 (1.1

million vaccinated) and another will be done in April. Haiti's current campaign, which began in January, is hampered by heavy rains and the changing political climate.

CDC is doing genomic sequencing of the outbreak strains and reviewing Sabin isolates gathered from 1994-2000, to see if this is a new strain or one that was undetected earlier. An active search for virus is being done in high-risk areas. The lessons learned include the need for a high level of AFP surveillance as well as a high level of OPV coverage until the research indicates that this can be dropped.

Biological Aspects of the OPV Strain Outbreak. Dr. Olen Kew, of the NCID Division of Viral and Rickettsial Diseases, reviewed the virological aspects of the outbreak. Sequencing done to determine if this was a wild or vaccine-related virus showed a 90% homology with Type 1 Sabin strain, as well as a high correlation between the two first isolates sequenced. The isolates are unrelated to wild-type IPV. This also indicated some epidemiologic link between the Dominican Republic and Haiti cases of the same summer.

A line chart of the polio virus strain types identified around the world showed a tight clustering of the three Hispaniola cases. In fact, the 85% concordance demonstrated was actually a great underestimate of the genetic distance between the Hispaniola type and the isolates from elsewhere in the world.

The interesting aspect was that these really were wild poliovirus, by any criterion other than immediate ancestry. They have sustained person-to-person transmission and a significant paralytic attack rate, and have reverted at all the critical attenuating sites sequenced so far. Their antigenic type is now non-vaccine like; they recombine with non-polio enteroviruses very much as wild polioviruses do as they circulate in the community, and they replicate at sub-optimal temperatures.

The evolutionary rate of Type 1 poliovirus is estimated to be 3% per year, which allowed calculation of the estimated origin of the Haitian isolate at around June 1998, and that of the Dominican Republic in June 1999. However, this is an unproven estimate.

Also deemed reasonable was the assumption that both the Dominican and Haitian lineages are similar to the rates of other circulating polioviruses. The Haitian isolate has a recombinant crossover site that greatly influences the attenuated phenotype, and the isolate's embedded nonstructural protein sequence was determined to be that of a non-polio enterovirus (NPEV). That characteristic was shared by the Dominican Republic's NPEV, along with its own distinct NPEV. This type of divergence has been seen before, in Egyptian and Chinese isolates.

Surveillance for circulating vaccine-derived polioviruses found no divergent isolates up to 1997, but none from Hispaniola could be procured due to the difficulties already described. Analyses of more recent PAHO isolates have shown no matches to the

Hispaniola viruses; they are >99% matched to the OPV strains. Sequencing of vaccine-derived isolates from AFP cases from all regions has now begun.

In discussion, Dr. Tompkins asked if the assumption was that the vaccine strain that reverted in July then reverted further and then went on to the Dominican Republic. Dr. Kew responded that the initial event was an OPV reversion in 1998, in a community environment with sufficiently low coverage to enable efficient transmission to the next child. The virus continued evolving with ever greater efficiency and then in 1999 split into two strains, one emerging in Haiti. There is little data on the virulence of the two strains, other than that the attack rate in the Dominican Republic was comparable to Type 1 wild virus. Additional tests of the Haitian virus being done in mice indicate that this is a hot virus.

Update on the Global Eradication of Polio. Dr. Sutter reported on the global polio eradication initiative. Recent virology data produced some unexpected findings, as just described, which have implications for the initiative.

There are now about 3000 cases annually. That is a rate not expected to increase much, and is down from 7000 last year. Only one case of Type 2 was reported in India, but since surveillance is poor in some places, this is uncertain. A huge decline in wild polio isolates was seen from 1998-2000 (1900 cases to 299), mostly focused in northern India. Most of the world is nearing the certification standard, including progress in the African region as well.

OPV Issues. The reversion in the Americas was surprising because the Type 1 strain is so attenuated. Community coverage was quite low in both countries, but more so in Haiti, making it even more puzzling as to why more cases did not occur there. The immediate implications of this reversion include: 1) the need to maintain a surveillance capacity; 2) the need for high immunization coverage; 3) the need to address polio status after certification; and 4) the need for caution even when eradication is vigorously pursued. More research is needed.

Five options for stopping vaccination were outlined: 1) stopping “cold turkey” after certification (not the safest course); 2) having a “big bang” global immunization day; 3) going from tri- to bivalent OPV, since Type 2 is nearing elimination; 4) going from OPV to IPV and then stopping vaccination; or 5) developing a “new vaccine,” not a very feasible option given the lengthy development period and safety issues.

The Dominican Republic and Haiti experiences served as a wake-up call about the need for guidance on when to stop vaccination. OPV not only causes Vaccine-Associated Paralytic Polio, but if its use is stopped after eradication, an OPV strain still can reemerge. This points up the need to coordinate cessation, to ensure containment of OPV viruses, and to ensure high OPV coverage until cessation. On the other hand, the highest immunity is felt by some to occur immediately after eradication, so the debate continues about waiting or doing something else.

IPV issues include that industrialized countries have switched to IPV. IPV use must be dominant, rather than maintaining a two-class approach of maintaining OPV use in developing countries. But IPV involves both manufacturing issues and issues of administration feasibility in developing countries. Scheduling issues include a choice of sequential or combined administration. To date, no developing country has used IPV only, so there is little information on its immunogenicity. Almost all studies using IPV in developing countries also used OPV heavily. Finally, there are questions of injection safety and of IPV use in outbreak control that will need to be addressed.

The research issues include the IPV schedules, IPV immunogenicity (humoral and mucosal); the coverage needed to limit OPV circulation in tropical countries; and the use of combined or sequential schedules of OPV and IPV until high routine coverage can be accomplished. Several WHO meetings have addressed what could be recommended for countries with sub-optimal coverage. The March 1998 meeting recommended cessation of OPV use and use of IPV when wild polio is eradicated, upon laboratory containment of polioviruses, and upon evidence that the Sabin virus will circulate only for a limited period of time. The WHO's World Health Assembly will review a paper on this in May, probably will discuss it further in 2003, and hopes to reach a conclusion in 2004.

Dr. Kew concluded with several observations, beginning with a quote from von Maltke that "In battle, no plan survives contact with the enemy." The Hispaniola outbreak may well affect the immunization cessation strategy. Even with eradication in sight, further research is needed, and the lessons learned must be quickly and evenly applied.

In discussion, the committee offered the following comments:

- There was no national sampling done in the Dominican Republic to indicate a background denominator. But 200 contacts were sampled (producing eight with the virus) and the environmental sampling done was representative of the country as a whole.

- Dr. Plotkin commented that the such virulent passage will occur as long as there is serial human passage; and where vaccination declines, the chances are maximized for any type of excreted Sabin strain to lose its attenuation and again become virulent. The prospect of furnishing 500 million doses of IPV to the developing world highlights the need for combination vaccines in the future. Including IPV therein practically eliminates its cost, and using IPV and OPV together will provide better seroconversion until OPV use is stopped, leaving the protection to IPV.

- Dr. Halsey asked if it was feasible that the viral mutations occurred over a long period in the excretions of one immunosuppressed individual, and if a common ancestor of the Haiti/Dominican Republic isolates was assured. Dr. Kew confirmed the latter as verified by multiple common sequences not of the normal attenuation reversion pathway. The first possibility raised of the involvement of

an immunodeficient child may be true; but that cannot be determined one way or the other; and it is not a necessary hypothesis.

- These recombinant viruses are readily neutralized by type-specific antibody. Although there is enormous antigenic variation for all three serotypes, the range is limited. The same kind of evolution is now being seen as in the wild poliovirus; and, once evolved from the atypical Sabin immunogenicity, they are similar to and no more dangerous than other wild polioviruses. OPV would be the preference for preventing transmission.

- In response to Dr. Modlin, Dr. Kew verified that Type 1 attenuations in VP1 were lost in the reversion, as well as changes in the nonstructural protein genes when they switched out with fresh circulating viruses. Dr. Modlin then asked if rather than the transgenic mouse model, the old-style FDA monkey model might be more appropriate, as the most conservative assay available for polio virus neurovirulence. Dr. Kew responded that the monkey test remains the gold standard for OPV, but wild polio viruses have rarely been tested for neurovirulence in characterizing them, and the fact that children are being paralyzed by these vaccine derived virus revertants proves their virulence. Finally, there already is some correlation to what is found in the mouse model.

- Dr. Fedson asked if the proposed research agenda includes social science investigation of what the developing countries want in an eradication strategy. Dr. Sutter reported that an initial research agenda was developed after Dr. Kew's first 1997 report that the vaccine-derived virus could be replicating in immunodeficient individuals. They are now defining the next 2-3 year agenda, which they hope to finalize soon. However, he doubted the social science component would be involved.

- Dr. Abramson recalled data presented in October indicating that the virus can be found in people 10 years after vaccination. He asked how stopping immunization with IPV could be done after a short period of time. Dr. Sutter responded that studies are still trying to define the likelihood of excretion from those who are immunodeficient, and whether that is likely to be seen in developing countries. However, vaccination cessation is not expected anytime soon.

- Dr. Deseda asked if the confirmed cases in the Dominican Republic were in infants and Dr. deQuadros reported them to be <5 years old. Dr. Deseda also reported several vaccination days held in Puerto Rico to try to immunize the children of illegal aliens, and their recommendation of IPV for those traveling to the Dominican Republic. Dr. deQuadros reported similar advisories issued in his country.

Dr. Phil Brunell asked if a "big bang" viral evolution occurred in light of this virus' very unusual rate of mutation. If the latter, that implies that the continued use of OPV raises the chance of this occurring again; but if evolved by serial passage in humans, OPV should be used more intensively.

Dr. Kew responded that there seems nothing different about the rate of mutation to what is seen in normal wild polioviruses; the evolution rate seems similar. He elaborated in a detailed response. First, he stated that the epidemiology cannot be separated from the virology. The only evidence that extended evolution of OPV virus occurs in person-to-person transmission is seen in areas of suboptimal vaccine coverage. 2) OPV is the most mutable virus known in nature; most mutations don't change the amino acids significantly. But the vaccine strains are adapted for replication in cell culture at about 35°, making them cold-sensitive variants with a relatively low replicative fitness in humans. The human intestine has a strong selective pressure to reverse those attenuating mutations, which reduces the overall replicative fitness of the virus. But what is excreted by normal healthy vaccinees are revertant viruses.

Types 2 and 3 have increased replicative fitness, and Type 3 has very high neurovirulence. It is suspected that transmissability is also increased. The Type 1 reversion process is slower, and additional mutations tend to stabilize the attenuated phenotype. 3) That brings us back to the environment of the reversion. Careful studies in the U.S., Cuba, and even in India, show little evidence of person-to-person transmission of Sabin strains. But conditions in areas of low vaccine coverage are such that the virus excreted has higher replicative fitness and may infect another individual, providing the potential for repassage and continuing evolutionary selection for even higher replicative fitness. That eventually produces very high neurovirulence in a virus that has essentially recovered all the properties of the wild virus. This is expected to occur most readily in Type 2, but now has occurred in Type 1.

Dose Reduction of IPV

Dr. Modlin reminded the ACIP that Dr. Chin Le had urged them to reexamine the basis of the need for the ACIP's dose recommendations in the immunization schedule. A Dose Reduction Workgroup under Dr. Reynolds has examined this issue in several of the antigens used.

Dr. Paul Offit reported the Workgroup's membership, and its exploration of the question of whether the eIPV immunization series could be reduced from four to three doses. This was delineated to three sub-questions: 1) do three doses of IPV induce adequate levels of circulating, virus-specific antibodies; 2) are antibody responses induced after three doses of eIPV long-lived; and 3) do three doses of eIPV induce long-lived, virus-specific memory responses?

1) *Do three doses of IPV induce adequate levels of circulating, virus-specific antibodies?* Dr. Offit outlined three studies[3] conducted in New York and Maryland of cohorts ranging from 65-300 participants. The top range of the eIPV formulation examined mirrored that used today. The poliovirus was grown in VERO (monkey) cells, and eIPV was administered at 2,4, and 12-20 months of age. Blood sera were collected 1-2 months after each dose. After doses #2 and #3, 99-100% of the children seroconverted. He also outlined Dr. Modlin's Baltimore study[4] of the same eIPV formulation, with poliovirus grown in MRC-5 (human diploid lung cells), with eIPV administered at 2,4,15 months and sera collected two months after dose #2 and three months after dose #3. The seroconversion was lower after dose 2. Dr. Patriarca has also indicated that Type 3 virus grown in MRC-5 cells may produce a lower immune response, as compared to the VERO cell-derived viruses.

Those studies indicate that: 1) 99-100% of children developed circulating antibodies after three doses of eIPV; 2) the studies provided two doses in the first year and a third dose in the second year of life; and 3) there is some question about the differences in vaccines prepared in MRC-5 and VERO cells.

2. Are antibody responses induced after three doses of eIPV long-lived? The best study to answer this would be one performed in a country without circulating poliovirus, which examines poliovirus-specific antibody responses found 15-20 years after three doses of IPV. Such a study does not exist. So, the Workgroup looked at Swedish and French studies[5] which found that poliovirus-specific antibody responses were long-lived 20 years after four and five doses of IPV, respectively. However, while that is encouraging, there are no data are available on the capacity of three doses of eIPV given within 2-5 years of age to induce long-lived, virus-specific circulating antibody responses.

3. *Do three doses of eIPV induce long-lived, virus-specific memory responses?* The rationale behind the importance of poliovirus-specific memory responses is that the incubation period for polio-induced CNS disease is fairly long (7-30 days). A long incubation period could allow adequate time for active differentiation of memory B cells to antibody-producing B cells (which requires 3-5 days) and protect against disease.

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[3] McBean, A.M., et al, *Rev.Infect.Dis.6:S552-S555; 1984;* McBean, A.M., et al, *Am J. Epidemikol.* 128-615-628, 1988; Faden, H., et al, *J. infect. Dis.* 162:1291-1297, 1990.

[4]Modlin, J.F., et cal. *J. Infect.Dis.* 175:S228-S234, 1997.

[5] Bottiger, M *Vaccine* 8:443-445, 1990; Vidor, E., et al. *Pediatr. Infec. Dis. J.* 16:312-322, 1997

Two studies[6] of virus-specific memory response were outlined. In the first, children were immunized with eIPV at 2,4, and 18 months of age. They produce anamnestic responses to OPV given at 5 years of age, with anamnestic response defined as high-titered response that is significantly greater than that found after the first two doses. In the second, children immunized at the same ages produced anamnestic responses to OPV given at 5 years of age, with the anamnestic response defined as high-titered response that is significantly greater than that found at 4 years of age. However, again, there are no data available on the capacity of three doses of eIPV given within 2 or 5 years of age to induce long-lived, virus-specific memory B cell responses.

The Workgroup did not recommend a switch from a 4-dose to a 3-dose series of eIPV, based on the following conclusions:

1. Three doses of eIPV (with the third dose given between 12-20 months of age) induce adequate levels of circulating, virus-specific antibodies.
2. Studies in Sweden and France show that circulating antibodies persist into adulthood after 4 or 5 doses in childhood.
3. Two or three doses of eIPV appear to prime for a memory response.
4. However, no country has experience with only three doses of eIPV.
5. An eIPV-only schedule has just been introduced in the U.S. Some physicians give the first three doses by 6 months of age, so if the fourth dose is dropped, some children may only get a priming series. Antibody responses decline after priming doses.
6. Neurovirulent poliovirus has been reintroduced into the Western hemisphere.
7. The advent of combination vaccines makes it preferable to give three doses within the first year of life. Doses given beyond the first year of life are likely to be important in the induction of memory responses.
8. If a three-dose schedule is recommended by ACIP, some children may only get two doses, which is likely to be inadequate.

The committee's discussion included Dr. Zimmerman's comment that, with global eradication, the data on eIPV in a four-dose series should be collected for the next 5-10 years to study the duration of immunity of the three-dose series, and to explore the possibility of dropping the fourth dose.

Dr. Bob Chen reported the February 2001 *American Journal of Epidemiology*'s report on the Dutch serostudy of a five-dose eIPV schedule. They found that the general population's seroprevalence for Type 1 was 96%; 93% for Type 2; and 89% for Type 3. In the Dutch Orthodox Reformed group, the seroprevalence was 65%, 59%, and 69% respectively. This raises the issue that even with a 5-dose eIPV schedule, Type 3 immunity will be borderline, even among Holland's 97% coverage rate.

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[6] Murdin, A., et al *Vaccine* 14:735-746, 1996.' Faden, H., *J.Infect.Dix* 168:25-28, 1993; and Faden, H., et al, *J.Infect.Dix* 168:452-454, 1993

OPV Stockpile in the U.S.

Dr. Joanne Cono of the NIP, reviewed the CDC's process of establishing an OPV stockpile to address any event of a polio outbreak in the U.S. She reviewed the U.S. polio immunization policies, which moved in January 1997 from all-OPV vaccination schedule to an IPV/OPV schedule, and then in January 2000 to an all-IPV schedule. By November 2000, OPV was not produced and no longer available in the U.S., and the OPV stores' shelf-life had expired. However, an OPV stockpile remains necessary as the vaccine of choice for mass vaccination to control polio outbreaks. OPV also offers higher seroconversion after one dose and greater intestinal immunity than IPV, and provides the beneficial secondary spread of vaccine virus.

The U.S. does not seem to be at risk of a polio outbreak, with high vaccination coverage. The NIS survey indicates that parents of only 1.9-3.1% of children reported no polio vaccination of their child by 19-35 months of age. The Western Hemisphere was also certified as free of wild poliovirus by 1994. But there are pockets of under-vaccination in the U.S. due to religious or philosophic beliefs, or among immigrants or other refugees who may lack health care access. Neurovirulent poliovirus has reemerged in Hispaniola, less than 70 miles from Puerto Rico and with frequent travel between each by boat/plane and weekly immigration of several hundred persons to Puerto Rico each week.

The possible OPV sources for use in a stockpile are the former U.S. manufacturer, Wyeth-Lederle (Orimune®) and perhaps Glaxo SmithKline. Orimune® is no longer produced in the U.S., but about 850,000 expired doses are in storage at Wyeth Lederle. FDA's preliminary testing indicates that it may meet minimum U.S. potency requirements. Further testing is being done. If potent, it could be an interim stockpile and used under an IND protocol (due to its expired status).

Glaxo SmithKline was the only respondent to a CDC solicitation for OPV manufacturers. Several GSK products are under consideration, but they are not produced or licensed in the U.S. They too would be used under an IND certification.

Committee discussion included the following:

- Dr. Plotkin asked if the RFP requested tri- or monovalent vaccine. Dr. Cono reported the original request for trivalent vaccine. Dr. Orenstein reported that WHO has considered using monovalent stockpiles after eradication, but to procure a licensed vaccine available for use in a large number of people, trivalent vaccine was selected. Both mono- and bivalent vaccines involve some concerns.
- The committee discussed possible alternative methods than an FDA IND certification for use of non-U.S. licensed products. Dr. Snider reported some discussion of whether the President could suspend current rules under an Executive Order. Clearly, high-level government action would be required, which is of concern to those addressing bioterrorism and other emergency events. Potential problems include unapproved diagnostic tests or drugs not approved

for off-label use. The bioterrorism activity is exploring ways to address these issues without literally requiring an act of Congress or Presidential order.

Public comment was solicited. Dr. Lazlo Palkonway suggested as a model the Canadian regulatory agency's Special Access Program, which allows circumvention of the rules when there is a lack of licensed product. Even with that, he acknowledged that they have their own problems in addressing an outbreak.

FEBRUARY 22, 2001

Hib Dose Optimization Workgroup Report

Dr. Dennis A. Brooks provided the second half of the Dose Optimization Workgroup Report, on Hib vaccine dose optimization. He outlined the composition of the Workgroup, which addressed the possibility of decreasing the number of doses of PRP-T or HbOC from four to three, considering both immunogenicity and efficacy. They examined two models, the Scandinavian model of a two-dose primary series with a booster, and the U.K. model of a three-dose primary series without a booster.

The three Hib vaccines used in the U.S. are Merck's PRP-OMP (PedvaxHib®), Wyeth-Lederle's HbOC (HIBtiter®), and Aventis-Pasteur's PRP-T (ActHib®). The focus was on the last two, since PedvaxHib® has a two-dose booster.

The immune responses to PRP-T and HbOC were charted, demonstrating a similar pattern: minimal to no response after dose #1, a limited response after dose #2, and a good response after dose #3. All the conjugated vaccines were efficacious in protecting against Hib . But overall efficacy could be affected by the burden of disease in the population, age of disease onset, and immune response to the first and second doses. The results of several prelicensure studies of Hib vaccines used in infants demonstrated an efficacy range from a 35% outlier among Alaskans after three doses of PRP-D (probably due to high disease burden and early onset of disease) to 100% in the U.S. after HbOC.

The Scandinavian model is a two-dose primary series with a booster. That area has a lower burden of disease than the U.S. as well as a later onset. Data of studies from Finland, Sweden, Norway, and Denmark were outlined. They demonstrated a high effectiveness of $\geq$95% for meningitis three years after vaccination and effectiveness of 75-100% for all Hib disease by 1996 in the three counties with available data. However, the U.S. has no experience with this schedule.

The U.K. experience was of Hib vaccine introduced in1992. They currently use PRP-T at 2,3,4 months of age, and no booster dose is given in the second year of life. The pre-vaccine Hib disease incidence was 23.8 cases per 100,000 in 1991-1992; post-vaccine incidence was 1.8 cases/100,000. As of 1995, the overall estimated efficacy of three doses of PRP-T in U.K. children aged 5 months to 3 years was 98.5%. That among children 24-35 months of age was 94.7%. Available data indicate a decrease in

efficacy in older children (2-3 years old) after the three-dose primary series with PRP-T without a booster.

The Workgroup's conclusions were that:

- PRP-T and HbOC are poorly immunogenic after a two-dose primary series in U.S. children and thus may not provide sufficient protection.

- A two-dose primary series at 3 and 5 months of age followed by a toddler booster is effective in Scandinavian infants.

- However, the effectiveness of the Scandinavian model should not be extrapolated to U.S. populations due to potential differences in the age of risk onset, unknown differences in the circulation of Hib, and potential genetic differences.

- Therefore, the data are inadequate to support reduction of PRP-T or HbOC from four doses to three among U.S. children.

The committee's discussion included the following:

- The English data surprised Dr. Hosbach. Even without immunization, children gradually acquire Hib antibody by 4 years of age. He also recalled study of using unconjugated vaccine when the vaccine was developed. However, there are no data on the latter; and while the herd immunity of the U.K. experience is still being surveilled, its leveling has been confirmed.

- Dr. Levin asked if there are more recent incidence data than 1995 (there are not) and asked what the U.S. data are. Dr. Orenstein found the two models' efficacy to be no different in light of the overlapping confidence intervals, even though the point estimates differed. He would want to know the data since 1995, to see if tighter confidence intervals and better efficacy estimates might emerge. Dr. Trudy Murphy reported low incidence in the U.S. (1:200,000) based on passive surveillance. An attempt to get more recent data from the U.K. was unsuccessful.

- Dr. Fedson noted that the British did not change their policy. Dr. Brooks reported the Workgroup's debate of whether to accept a 3-4 point decrease in efficacy.

- Dr. Plotkin felt the need to delete Hib from upcoming combinations speaks against eliminating a dose, despite the demonstration of efficacy from two doses.

- Dr. Peter supported continuing the present policy, but pointed out that there are no data on whether the carriage rate has changed in older persons. There are similarly no data to tell if the right curve still applies in a vaccinated population. Natural boosting may no longer occur simply due to less circulation of the organism.

- Dr. Modlin summarized no strong feeling among the committee to change the policy now, although that may be revisited upon new data.

Unfinished Business: Draft Language to Address of a DTaP Shortage

Dr. Bisgard presented draft language and some data on the DTaP shortage. In the 1990s, 81% of pertussis-associated deaths were among infants aged <4 months. She presented a graph of hospitalization data indicating that 60% of children aged <6 months with pertussis are hospitalized, decreasing to a hospitalization rate of 24% in those aged 6-11 months, 17% among those aged 12-23 months, 8% among those aged 24-35 months, and 4% among those aged 3-9 years.

She requested comment on the proposed language:

"Because pertussis is most severe among infants and current available supplies of DTaP are limited, the ACIP, in consultation with other groups including the AAP and the AAFP, recommends the following to ensure the vaccine supplies are sufficient for all infants to receive the initial three-dose primary DTaP series:

- Effective immediately, all health care providers should defer administration of the first DTaP booster of the five-dose series, which is dose four, usually given between 12 and 18 months of age, until adequate supplies are available to administer all recommended doses to children.
- When adequate DTaP vaccines become available, steps should be taken to recall all children who did not receive the first DTaP booster for remedial immunization.
- In order to ensure immunity to pertussis, diphtheria, and tetanus during elementary school years, administration of a preschool booster at ages 4-6 should continue in accordance with existing ACIP recommendations."

She noted that another bullet should be added that children traveling to diphtheria-endemic areas should receive that booster, as well as children on some Indian reservations where diphtheria is endemic (e.g., in South Dakota).

Committee discussion included:

- This will be crafted and retained until it is advisable to publish it in the *MMWR* to deal with the shortage. If the problem appeared sufficient to require dropping the fifth dose, the last bullet would be changed.

- Dr. Peter suggested adding background noting the potential of a shortage but that no change in public policy is needed, to avoid perception that there is a long-term shortage.

- Dr. Abramson advised including hospitalization data if there are any. Discussion would be spurred at the AAP spring meeting if a high hospitalization rate is shown for children between the third DTaP and age 5. Consideration will be needed about which dose to eliminate. If hospitalization is low, removing the fifth dose would be advised.

- The NIS 1999 data indicate that 90% of children are immunized with dose #4 at age 12-20 months, 80% at age 12-18 months; and that the mean/median age for dose #4 was 16 months.

- The Red Book states that children <6 months of age with pertussis "often require" rather than "require" hospitalization, but it makes it clear that this is a severe disease.

- Dr. Barbara Watson noted that in Philadelphia since 1993, all pertussis cases in those aged 6-11 months and <1 year have been in under-vaccinated children with only 1-2 doses of vaccine.

- It was noted that some include the fourth dose in the primary series, suggesting an FDA reaffirmation of the primary series. Dr. Midthun stated that whether or not the fourth dose is a booster depends on the acellular vaccine considered. The SKB Infanrix® had demonstrated efficacy after 2,4,6 months that extended for several years; the Certiva® Swedish data's translation to a 2,4,6 month schedule was addressed in the bridging study of immune responses. It found that the U.S. schedule gave a significantly lower immune response than the 3, 5,12 month Swedish schedule; although adding the 15 month booster gave slightly higher response. The wording needs to remain a little fuzzy, but an accompanying Q&A document would be helpful.

Dr. Wharton stated that the staff would use this draft language and consult with the committee in the event of a need to alter it future. The staff will continue to keep the ACIP and Dr. Rennels advised, and a 1-2 paragraph Notice to Readers will be published in the *MMWR* along with a update on Td vaccine.

Updates

National Immunization Program (NIP). *Coverage.* Dr. Orenstein provided provisional data for the year 2000 for eight of the ten vaccine-preventable diseases of childhood. There are <100 cases of measles in the U.S. for the first time; there were almost 28,000 ten years ago. There is a record low for mumps as well, attributed to MMR vaccine. And although rubella is not yet at a record low, it is still very low, mostly found in young Hispanics and those new to the U.S. from countries not yet doing rubella vaccination. The rubella number may be reduced further with new data. Immunization

coverage is at record- or near-record highs that approach 90% for most VPDs. Varicella reflected an exponential rise to the mid-60% range, although some slowing occurred in the last few months.

Joint Measles Declaration. At the end of January, the Red Cross convened an historic meeting at which a joint declaration on measles was issued. This is still the greatest vaccine-preventable killer of children. The WHO estimates about 900,000K children under 5 years of age die of it annually, mostly in Africa.

The joint declaration advocated for: 1) adequate human and financial resources to reduce measles mortality throughout the world; 2) supported strategies in the Global Strategic Plan, including the recommendation to include rubella vaccine use in measles campaigns; and 3) identified ways to support the goal of the Global Alliance for Vaccines and Immunization (GAVI) to save lives through the appropriate use of vaccines. The signing organizations included the AAP, CDC, the Gates Children's Vaccine Program, the International Pediatric Association; the March of Dimes, PAHO, the Task Force for Child Survival and Development, the UN Foundation, UNICEF, USAID, and the WHO.

Budget. Major budget increases for immunization were included in the 2001 budget, including infrastructure funding for the 317 Program, which had previously been halved due to the states' large carryover. Most of the $42.5 million will likely be used for childhood immunization, but the states are being encouraged to use some for adolescent and adult immunization. Another $20 million was allocated for vaccine purchase; $5 million for global polio eradication; and $5 million for vaccine safety. The latter will support development of the Clinical Immunization Safety Assessment (CISA) Centers conduct of clinical evaluations, as well as support expansion of the Vaccine Safety Data Link.

Registries. Registries are functioning in places. The states estimate that the immunization histories of 21% of children aged <6 years reside in some population-based registry. The Healthy People 2010 goal for registries is to have 95% of those children in fully operational registries. All 50 states are developing and implementing registries. Examples of registry data use includes the Oklahoma registry's use of its data to evaluate any adverse effect from IPV on immunization (none was found). An analysis of the Oregon registry's data showed a sharp drop in hepatitis B immunization given within 5 days and 56 days of birth, with the change in recommendations and with concern over thimerosal.

Committee discussion included:

- Dr. Schaffner asked that the comparative morbidity and morality data slide include age, and consider including varicella, hep B, influenza and pneumococcal immunization. He also suggested creating another slide to reflect annual adult immunization.

- Dr. Peter asked the Congress' reaction to the IOM report "Calling the Shots" and if they would effect its recommendations. Dr. Orenstein confirmed that they have the report, and the IOM had briefed the Congress when the infrastructure funding was added. The NIP will meet with IOM's new advisory committee to examine how to begin to advance those recommendations. Three regional meetings are planned to obtain federal, state, local, and private sector input to the immunization system. There also will be more transparency in the process of awarding grants, development of clearer formulas, etc., in collaboration with ASTHO.

- Dr. Brooks asked how much of the registry funding could be used for registry maintenance. Dr. Orenstein said that the $42.5 million could be used for establishing and maintaining them, and NVAC has recommended the development of a sustained support system not now in place at the federal level. There is some potential of using state Medicaid funding to enhance registry development, but some funds will still have to come from state/local resources.

- Most registries are "home-grown," but are some guidelines are being created (e.g., Dr. Alan Hinman developed 13 functional criteria that they should meet). The NIP is resisting any templates, and instead developed with the NVAC the minimum data that registries should have in place. Among the variety of activities going on now is the Robert Woods Johnson Foundation's "All Children Count" program and the American Registry Association's meetings that help states to share their experience. The biggest impediments to date remain funding and procuring the participation of private providers.

- Dr. Modlin suggested a registry development progress report as an agenda item. Dr. Peter offered to present the impending NVAC report on registries in the national system.

- Dr. Katz reported, regarding measles, the intent of the American Red Cross to mimic the Rotary model by collaborating with the Red Crescent and other organizations around the world to foster grassroots implementation. He also noted that few states have incorporated the IOM recommendations of local funding to their programs, but still rely heavily instead on the federal programs' funding (i.e., 317, VFC, CHIP, etc.). The committee Dr. Orenstein mentioned will address that.

Food and Drug Administration (FDA) Dr. Karen Midthun reported on the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held at the end of January. The VRBPAC recommended the two influenza virus vaccine strains and made preliminary recommendations for the B strain to be included in the vaccine for the 2001-2002 season. They also discussed the licensed Lymerix® vaccine's pre- and post-licensure safety data. A VRBPAC meeting on March 7-9 will discuss GSK's license application for the DTaP/IPV/hep B combination vaccine. They also will discuss

approaches to licensing new pneumococcal conjugate vaccines, since the early 2000 licensure of Prevnar® by Wyeth- Lederle, precludes any placebo controlled study in the U.S. to evaluate other pneumococcal vaccines. The March 9 meeting will finalize the influenza recommendations. NIAID and FDA will co-host a pneumococcal conjugate vaccine workgroup on Monday February 26 to discuss the correlates of protection for pneumococcal vaccine.

Dr. Midthun expanded on the VRBPAC's discussion of the safety of the Lyme disease vaccine, Lymerix®, in response to public concern. They discussed safety data to date and plans for continued evaluation of this product. The pre-licensure safety data showed no differences in incidence of arthritis between the control and vaccinated groups. There was a theoretical concern that the vaccine could predispose to arthritis, based on the observation that treatment-resistant Lyme disease has been associated with reactivity to OSP-A, and Lymerix® is a recombinant OSP-A vaccine. Exploration of this theoretical concern in clinical development of the Lyme disease vaccine showed no association between arthritis and the Lyme disease vaccine. There was an increased incidence of arthralgia in vaccine recipients compared with placebo recipients; the arthralgias were mostly transient.

SKB agreed to do a large post-marketing study to ensure that there were no problems in this area. They are continuing to work on that, attempting to accrue 25,000 vaccinees and three unvaccinated controls for each vaccinee in a prospective cohort study at Harvard Pilgrim Health Plan. Other sites are being enlisted as well, since vaccine uptake has been lower than anticipated, and only 3000 vaccinees have been accrued so far. SKB hopes that including other centers will increase the vaccinated cohort to 9000.

Preliminary data from the post-marketing study again show no significant difference in the rates of arthritis. However, effects reported to VAERS include arthritis and arthrosis. Although the VRBPAC found no convincing evidence of a sufficient difference between the pre- and post-licensure data, they urged more accrual to the post-marketing study to gather data more quickly. They also suggested that FDA work with CDC to issue a VIS to better inform patients of what to expect, and to work with the sponsor so that the package insert better reflects occurrences to date.

When asked about the probable licensure date of the GSK DTaP/IPV/hep B combination, Dr. Midthun could not provide an estimate. Aside from getting the VRBPAC's input on the safety/efficacy data presented, manufacturing or product issues also have to be addressed.

National Institutes of Health. Dr. Carole Heilman provided further input on the previous October meeting's discussion of bioterrorism issues and how they affect policy decisions. NIAID's infrastructure and bioterrorism research agenda supports basic research to genomic sequencing of bioterrorist organisms, design/testing of diagnostics,

and design/development and clinical evaluation of therapies and vaccines. She specifically shared information on the development of anthrax vaccine and new data on smallpox.

NIAID convened a small workgroup on smallpox to discuss whether the current supply of Dryvax® could be expanded or extended, based on earlier research suggesting that a 1:10 solution of Dryvax® could provide a 90% immunization rate. A pilot study at the St. Louis University VTEU enlisted healthy adults who had not been vaccinated for smallpox, placing 20 in each of three groups that received, respectively, undiluted vaccine, vaccine diluted 1:10, and that diluted 1:100. Measurement endpoints were positive skin lesions. Although the results showed a 95% "take" rate in the undiluted vaccine, it dropped to 70% in the 1:10 dilution and to only 20% in the 1:100 dilution. Such results pose implications to policy considerations about the use of limited stocks when further dilution produces lowered efficacy.

NIAID is also working closely with DOD in development of an anthrax vaccine. The focus is on three rPA vaccine candidates with work under way at USAMRIID and the DERA and AVANT companies. An agreement is in the works for Phase I testing this year by NIAID on the three (recombinant protective, surface, and purified antigen). Animal data already indicate that these vaccines probably induce higher antibody levels than the current AVA vaccine. Aside from the focus on rPA, NIAID is also exploring other candidates. A functional genomic and proteomics study with the Office of Naval Research will characterize the gene protein expression patterns, particularly regarding germination patterns of anthrax.

Finally, Dr. Heilman reported that the diluted influenza strain vaccine that they tested produced the same antibody. Other strains could be similarly explored if needed.

National Vaccine Injury Compensation Program (NVICP). Dr. Geoffrey Evans reported on the current status of the NVICP. About two dozen claims remain for vaccines administered before enactment of the program. These are otherwise known as the pre-1988 claims. Approximately $1.2 billion has been paid out in claims (almost all for the pre-1988 claims), leaving $1.5 billion in the Trust Fund. Efforts to reduce the vaccine excise tax from $.75/dose to $.25/dose continue with the Vaccinate Americas Children Act that is pending in both houses of Congress.

Sixty-six active claims were filed this year. The hepatitis B, Hib, and varicella vaccines were added to the program in 1997. Over 300 hepatitis B claims currently filed are expected to require approximately 3-5 years for adjudicaiton. There have been 24 claims for DTaP vaccine and 8 for rotavirus vaccine.

The NVICP is preparing to add intussusception to the Vaccine Injury Table through rulemaking. Once a notice of proposed rulemaking is published in the Federal Register, a 6-month public comment period including a public hearing follows. The changes become effective 30 days after publication of a final rule. Once added to the Table,

those experiencing rotavirus vaccine-related intussusception may receive a legal presumption of vaccine causation if specific time frames and other legal requirements are met.

In a related development, coverage for all NVICP vaccines was expanded by the Children's Health Act of 2000, which provides for compensation in those cases where both inpatient hospitalization and surgical intervention occurs. Prior to passage, compensation in injury claims depended upon demonstration of at least 6 months of continued effects following immunization. Since most cases of intussusception resolve completely, whether medically or surgically treated, claimants would not otherwise be entitled to compensation. This legislation, for example, would allow compensation for those individuals who experienced intussusception following rotavirus vaccine and required hospitalization and surgery, but who did not have the six months of continued effects.

Under current law, vaccines covered under the NVICP must be recommended by CDC for routine administration to children and have an excise tax enacted by Congress. Both prerequisites have been met for Prevnar® (pneumococcal conjugate vaccine) with publication of the ACIP recommendation in the October 6, 2000 *MMWR* and enactment of the excise tax effective December 18, 1999. However, the vaccine is added officially only after the Secretary publishes a final rule following the public comment period and hearing outlined above. As an interim measure to inform the general public and immunization community, consideration is being given to publishing a notice in the Federal Register that the vaccine has been added to the Table under Box #13 (newly licensed vaccines). Once the final rule is published adding pneumococcal conjugate vaccines to the NVICP, it will have its own separate category listing on the Table as other "covered" vaccines. The NVICP Website has been updated accordingly (www.hrsa.gov/bhpr/vicp).

The Congressional Government Reform Committee's report on the NVICP recommended the following: 1) ensure that the Vaccine Injury Table (VIT) reflects the current science; 2) determine a reasonable alternative standard for non-table claims; and 3) make the adjudication process less adversarial and more streamlined for off-table claims. The second goal was set because, unlike the claims filed for vaccines originally in the program, claims on new vaccines have little literature to describe the risks and resulting conditions. For example, the only condition listed on the table for hepatitis B vaccine is anaphylaxis. Rather than address causation with every claim, the initiative to create another approach for off-table claims was launched.

Ensuing discussion included:

- Although the data show a clear association between rotavirus vaccine and intussusception for only two weeks after vaccination, the inability to determine a cutoff point on the likely bell-shaped curve of outcomes prompted the program to extend the benefit of the doubt to an additional two weeks.
- Dr. Bernier asked why different standards would apply to a Table versus a non-

Table injury, and how that relates to the program's desire to change the burden of proof required. Dr. Evans responded that the Table has a 95% causality standard which is appropriate and should continue, considering that VAERS reporting requirements are statutorily tied to the Table, and their listing is also used to some degree for the wording for vaccine information statements. It is likely that if a lower standard for burden of proof is put into place, it will not have the same causality inference that exists with Table conditions.

- Dr. Offit asked why, rather than reducing the tax to $.25, the Fund is not spent on vaccine safety? Dr. Evans noted that the GAO's report on the Trust Fund did not make any recommendaton in this regard because it is so politically charged. Possibilities included using more of it for compensation by relaxing the standard of proof, or using it for vaccine safety research in light of recent budget cuts across government agencies. The fact that it is used for deficit reduction is another factor to be considered in any future discussions. Congress also passed legislation prohibiting any other use than for compensation and administration budgets.
- Dr. Kristine Severyn noted that the new VIT provides intussusception coverage only for inpatient hospitalization, not for those treated with an enema. Dr. Evans speculated that Congress may have felt that only surgery should be compensable due to its higher risk. The regulation is based on law; it is not something the Secretary can change administratively.

National Vaccine Program Office(NVPO). Dr. Martin Myers summarized that the NVPO operates across the different agencies of the DHHS as well as with USAID and the DOD. The NVPO administers the Interagency Research Program which conducts interagency research to specifically address unmet needs (e.g., those arising between funding cycles). In 2000, the priority unmet need was vaccine safety; in 1999, the needs were pandemic influenza and new priority vaccines, particularly for TB. The priorities for 2001 were vaccine safety and adolescent/young adult immunizations. The latter uses 11% of the NVPO's $6 million funding.

Another high-focus area for NVPO is the laboratory containment (effective, not absolute) of wild-type poliovirus as a part of polio eradication. Dr. Myers provided the WHO Website (www.who.int/groupv-documents) to access the WHO action plan for laboratory containment. Once the inventory of laboratories with poliovirus specimens is complete (the end of 2002), the biosafety levels for work on samples potentially containing wild-type poliovirus will rise to BSL-3 and then to BSL-4.

A workgroup was convened by the NVPO on October 25-27, 2000, to discuss development of a vaccine to prevent perinatal cytomegalovirus (CMV) disease. They reached a number of conclusions: 1) that the impact of CMV as a public health problem is substantial, but not widely recognized; 2) CMV is the leading cause of *in utero* damage, particularly hearing loss, to a developing fetus (since use of rubella vaccine was inaugurated); and 3) the IOM report on vaccines for the 21st Century listed prevention of CMV-induced hearing loss and progressive hearing loss as a high priority.

The workgroup considered a number of approaches with which to study candidate vaccines and the potential target populations with which to study vaccine efficacy and safety. They reviewed the status of a number of different strategies to vaccine development, considered several unique challenges to developing such a vaccine, and reviewed where the gaps in knowledge are, and the next steps for the Interagency Vaccine Group. A meeting summary is being prepared.

Dr. Myers described the Pandemic Influenza Preparedness Plan developed by the Interagency Vaccine Group with input from NVAC's Pandemic Influenza Workgroup. DHHS is currently reviewing the plan. It outlines the issues related to a pandemic and the approaches with which to address them. Sixteen technical annexes in various stages of development will provide guidance for a response. Three of these drafts (infection control, selecting alternative sites for care, and management of scarce resources) were provided to the ACIP members for comment, particularly from the agency liaisons.

The NVAC review of the draft plan offered several suggestions: advising a flexibility of national responses, using the 1957 pandemic as a planning scenario; using little or no vaccine scenarios (where/when vaccine should be supplied, assuming little availability early on); strongly coordinated communication strategies; ensure that the plan is national in scope (since implementation will be largely local); and recognizing the international arena and that a prepandemic research component is central to a successful response. The NVAC agreed to convene an antiviral technical group to discuss how to use antiviral agents, the availability of which will be varied, in a coordinated pandemic response.

The planned presentation at the last NVAC meeting on autism and ongoing vaccine studies was delayed to June 2001 due to a simultaneous Cold Spring Harbor meeting that involved all the NVAC speakers. Dr. Myers hoped that the related IOM report would also be available in June.

National Vaccine Advisory Committee (NVAC). Dr. Georges Peter reported on the NVAC meeting held the prior week. A workshop on rotavirus vaccine and intussusception will be held September 5-7, 2001, with four of five sessions focusing on Rotashield® vaccine. The proceedings of the May 2000 workgroup on aluminum in vaccines will be published in *Vaccines* soon; recommendations will be developed on CMV; and the committee heard presentations on global immunization initiatives (Gates Foundation and the NIH Fogarty Center). NVAC revised the standards for adult immunizations in the last two years in collaboration with the National Coalition for Adult Immunizations and NIP. These were tentatively approved by NVAC and the ACIP Workgroup, and are now in review by the American College of Obstetrics and Gynecology, the American Medical Association, the American College of Physicians, the Society for Adolescent Medicine, and the Infectious Disease Society of America. They are expected to be published in *MMWR* next January during Adult immunization

Week. The Child and Adolescent Immunization Standards were also revised by Drs. Jean Santoli and Lance Rodewald. After review, it is hoped they can be issued in October with the adult standards.

The IOM Vaccine Safety Committee was formed. NVAC will review their reports and provide input. The NVAC review of the IOM report (issued over a year ago) "Vaccines for the 21st Century; a Review for Decision Making" is on the NVAC site. The report provides a model mechanism for establishing priorities for vaccine development.

NVAC established three new workgroups to address: 1) the introduction of new vaccines (including financing, the original topic); 2) the development of guidelines on immunization mandates for recommended vaccines (topic suggestions are welcome and a public meeting will be held); and 3) strengthening the supply of vaccines. The latter will hold a teleconference call shortly to identify the supply's vulnerabilities and challenges. Dr. Modlin asked Dr. Lucy Tomkins to represent the ACIP on the latter group.

The next NVAC meeting will be held on June 4-6, with June 4 reserved for the meeting of the Subcommittee on Vaccine Safety, and June 5-6 for the full NVAC meeting. Finally, Dr. Peter defined the NVAC role as one to advise the Assistant Secretary on programmatic issues. The ACIP's role of providing technical advice is parallel, and Dr. John Modlin represents the ACIP on NVAC. A VRBPAC liaison representative, Dr. Robert Daum, has also joined; as has Ms. Jacqueline Noyes to represent the ACCV.

In discussion, Dr. Abramson noted that the international Brighton Collaboration seems to be addressing similar things to the IOM, and asked about collaboration between the two. A member of the audience, who is one of the Brighton Collaboration coordinators, reported their work to establish a standardized set of case definitions for adverse events subsequent to vaccination. With that, comparison should be possible of the vaccine safety data of clinical trials and postlicensure surveillance. She expected there to be no conflict with the NVAC work.

National Center for Infectious Diseases (NCID). Dr. Alison Mawle updated the committee on a unique exposure last fall to recombinant rabies virus vaccine. The use of this oral vaccine of wildlife began in 1990 as adjunct to the traditional public health methods of rabies control, specifically for raccoon rabies control. The >15 million doses distributed in bait were very successful, resulting in virtually undetectable racoon rabies now. But in September 2000, a woman was bitten on her arm when she tried to remove a bait from her dog's mouth. In 10 days, she developed an inflammatory reaction around the bite site, which was treated with antibiotics until it was found to be vaccinia. CDC laboratory tests showed a classic poxvirus, and PCR analysis detected both vaccinia and rabies glycoprotein. Mice inoculated with the cell culture material remained clinically normal and the woman was treated with convalescent serum holding neutralizing antibodies to the vaccinia virus.

Rabies is well controlled in the U.S. Of the five deaths reported in 2000, four were from bat exposures, and one was from a bite from a foreign dog. To CDC's knowledge, this was the first time a human was exposed to bait vaccinia rabies vaccine virus. It was the state's widely publicized campaign about the bait distribution that alerted the ER physician to the possibility of vaccinia. The vector is highly attenuated, but not enough to prevent a wound infection; it can still replicate in mammalian cells. Dr. Chuck Ruprecht of NCID added that the patient also had an eczema-like cutaneous disease, which was a complicating factor.

Changes in the General Recommendations Statement

Dr. Modlin introduced this topic, hoped that the final vote on the recommendations could be taken at the June meeting. Dr. Bill Atkinson reported for Dr. Tompkins, the Chair of the General Recommendations Workgroup, who had had to depart early. He noted that this was the eighth time the document had been discussed, outlined new text, and requested the committee's opinion on several sections.

Areas previously approved by the ACIP were those addressing: 1) minimum intervals, ages, and a "grace period"; 2) vaccination of internationally adopted children (the members were asked to read new wording on the latter), and 3) nonsimultaneous administration of live vaccines.

1. A new footnote (page 7) references local/state requirements for vaccines to be administered at certain ages, affecting school entry requirements. This may not allow for the ACIP–recommended four-day grace period implemented to make MMR compatible with the other antigens' grace period. In the footnote's last sentence, "ACIP hopes" that this will be considered in a review of state/local vaccination requirements.
   Committee comment included:
   - "ACIP hopes" is interpretable, and effecting state laws and regulations for new antigens can take years. Drop the footnote. The intent will be implemented regardless, with or without the footnote.
   - Both the AAP (Dr. Zimmerman) and the NIP (Dr. Orenstein) supported the four-day grace period and the footnote to support the practitioner in effecting it. However, there was consensus to delete the last sentence expressing the ACIP's hope for regulatory consideration of this recommendation.
2. The 1994 recommendations' two pages of definitions (glossary) was dropped.
   - Leave it in; even physicians call in to ask the difference between intravenous immunoglobulin and immune globulin.
3. New or substantially modified material in the January 2001 draft include a rewritten introduction and text on options for reducing the number of injections at the 12-15 month visit.
   - Focus on principles rather than minutiae: advise first priority to giving the first vaccination series, and then the vaccines to address the child's highest risk (e.g., pertussis rather than polio).

4. The text on aspiration prior to vaccine administration was altered to agree with the Red Book (i.e., the data are insufficient, and leaving it to the practitioner.) Nurses in particular have strong feelings about this, since it is part of their training to select another vaccination site if blood is taken into the needle.
   - Committee comment focused not so much on changing the injection site as on discarding a syringe holding vaccine that may costs $50/dose. Some prepackaged products also would require discarding the vaccine if the needle cannot be reinserted. There was general agreement to align the text with that of the Red Book.
   - Ms. Lynn Vonta, of the National Network of Immunization Nurses and Associates, expressed their interest in working with the ACIP in education and maintaining scientifically-appropriate practices and updating their own practices as necessary.
5. The 1994 recommendations were to disregard any vaccines given by incorrect route or site and to readminister unless serologic testing is done. The sparse data that exist vary according to the route and site of injection. The ACIP was offered three options for wording: 1) leave the wording as is, admitting that subcutaneous vaccine administration probably has little or no effect on immunogenicity (based on varicella data); advise repeating doses of other vaccines given by the wrong route; 2) accept any route or site as valid and throw out all the 1994 wording; 3) accept everything but for the antigens for which data indicate inadequate seroconversion (i.e., intradermally or gluteally administered hepatitis vaccine).
   - Committee comment: The Red Book committee would find the second option the simplest, but it would favored the third option, which itself still has sparse data.
   - Proper training and guidance is needed for proper injections, but hazarding a large local adverse reaction in a child from over-immunization is not a solution.
   - The third option also would avoid the risk of not just a lacking immune response, but actual vaccine failure (e.g., with rabies vaccine).
   - There was general agreement to select the third option.
6. The waiting period after vaccination was dropped to parallel the Red Book, except for text that "some experts recommend this waiting period" to check for an allergic reaction.
   - Committee comment: Most pubic clinics do not use a waiting period. However, data have demonstrated syncope and resulting head injuries in young adolescents and anaphylactic reactions do occur.
   - There was consensus to check the existing data and to discuss that in June for a final decision.

Other suggestions for the General Recommendations were:

7. Should the VAERS report form and the Vaccine Injury Table be included? Committee address: Insert their Web addresses.
8. Table 5 is big (Guide to Contraindications and Precautions). Since this changes,

should it be deleted from the General Recommendations and only published as an annual document in the revised Harmonized Schedule?

- Committee comment: Correct contraindications are essential; they are often posted publicly in practitioner offices with the yearly harmonized schedule, and many practitioners do not use the Web. But if the Schedule is released concurrently with this, there is no need for it in both places. Refer this to the Workgroup on the Harmonized Schedule.
- Since the NVAC hopes to complete the adult and pediatric/adolescent immunization standards by fall, at least refer to them as "in press."

The time line to complete the General Recommendations is to receive committee/liaisons comments by the end of February, 2001; to do any revisions by April; to return the draft 4.0 document to the ACIP members and liaisons by May; to have final approval by the June meeting; and to publish them in summer 2001.

Hepatitis B Vaccine and Multiple Sclerosis

Dr. Hal Margolis reported on two new papers published about the association of multiple sclerosis and hepatitis B vaccination. A nested case-control study was done in the Nurses Health Study, of two groups recruited in 1975 and 1989, respectively. Positive MRI and physician ascertainment of MS among these women was 86% for the first group and 96% for the second. Hep B vaccination was ascertained by questionnaire and validated in 64% of the medical records (35% could not be found). The controls were healthy women and a breast cancer control group. A total of 190 cases, 534 controls, and 11 breast cancer patients were enrolled.

The overall result of a comparison of vaccinated to unvaccinated (healthy controls) was an age-adjusted relative risk of 0.9, crossing 1.0 within a 95% confidence interval. The later onset of MS showed no increased risk or association with the use of recombinant vaccine. The results of comparison of the vaccinees to the unvaccinated breast cancer group showed an age-adjusted relative risk of 01.2 within a range of 0.5-2.9, within a 95% confidence interval.

The study concluded that there is no evidence of increased MS risk among women vaccinated against hep B. The study design was robust, as a nested case-control design with high rates of participation, use of vaccination records, and use of a two year period from onset of disease to minimize error from self-reported date of onset. These results were consistent with ecologic studies in Canada of population-based surveillance of adults and children. However, it contradicts an increase (albeit non-significant) reported by French and U.K. studies (the latter a database retrieval study).

Another study reported was a vaccination study of patients with MS. It showed no evidence of short-term disease exacerbation and it parallels another study of influenza vaccines that was thought to represent immunization issues in general. Both studies were thought to be rigorous and ultimately reassuring to those receiving hep B vaccine and their physicians.

Committee discussion noted:

- There was a slight increased risk between the women whose records could be found versus those without them.
- Dr. Chen reported another case-control study using VSD data, to be presented at the European Society of Pediatric Infectious Disease, that shows no association. But there are still caveats. For example, two other studies were conducted by reputable investigators and funded by an independent French agency, but were not publishable due to potential bias confounders. And the U.K. study seems to indicate atypical MS; more medical record studies that are based on the ICD diagnosis codes are needed. He urged the ACIP not to disregard the potential impact of these studies, and not to dismiss the whole issue too quickly. Dr. Severyn agreed, noting that other demyelinating diseases not classified as MS could be developed after hep B vaccination. This should not be dismissed. She also noted that the studies cited were funded by pharmaceutical companies.
- Dr. Plotkin recommended that CDC have statisticians look at all the studies and judge the statistical accuracy of their conclusions.
- The hep B statement will be reviewed. Dr. Modlin hoped to send it to the committee before the June meeting for a final vote.

IOM Report of the Immunization Safety Committee

Dr. Marie McCormick, of the Institute of Medicine, reported the request by CDC and NIH to the IOM to study emerging immunization safety concerns. This was done due to the increasing number of hypotheses that link vaccines to adverse events related to numerous medical conditions, varying levels of relevant scientific data, and increasingly polarized discussion of such concerns. In response, the Immunization Safety Committee was formed to provide timely, objective, and expert review of vaccine safety issues. Unlike the typical IOM committee, it will do so on a fast track. They plan to meet about three times a year for the three-year contract period, to examine specific vaccines (and perhaps more with related issues) and then within 60 to 90 days complete a brief but focused report on the hypotheses in question. The findings (both scientific and a lay summary) will be disseminated widely to policymakers, health care providers, and the public. Although quick and short, these reports will enjoy the same National Academy of Sciences peer review as their longer counterparts.

The process is as follows: the Interagency Vaccine Group (IAG) will identify the topics. The first three topics are: 1) MMR and autism; 2) thimerosal and autism and developmental disabilities; and 3) exposure to multiple antigens and adverse effects. However, the order of the topics chosen can be rearranged. The multidisciplinary expertise of the committee was outlined. The rationale for their selection was to have an objective, independent committee not subject to criticism based on conflict of interest (including recent funding from CDC) and to and ensure consistency in the membership.

The committee's charge is threefold: 1) to conduct a plausibility assessment, including the evaluation of the causality evidence, biologic plausibility, and strength of competing hypotheses; 2) to assess the significance of the event, considering the number of persons affected, the seriousness and treatability of the adverse event and natural disease; and 3) based on these two assessments, to provide guidance on potential future activities (e.g., research, surveillance, communication, and policy review). The committee will not make public health policy or set agency agendas, but it may recommend that the DHHS advisory bodies (which do set policy/agendas) review the evidence if the event constitutes a serious threat to public health.

The sources for these assessments will include the peer review literature (the primary source), as well as VAERS case reports and other sources. The methodology used by previous IOM vaccine safety committees will be used, particularly as it relates to causality assessment.

Dr. McCormick outlined the MMR/autism meeting planned for March 8-10, 2001. The March 8 meeting will be open to the public and consist of two sessions: etiology, assessment, and classification/epidemiology of autism and another on the hypothesis that links vaccination with MMR to inflammatory bowel disease, and autism, including presentations on recent data. Both sessions will have a panel to discuss the presentations and question the presenters, and there will be a public comment period. The second two days of the meeting will be closed to the public while the committee conducts its deliberations. Dr. McCormick reported the committee's willingness to attend the ACIP to present its findings, and requested the members' comments or suggestions on approaches to the hypotheses or on dissemination of the findings.

Committee discussion included the following:

- *Should any career involvement with vaccine research disqualify a participant?* Dr. McCormick responded that this committee is not "the" model for vaccine safety; such specifics should be reviewed by experts in the field. To respond to the different issues being addressed, this committee's broad general expertise was chosen.
- *What topics might be chosen, and how*? The IAG selects, but MMR and autism was high on everyone's list. Dr. Myers added that NVAC's Subcommittee on Vaccine Safety and Communication will be the forum through which public input is possible to the IAG's topic deliberations.
- *Will the IOM consider reviewing previous decisions based on factual errors (e.g., data do not support the biological plausibility of a hep B association with MS)?* Hepatitis B is on a list of about 30 topics, but the IAG is the selector.
- *The IOM methodology in past has been unhelpful when data are insufficient to accept or reject a hypothesis. With rising accusations, perhaps the burden of proof should be on those alleging damage.* The committee is aware that they will often be facing weak or spotty evidence, and are taking that seriously. They are trying to develop a method of response that goes beyond a simple yes or no.
- *Will you review the UK Medical Research Council's review of topic #1?* Yes.

Discontinuation of Cholera/Typhoid Fever Vaccines Manufacture

Dr. Eric Mintz reported a decision by Wyeth Lederle last June to halt their production of cholera and typhoid fever vaccine. Neither vaccine on the market has yet exceeded its expiration date.

Cholera: The last ACIP recommendations on cholera were done in 1988, and advised its use only to satisfy travelers' needs and for "special high-risk groups in highly endemic areas." Since the WHO and CDC do not recommend vaccinating travelers for cholera, it is no longer an entry requirement. The Wyeth vaccine was only 50% effective and offered only a 3-6 month duration of protection, but it was the only one licensed in the U.S. Two others available in Europe and elsewhere are not licensed here. The demand is limited; only 37 cholera cases occurred in U.S. travelers in the six years from 1995-2000.

Typhoid: The last ACIP recommendation on typhoid vaccine was issued in 1994. It advised vaccination for travelers to areas with recognized risk of exposure to salmonella typhi (Asia, Africa, and Latin America) who have prolonged exposure to potential contaminated food and drink, for those with household contact with a carrier, and for laboratorians who work frequently with salmonella typhi. The vaccine's efficacy was 51-77% (another analysis ranged from 63-80%). There are two other vaccines licensed in the U.S., but only the Wyeth vaccine was licensed for use in children aged six months to two years. There were 33 cases in U.S. children aged 6-23 months in the six years from 1994-1999. CDC's advice is generally to stress parental caution about food and drink when they travel with young children in affected areas.

Committee discussion included the following:

- NIH is developing a conjugated capsulated polysaccharide vaccine that appears effective in children aged ≥2 years, and it seems to produce antibody responses in those younger. The liquid formulation of the oral TY21-A typhoid vaccine was well accepted by younger children in Chile, but was not licensed or used for that age group.
- Other than those, the Swiss Institute in Bern applied for an FDA license for Oracol® about two years ago; and SmithKline has a whole cell (killed) vaccine licensed and sold to travelers in Europe. It has not been submitted for licensure in the U.S.

APERT Trial Presentation

Dr. Joel Ward, of the University of California/Los Angeles, presented the results from the APERT trial. This eight-site NIH prospective trial was conducted over about 2-5 years to define the epidemiology of pertussis in adolescents and adults. The methods included intensive microbiologic and other epidemiologic surveillance techniques. APERT was a randomized double-blind trial of hepatitis A and acellular pertussis vaccine. The study sites were at NIH/NIAID VTEUs as well as the two Principal Investigators' sites. An independent committee selected the vaccine for the trial.

The study was undertaken becuase pertussis episodes of prolonged cough (>5 days) are frequent (4-5% per month in some study subjects, with some seasonal variation). The evidence indicates that pertussis infection in adults and adolescents occurs as immunity wanes over 5-10 years if a booster dose is not given. Those infected can be totally asymptomatic, or have symptoms ranging from mild to moderate disease or classical whooping cough. Although early treatment can help mitigate it, pertussis is rarely considered or diagnosed, even though epidemiologic studies indicate >50% of children's cases can be traced to contact with the reservoir in earlier adolescent/adult cases.

The problem is the difficulty of diagnosis in adults. Since it is not normally considered in the U.S., cultures are rarely obtained. And when done, their limitations are multiple: they are usually done late after infection when the cough has been present for some time; their preparation requires microbiologic expertise; the serology is complex (nine different assays); and test standardization is lacking. The study explored using PCR as an alternative methods, but found little benefit.

So, the study's objectives were to: 1) define the incidence/epidemiology of pertussis infection and disease; 2) assess the efficacy and safety of trivalent acellular pertussis vaccination (as well as examining immune response to the vaccine and naturally-occurring infection/disease); and to explore correlates of protection.

The study design was a prospective, controlled, randomized, double-blind study. Eight center sites participated over two years, and 2781 subjects were involved in two vaccine groups (a three-component aP vaccine compared with a hepatitis A vaccine). Active prospective surveillance was done through phone calls to the participants every two weeks. Intensive microbiologic and clinical evaluations were performed on any study subject who reported a cough illness of $\geq$5 days. Acute and convalescent sera were obtained. Interpreting the antibody response was a challenge since both childhood immunization and natural infection had to be considered.

The study provided one dose of vaccine on entry to the trial and conducted clinical evaluations and blood specimen collections pre-study. Sera was collected regularly over time and at day five of any cough illness. In all, 13,881 serum samples were collected, an average of five per subject.

Dr. Ward outlined the composition of the study groups. They were randomized between aP and hep A vaccines and were separated by thirds among healthcare workers, students, and community volunteers. Most participants were white women; the age ranged from 15-65 years of age, and $\geq$72% had pertussis vaccine previously in childhood (although this was not independently verified).

He presented the most recent safety data on adverse effects in the first 14 days after vaccination. There was no elevated temperature/fever for males or females or between the two vaccine groups. The general malaise or decreased activity reported over 14

days showed no significant differences by gender or between the groups. The big difference was in muscle lumps at the injection site, between pertussis (much higher at 6%) and hepatitis A vaccine (2%), as well as a delayed appearance of lumps seven to eight days later. The difference was also by gender: almost all swelling was reported by females. There was more swelling reported at the injection site by the pertussis group (2-5%) versus the hepatitis A group, again all from females. The same was true for redness, although there were fewer reports and the extent was not very severe, and for soreness at the injection site.

There were no serious adverse effects attributed to the vaccine. Outcomes were essentially the same in the two groups, and there were no adverse outcomes in the 60 pregnancies that occurred over the study period.

The incidence of cough illness >5 days (to exclude viral illnesses) was calculated at an average of 0.63 episodes per year per person. Half of the study subjects had more than one illness/year; 15% had two, and 8-9% had three illnesses/year. There was a slight but noticeable trend of increasing cough illness with age that was also present across all the age groups. The duration of cough >5 days was charted, showing a mean of 24.4 days. The standard illness lasted 20.7 days, in a range from 5 to 60 days. One confounder was smoking, which accounted for a 39% higher incidence among smokers. There was also a geographic confounding factor.

There was no significant difference found in cough illness or duration of cough between the two study groups, which is not to say that pertussis or coughing illness was not prevented. The duration of cough only differed 1-7%, a range for which the study was too underpowered to detect a difference.

The primary serologic case definition required a positive culture, positive PCR, or positive serologic result. Aside from PCR and culture determination, twofold or greater independent antibody rises were required to avoid false-positive determinations. Five other less stringent categories (more sensitive but less specific) were also created to allow comparison of paired sera samples. These included subsets with cough illness of $\geq$5 days and onset 28 or more days after immunization. These categories were useful in assessing disease incidence.

The results of pertussis outcomes (all with cough illness) were as follow. Culture/PCR analysis indicated five cases in the hepatitis A group and one case in the aP group, although that case was in a subject with PCR-negative results and no change in antibody. This may have been a laboratory contamination, but it was included as a case. If that case is eliminated, a strong trend to protection is shown. Serological analysis produced an additional case in the aP group and an additional four cases in the hepatitis A group, for a total of two cases in the aP group and nine cases in the hepatitis A group. The point estimate of efficacy was 77-88, but dropped in the lower sensitivity categories to 45-49.

The proportion of individuals 15-64 years with cough illness meeting the primary case definition of pertussis preventable by acellular pertussis vaccine ranged from 1-6% of cough illnesses.

The pending APERT analyses include consideration of other sreologic case definitions for incidence and efficacy; the differences in pertussis antibody response characteristics in those persons who were and were not vaccinees, and a pertussis vaccination program for adolescents and adults.

Three potential approaches for pertussis vaccination were outlined: 1) continue only childhood immunization; 2) immunize adolescents at middle school entry with a dTap booster and ten-year boosters in adults; and 3) immunize adolescents and adults who may transmit pertussis to young infants, such as expectant parents, daycare center teachers/staff, and medical personnel. Consideration should also be given to vaccinating individuals with asthma, cystic fibrosis, or other cardiopulmonary conditions, and for outbreak control.

To complete the analysis, a cost-benefit calculation is needed for optimal dTap vaccination of older individuals. Although APERT did not assess secondary risk, the literature holds data on secondary transmission, and APERT offers data on morbidity, duration of illness, costs associated with medical care, and loss of work and other indirect costs. GSK has assembled a multinational cost-benefit team to model both direct and indirect costs, including secondary transmission issues.

Although the vaccine efficacy reported by the study was not significant, including for the primary case definition, the data do present a very strong trend and point estimates that are consistent with estimated vaccine efficacy for young children. Dr. Ward expected the efficacy in an adult to equal that in a DTaP-primed child, but duration of protection remains unanswered.

The study's conclusions were that: 1) the incidence of prolonged cough illness (>5 days) in the U.S. is >50% of person-years, but pertussis accounts for only 1-7% of that; 2) the incidence of pertussis cough illness in adolescents and adults is at minimum 4-7 cases per 1000 person-years; 3) this incidence represents 80-100,000 cases/year in the U.S.; and 4) such illnesses are often long-lasting and not benign. 5) Culture and PCR are relatively insensitive in diagnosing illness in adults, even at the fifth day, which indicates that infection could occur days or even weeks before the cough begins. NIH is considering human challenge trials to study the physiology of pertussis. 6) The interpretation of serological responses is a challenge because adults and adolescents are primed. 7) Regarding safety and efficacy, acellular pertussis vaccine produced no serious adverse effects, but did produce some local reactions, especially lumps and swelling in women. 8) The trivalent aP vaccine reduces disease incidence. Although the APERT measure of efficacy is imprecise, a duration of protection parallel to that of unprimed children is expected.

The data are assumed to be comparable or even identical to those of the previous seven infant pertussis vaccine trials. Immunizing adolescents/adults should not involve major incremental costs (e.g., from adding aP to a dT booster). A detailed cost-benefit analysis is underway.

Given that, several approaches are possible: 1) routine adolescent DTaP immunization would be relatively easy to accomplish and provide some significant benefit; 2) immunizing older family contacts could be useful and is justified to protect young infants who may contribute most of the morbidity, hospitalization, and death from pertussis; and 3) another target population could be those with asthma, cystic fibrosis or other cardiopulmonary conditions, or those who are immunocompromised; and finally 4) the vaccine is useful for outbreak control.

The committee's discussion included the following:

- *What is the duration of immunity in adults and how many boosters would be required?* This differs by antigen and analysis is not complete, but > 2 and <10 years seems indicated.

- *Did both vaccines have an alum adjuvant?* Yes.

- *Did you look at cord sera of the pregnant women?* No.

- *Will there be any data on correlates of protection?* Only anecdotally, by case and by antibody type. Another year will be needed to analyze the other sera assays to draw a good decay pattern for each subject, and to analyze the cough pattern and pertussis case by each of the six diagnostic criteria. The study was designed to enroll about 40 cases, but even with a six-month extension, only 11 were found.

- *Was the cough illness duration of those with confirmed clinical diagnoses any different (i.e., longer) than the case definition of 2 weeks?* This would be hard to do with only 11 primary cases, but most of those were quite ill; almost all were at 14-25 days of cough. Multiple medical visits were common, and some were treated with erythromycin (the cases that were aborted).

- *How would you generalize the PCR results to public health practice?* There were no false positives, but the PCR is relatively insensitive because it did not identify 50% more cases as expected.

- *If the smokers are not included, was there any difference in efficacy between the hepatitis A and pertussis vaccine groups?* The smokers confounded occurrence of cough, not pertussis.

- *Why was there no "no vaccine" control group?* The reality is that most people don't want to enter a trial with no perception of benefit. An independent panel

picked the vaccine and the control, and there are no scientific data to indicate that hepatitis A would influence the incidence of pertussis in a blinded trial.

- *Was there an epidemic of pertussis at any time?* No, although we hoped for one based on a projected 3-4 year cycle, and extended the trial six more months to allow for that. California had an epidemic immediately after. But the 11 primary cases from March 1997 to March 2000 were charted and showed no clustering and no pattern connected to immunization.

- *What's the next step with the data from this trial?* Dr. Clover reported the Adult Immunizations Workgroup's interest in working with Dr. Ward's data and CDC's on the household transmission from adults to infants, and looking at the cost data, before discussing any recommendations. Dr. Ward reported the GSK funding of a literature review and modeling, including APERT data, to make some cost-benefit projections. Dr. Howe expected this to be ready for the fall meeting.

- This will be kept on the agenda as an ongoing action item, perhaps touched upon at the June meeting. Dr. Ward suggested contacting Hughes Bogart at GSK for the latest data report. Dr. Murphy reported that CDC is also doing studies of the source of disease in infants, including some cost studies related to the burden of disease. Dr. Wharton reported plans to focus on the cost of disease for pertussis generally, but hoped that some information also will emerge on adult and adolescents and the risk factors for young infants.

- Dr. Chen asked if this study could do some long-term follow-up on efficacy, but Dr. Ward said no. That would require collection of specimens and clinical evaluations, work better done in an HMO population than a recruitment population. Tracking down the latter would be very difficult.

Update on Hepatitis A Vaccine Activities

Dr. Beth Bell reported on the impact to date of the major change made to the ACIP recommendation on routine hepatitis A about eight months earlier. The strategy was to effect an incremental implementation of routine hepatitis A vaccination of children. This proceeded from the 1996 ACIP recommendations to vaccinate children living in high-rate communities (e.g., American Indian/Alaskan Native) at ≥2 years of age, providing catch-up vaccination to children before school entry, and finishing catch-up vaccination within five years of implementation. This was continued in the 1999 recommendations, which extended this routine vaccination to those living in states and communities with consistently elevated hepatitis A rates. The ultimate idea was to move to national immunization of all children.

Dr. Bell shared the 1999 CDC/Indian Health Service survey of IHS providers in the U.S. At 79 facilities, 92% vaccinated preschool age children and 64% vaccinated to school age. The estimated coverage of preschool-aged children was 59%. The same

collaboration last summer reviewed charts of about 2000 children from a large southwestern reservation to assess the vaccine coverage of children aged 4-7. Of those, 79% got at least one dose of hep A and 53% completed the series. A proportion of 61% got their first dose by 36 months, suggesting that hep A vaccine is being incorporated into routine child healthcare on this reservation. Their hep A incidence seems to reflect this. The reservation's counties had an outbreak in the mid-1980s and again in the mid-1990s. Continuing that pattern, an outbreak should have occurred in 2000, but only two cases were reported.

In the early to mid-1990s, the hep A incidence among American Indians was significantly higher (70/100,000) than that of non-American Indians (10-12/100,000) in 15 rural counties that include reservations. But the 1996-2000 data reflect a greater decline of hep A incidence among American Indians than among non-American Indians (1/100,000 versus 14/100,000, respectively). A similar trend was shown in 2000 among Native American and non-American Indian residents of five large urban cites with large Indian populations (3/100,000 versus 6/100,000 respectively), and the overall rate in 2000 among Native Americans was lower than the national average.

The data indicate that, although there are cyclic and periodic aspects to hep A incidence, a trend exists that seems to reflect an alteration of the epidemiology of hep A in these populations. Additional coverage surveys are needed in other high-rate communities to put this in context, however, as well as from non-IHS facilities, since 50% of American Indians are not cared for in IHS facilities and live in urban areas.

Dr. Bell reviewed the epidemiologic foundation for an incremental strategy. It proceeded from the fact that specific states and counties could be identified with consistently elevated rates of hepatitis A. These areas accounted for the majority of reported disease that persisted over time. CDC calculated and mapped the areas that exceeded the U.S. rate of ~10/100,000 cases from 1987-1997, which were clustered in the west and southwest. The 1999 ACIP recommendation called for routine hep A vaccination of children in those areas with twice the national average rate, and consideration of that where it was above 10/100,000 but less than 20/100,000 cases. The Vaccines for Children Program approved those recommendations in 1999, and the number of pediatric hep A vaccine purchases increased in1999 and again even more in 2000.

The 1999 ACIP recommendation statement regarding implementation suggested that: 1) children living in states with rates >20/100,000 routinely vaccinate children statewide; and 2) states with rates <20/100,000 should consider the feasibility of such vaccination, considering the clustering of cases and impact of disease. Possible vaccination strategies were also suggested for children or adolescents, one or more single age cohorts, campaigns in certain settings (e.g., day care), or vaccination when children present for routine healthcare.

The states with hep A rates ≤10/100,000 in 1987-97 were mapped, and a bar chart was shared of pediatric hep A vaccine doses purchased in 1998 and 1999. Most of those purchases were from the 17 affected states included in the 1999 recommendations. In a survey, 15 of the 17 states said they were providing vaccine for routine vaccination; nine had it available statewide; five had targeted age groups; three used other targeting methods; and four required routine vaccine.

A line chart of hep A incidence in the US reflected a marked drop in the incidence from 1952-2000. The 1960s-1970s showed periodic outbreaks; peaks were shown in 1989 and 1997; and then a precipitous drop plunged below the historic average. The 1999 rate was 6.2 per 100,000 and the provisional rate for the year 2000 is 4.5. The lowest rate ever reported in the U.S. prior to that was 9.1 in 1992. Another line chart of average hep A incidence showed a drop in the 11 states with consistently elevated rates, from 49/100,000 in the period 1984-2000 to about 9/100,000 in 2000.

Dr. Bell outlined a demonstration project conducted in Butte County, California, from 1994-95 through 1999, the longest period of follow-up ever done for routine childhood hep A vaccination. At the beginning, about 30,000 children (aged 2-12 years) of the county's total population of 200,000 were vaccinated. Free vaccine was given to all providers/children in the county. The vaccine was administered in provider offices and school-based clinics. The county kept an immunization registry and maintains active surveillance for hep A rates, including laboratory reports. The county coverage in 2000 was 62% for the first dose and 40% overall for the target population aged 2-17.

The hepatitis A incidence of Butte County was charted, revealing periodic outbreaks broken by interepidemic periods of about ten years. Since the vaccination program began in mid-1994, the number of cases in Butte County have dropped to two cases in 1999 and four cases in 2000, the lowest rates there ever. But interpreting these epidemiologic patterns is confounded by not knowing if this is simply the bottom of an interepidemic period or a true indicator of disease suppression. Nonetheless, a comparison of the Butte data to that from Yuba and Sutter counties, and to California as a whole, showed Butte in 2000 with the lowest rate of any California county.

Dr. Bell summarized that national hep A rates are at historic lows. Monitoring is needed to put this in context since this is a cyclic disease. The ACIP recommendations are being implemented, mostly voluntarily, and using many strategies. The challenge will be to sustain ongoing vaccination in the face of falling rates. The long-term hep A prevention strategy anticipates a likely continuing lower incidence with the catch-up vaccination of children and adolescents. Incidence will be further reduced and transmission will be eliminated through vaccination of high-risk adults and routine vaccination of infants/young children.

Committee discussion included the following:

- *Was the lowered incidence of the last few years mostly in adults?* Yes, but it dropped in all age groups.

- *Are there any data on the percent of adults vaccinated either because they are in a high-risk group or just because of international travel?* No. Outbreak investigations have found appalling low immunization rates, even among high-risk individuals who have private health care providers. It could be that most adults being immunized are getting vaccinated in travel clinics.

- *Was there any common decline in the 38 states not using the recommendations?* Only a small decline.

- *Are seroprevalence studies and modeling being done to estimate possible increased risk in adults as the children are partially vaccinated? It is amazing that with 60 % coverage, transmission seems to have been interrupted.* The latter is not completely certain. From 1995-1997, the marked decrease was in vaccinated age groups and not in adults, and there were outbreaks of adult-to-adult transmission among illicit drug users. But that issue raised is important; a national prevalence survey is ongoing, and prevalence surveys are being considered where the vaccinations are occurring.

- *Is there any new information on the progress to licensure of a hep B vaccine?* Dr. Midthun could not comment on the absence or presence of files in review by the FDA.

- *Dr. Severyn asked for comment on the cost-benefit ratios on the use of hepatitis A vaccine among travels, recalling a negative article in the British Medical Journal.* In general, many analyses related to travelers conclude it to be fairly cost effective, but there are determinants, including frequency of travel, destination, and how long the stay there will be. CDC presented data on the cost effectiveness of routine vaccine (paper by Jake Jacobson and Hal Margolis) that concluded a favorable cost benefit of hep A with these considerations.

Cost Effectiveness of Universal Childhood Hepatitis A Vaccine

Dr. Jake Jacobs, of Capital Outcomes Research, shared the results of his two cost-effectiveness studies, which were funded by Glaxo SmithKline. The first study, begun before the ACIP recommendation, was of adolescent vaccination in the ten states with the highest adolescent/adult hepatitis rates. The abstract of that study was published, and the final report will be done on completion of analyses of disease transmission and quality of life.

The U.S. spends $1.2 trillion/year on medical care, but still has below-average health outcomes for industrialized countries. We are twenty-third of 24 in child mortality and sixteenth in life expectancy. Only Turkey is worse. Part of the problem is that much of

health care spending goes for low-yield technologies or medical interventions that are expensive and produce relatively little benefit.

Another important distinction is that prevention programs such as a hepatitis A vaccination initiative are designed to reduce disease, not to reduce costs. Most medical interventions do not reduce costs to the health care system. For example, the Tengs, 1996, study showed that of 310 medical interventions studied, 274 actually increased costs. They were not intended to pay for themselves; only to be "reasonable" given health benefits. "Reasonable" infers that societal benefits exceed the health care cost (e.g, through reduced work lost due to mortality and morbidity), or should cost <$50,000/year of life save or Quality Adjusted Life Year (QALY) saved. Most childhood vaccines qualify as cost effective. In particular, the economic or social benefits of polio, pertussis, varicella, and hepatitis B vaccines exceed their costs. In fact, the first three provide $3-$5.70 of benefit per $1 of cost.

A Markov model was used to develop age-specific parameter estimates of hepatitis A vaccine benefits, using disease incidence, vaccination protective efficacy, disease outcomes, medical cost, and cost of work lost, tracked from age two to 100 years. A 3% discount rate was used to bring costs and benefits, including life years saved, to present value. The economic endpoints measured were the ratio of societal benefits to costs, and those to the health system perspective were cost per year of life saved.

Over 900,000 children are born annually in the 11 states of the ACIP recommendation. The model estimated that 4.4% (~41,000) would develop symptomatic hep A at some point; the estimated reduction due to vaccination was 85% (down to 6200). The *societal benefit* of prevented work lost was a drop from 2.3% to 0.4%; fatalities dropped from 1.6/100,000 to 0.4/100,000 (about one added day of life expectancy child vaccinated). The *cost benefit* was based on an estimated cost for an entire birth cohort of $52 million for vaccine and administration. Hep A treatment cost reduction was estimated at $25 million; prevented work loss was $28 million; and prevented mortality was $52 million. That netted estimated benefits, for each dollar invested in the vaccination program, of $2.12 for young children, and $1.80 for adolescents.

The health care system benefit showed annual vaccination costs of $47- 49 million offset by treatment costs of $50 million, or $11,000 per life year saved for 2-year olds and $14,000 for adolescents. Both at the public and private sectors' vaccine cost, hepatitis A was cost-effective, even if cases are under-reported by ≥50%.

Dr. Jacobs also provided the cost analysis results for long-term vaccine-protected efficacy ($20,000 per life year saved for 20 years of protection). It demonstrated cost effectiveness even for the states with higher incidence than the 11 states covered by the ACIP recommendation.

There are several factors that could cause over- or under-estimation of cost effectiveness: 1) the model does not consider the reduction of disease transmission; 2)

new analyses will consider the lower infection rates of the last 2-3 years as opposed to the 1990-98 infection rates used previously; and 3) alteration of transmission rates is being examined through a summary of six studies of families with hepatitis A, four with household contacts' immunity status determined by identification of an index case. They were tested at least twice to determine transmission status. The other two studies were similar, but measured development of overt disease rather than seroconversion, and included those immune as well as those susceptible. These trials' age-specific transmission rates were combined with census data on household size and age composition and NHANES data on the proportion of those potentially susceptible to hepatitis A. The results of the study of transmission to household contacts showed a 27% seroconversion rate and a 4% overt disease rate. In the 11-state vaccinated birth cohort, that implies that nearly 10,000 hepatitis A cases will be prevented just among family contacts.

Finally, data is being collected to evaluate the prevention of nonfatal outcomes for hep A, in a time trade-off technique (i.e., how much of your one's expectancy one would trade to avoid having hep A). He reported initial results with about 10% of the analyzed data that was collected from former or recent hep A patients and the general community. The current value is 0.57, which falls "somewhere between the value of life with frequent migraine headaches ... and liver cirrhosis." Based on that, they estimated that vaccination of children would cost about $7,600 per quality-adjusted life year term.

There were no questions for Dr. Jacobs.

Staphylococcal Vaccination Phase II Efficacy Trial

Dr. John Jernigan, of NCID, introduced the presentation of the Phase II efficacy trial of the *staphylococcus aureus* polysaccharide conjugate vaccine, StaphVAX.® *Staph aureus* is an important cause of nosocomial pneumonia and surgical- and bloodstream infections. In addition, 54% of staph is now antibiotic resistant.

Dr. Gary Horwith of the NABI reported that, of the culture-positive infections occurring annually, 44% are gram-positive and of those, 35% are *Staph aureus*. This equates to about 1.2 million *Staph aureus* infections annually. Sixty-three percent of bacteraemias in-hospital also are gram- positive, and most of them are *Staph aureus*. About 9-11 million Americans are at risk for nosocomial infection; 1.3 million hospitalized patients had a culture-positive *Staph aureus* infection in 1999, making it the most common nosocomial pathogen in the previous six years. Staph-aureus-associated hospitalization results doubled hospital stays, deaths, and medical costs. Methicillin-resistant *Staph aureus* (MRSA) causes even more deaths than methicillin-sensitive isolates.

Most staph isolates are Type 5 or Type 8, and antibiotic resistance is present in the Americas and Europe. Studies of the Vancomycin-resistant strains include a bivalent *Staph aureus* vaccine challenge against the New Jersey and VISA strain in a murine lethality model. It demonstrated protection in an animal model. Of the 16 VISA strains

provided to NABI by the NIH Network on Antimicrobial Resistance in *Staph aureus* (NARSA), 14 were identified as Type 5, one as Type 8, and one was the uncommon Type 336 (a polysaccharide present on the cell wall upon a defect or outright absence of a capsule).

StaphVAX® is a conjugate capsular polysaccharide vaccine. It is made from the capsule of a polysaccharide purified of the *Staph aureus*, either Type 5 or 8, that is then conjugated with a detoxified protein from *Pseudomonas aeruginosa* expressed in a detoxified *E. coli*.

The preclinical data indicate that the capsular polysaccharide is antiphagocytic, hiding the bacterium from the immune system. The antibodies that are generated are very type-specific and they are responsible for the opsonophagocytosis that clears *Staph aureus* out of animals, including humans.

The bivalent (Type 5 and 8) vaccine covers >80% of the *Staph aureus* pathogens. The conjugate is immunogenic and induce a functional antibody of high affinity. It was shown to be protective in animal models presenting different types of infection paths. None of the antibiotic-resistant strains tested, including VISA strains, affected the vaccine's protective quality. Dr. Horwith pointed out that, while everyone has *Staph aureus* (5-15 µg) in our bodies, it is insufficient in quantity to produce antibody.

He then outlined the conduct of the StaphVAX® clinical trials. They began in 1991 with a collaboration between NIH, FDA, and Walter Reed Hospital that took the work though Phase I. In 1993, NABI (which was then Univax) conducted Phase II and began the Phase III study in 1998. The vaccine produced a good antibody titer at 10-14 days. A dose response was also seen in end stage renal disease (ESRD) patients at day 42. Revaccination at 18 months after the first dose boosted immunity back up to pre-existing antibody levels without any reactogenicity from repeat doses.

So, Phase I and II demonstrated the vaccine to be consistently well-tolerated and safe, and provided immunogenicity in end-stage renal disease patients.

The Phase III study (NABI-1356) is the first large-scale efficacy trial done among ESRD patients on hemodialysis. It was a double-blinded multi-center study conducted in California (Kaiser Permanente, Gambro, and TRC dialysis centers). The participants were stratified as *Staph aureus* culture-positive or -negative at study entry and by the type of dialysis used, and then randomized 1:1 to receive vaccine or to be in placebo groups.

ESRD patients have high rates of infection; frequent violation of the skin barrier, and usually have an indwelling foreign bogy (graft and AV shunt). They have a reduced immune response due to impaired neutrophil function (particularly those with diabetes), have renal failure, and are generally elderly. The company felt that if this vaccine could prove helpful in these patients, its safety and efficacy among immunocompetent

persons would be proven. The participants were at least 18 years of age; stable on a hemodialysis program for ≥8 weeks on study entry; and had a fistula or heterologous graft. They could not have any immunosuppressive agents or have active infection within two weeks of vaccination.

In all, a cohort of 1991 participated at 73 dialysis centers. The last participant was vaccinated in August 1999. They median age was 59 and the mean was 58; 52% had diabetes, and 65% of those with bacteremia had diabetes. Of those who developed a bacteremia during the course of the study, 65% were diabetic.

Of the 1804 patients who received the vaccine, 1798 were evaluated who remained on the protocol. The results showed an 84% response to the Type 8 vaccine component, and an 88% response to the Type 5 component. "Response" was defined as a doubling of antibody over baseline and an antibody titer of at least 25 µg/ml.

The safety profile was comparable to that of any intramuscular vaccine. There were statistically significant responses of induration, erythema, heat, pain, and malaise. Local reactions were all mild to moderate for a 2-3 days. None required medical care. Serious adverse effects (n=262) were expected in an ESRD cohort. They were comparable between the study groups and were not related to the vaccine or the placebo.

The study was powered to address mortality. Of the 152 deaths in the StaphVAX group, nine might have been related to vaccine versus 11 out of the 146 in the control group. Those results were not statistically significant.

The cumulative efficacy at the endpoint, which was arbitrarily set at week 54, reflected a 26% reduction in *Staph aureus* bacteraemia, which was not statistically significant. But the earlier measurements from week 2-40 reflected an efficacy of 57%, which was statistically significant.

They recovered 71% of the isolates and typed them, finding 80% to be Type 5 or 8, as predicted in the original sero surveys. The bacteremia risk was highest in those who were nasal-carriage positive and in the placebo group (7.2%) and 3.2% for those nasal carriage negative and receiving StaphVAX.®

The disclaimers provided for the post-hoc analysis included that it may be subject to intentional or unintentional biases in favor of demonstrating an effect. Two analyses were done: a permutational analysis and a cubic-spline analysis. All the data were used. The methods also adjusted for the statistical significance of a post hoc analysis and for repeated examination of the data.

He described the permutational analysis of 10,000 datasets generated from all 1798 subjects studied (vaccine and placebo). It compared true outcome from the vaccine recipients to that of the dataset. The outcomes were tested for contiguous efficacy for

a clinically relevant period set at ≥180 days. A weighted efficacy analysis was also done to emphasize those who remained infection-free for >180 days. The p value for the contiguous efficacy was 0.012 or 13 within a 95% confident interval and 0.023 for the weighted contiguous efficacy. The cubic spline analysis showed an efficacy drop at 40 weeks.

The NABI study conclusions were that the StaphVAX® efficacy was demonstrated through about ten months, shown by a reduction of bacteraemias corresponding to antibody levels of 80-100 µg. The vaccine was well tolerated. If StaphVAX ® reduces bacteraemias by 60%, the potential impact on the 246,000 ESRD patients at risk, with a bacteremia incidence of 5%, (12,300 annual bacteraemias) is a prevention of 7200-7300 bacteraemias annually. Even if the vaccine cannot be boosted, (to be evaluated), there would still be ~6150 bacteraemias prevented over the ten months of vaccine efficacy. The demonstration of safety and efficacy in this ESRD population indicates this vaccine to be an effective tool.

The committee's discussion included the following:

- *Does the vaccine essentially enhance phagocytosis; and if so, doesn't its effect depend on the phagocytic function in the immunocompromised patient?* Yes. *Is there any effect on carrier state?* No. *Was there any difference in the breakthrough bacteraemias between the groups?* There was no specific analysis of the subtypes done due to the number of isolates that could not be recovered. *Was the protective rate in the mouse similar to that in humans?* Yes.

- *Do you plan to do booster dose studies in subjects other than ESRD patients?* Yes, both to revaccinate about 150 of the same participants (about 1-2 years after dose #1) to see if the titers can be raised back to the original level, and to also vaccinate orthopedic patients.

- *Did you get blood samples from the breakthrough patients at the time they were bacteremic?* Only four specimens were collected, so this is hard to extrapolate. *Was there any relationship between the people with bacteremia and having a poor response or lower levels?* No, not on an individual level.

- *Is there any correlation between immunogenicity and efficacy?* The study did not stratify for this.

- *What is the status of vaccine development plans?* The booster study will be done, and an additional Phase III study may be done in the same patient population, but that is still in discussion with the FDA. FDA's position now is that since the vaccine did not reach the protocol-defined endpoint, another Phase III trial is needed.

Dr. Snider suggested that ACIP work with HICPAC on a recommendation for this vaccine, as was done for the BCG recommendation.

Public Comment.

Ms. Lynn Redwood first expressed her disappointment that not only was no preference given to thimerosal-free vaccines, they were not even addressed at this meeting. She recalled that the previous July, Dr. Bernier had testified to the Government Reform Committee about thimerosal-free vaccines and had committed to removing the thimerosal by early 2000. Last December, Rep. Mac Collins told her that CDC had committed to giving preference to thimerosal-free vaccine for infants at this meeting. She failed to understand why a preference could not be stated, knowing that SKB has more than enough thimerosal-free Infanrix® for every child in their first six months of life, and reserving thimerosal-containing vaccine for the fourth and fifth doses.

Second, she found the information provided on the previous day about the vaccine safety data to be misleading. The report cites was not meant to support or refute a causal relationship. In addition, the comment about there being no statistically significant association between autism incidence and thimerosal-containing vaccines was faulty. The children in that study averaged 3½ years of age, too young to be diagnosed with autism, which is typically undiagnosed until about age six. What is seen and diagnosed is speech, language and neurodevelopmental delays; tics; and echolalia. The last data report of that study raised the numbers of children with autism from 67 to 187, which is to be expected as children get older.

She noted that while the Harvard Pilgrim Hospital data only covered 30,000 children, the VSD has 213,000. The Harvard data were nowhere near as robust or as accurate as the VSD data, and were only added after the initial VSD data became available. She found the VSD data to call to question the validity of the Harvard Pilgrim data.

She questioned FDA's method of determining how much thimerosal American children have received. They averaged the exposures over six months of time, which any toxicologist would say cannot be done. Mercury has a long half-life, and a large dose is not comparable to small daily doses. One thimerosal-containing dose exceeds all federal safety guidelines for lowest observable effect.

Finally, she stated that, acknowledged or not, an autism epidemic is underway. She cited several areas as examples of this, including her own county, in which one of 125 kindergarten children was diagnosed with autism. She traced the rise in prevalence to the onset of use of Hib and hepatitis B vaccine, which tripled a child's exposure to mercury in the first six months of life. Finally, she asked why the committee had not expressed preference for thimerosal-free vaccine in the first six months of life.

Dr. Modlin responded that the committee had not given that preference due to their concern, with the state of the vaccine supply, that they may have to choose between putting children at risk of pertussis versus increased risk of diphtheria or even tetanus.

With the information in hand now, the risk of disease still outweighs the theoretical risk of thimerosal. Ms. Redwood objected that she was not proposing nonvaccination. Dr. Modlin understood that, but reiterated that the disease risk was very real.

Dr. Kristine Severyn asked if there is an ACIP statement on the use of Synygis® for prevention of RSV in premature infants. Dr. Modlin responded that the ACIP had not, but the AAP had made a statement on Synygis® and other immunoprophylactics for RSV. Dr. Severyn reported comment from many families whose children are receiving that injection at $1000 a shot. She suggested that the ACIP consider addressing this in a public forum. Dr. Modlin answered that the committee would consider it.

With Dr. Modlin's thanks and no further comments, the meeting adjourned at 3:40 p.m.

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

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John Modlin, M.D. Date
Chairman
Advisory Committee on Immunization Practices