ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Atlanta Marriott North Central - Atlanta, Georgia

5:00	**Revised Recommendation for Vaccination of Children Against Hepatitis A** Discussion on change agreed upon at the October 1998 meeting and approval of draft recommendation	Discussion Decision	Dr. B. Bell (NCID, DVRD)

5:45 Adjourn

February 18, 1999

8:00	**Unresolved Issues from the Previous Day**	Discussion	Dr. J. Modlin (Dartmouth Med. School)
8:30	**Recommendation for Lyme Disease Vaccine** Discussion of the revised statement Approval of the Lyme disease vaccine recommendation	Discussion Decision	Dr. D. Dennis (NCID, DVBID) Dr. D. Fleming (Oregon Hlth. Div.) Dr. N. Hayes (NCID, DVBID)
10:00	**Rotavirus** Re-address issues around use in premature children	Discussion Decision	Dr. J. Modlin (Dartmouth) Dr. C. Vitek (NIP, ESD)

10:30 BREAK

	Vaccines for Children Program Update on general principles of VFC Finish consolidating resolutions	Information Discussion VFC Vote	Dr. J. Livengood (NIP, ESD) Mr. D. Mason (NIP, OD)

12:30 LUNCH

1:30	**Standardization of Decision Rules for Vaccination** Draft recommendations	Information	Dr. R. Bernier (NIP,OD) Ms. S. Feikema (NIP, DMD) Dr. F. Guerra (San Antonio Hlth. Dept.) Dr. E. Maes (NIP, DMD)
2:30	**Electronic Updating of ACIP Reports and Recommendations**	Information	Dr. J. Ward (EPO, OD)
3:00	**Maintaining Public Confidence in Vaccines** NIP's Vaccine Risk Communication Efforts IDSA/PIDS Vaccine Initiative What role should ACIP/CDC play in dispelling myths and misinformation about vaccines?	Information Discussion	Dr. R. Chen (NIP, ESD) Dr. B. Gellin (IDSA) Ms. B. Hibbs (NIP, ESD) Dr. S. Katz (Duke University)

3:30 Public Comment

3:45 ADJOURN

ATTENDEES:

Committee Members
Dr. John Modlin (Chair)
Dr. Richard Clover
Dr. David Fleming
Dr. Mary Glode
Dr. Marie Griffin
Dr. Charles Helms
Dr. David Johnson
Dr. Chinh Le
Dr. Paul Offit
Dr. Bonnie Word

Ex Officio Members
Dr. Robert Breiman (NVPO)
Dr. William Egan (FDA)
Dr. Geoffrey Evans (HRSA)
Mr. Randolph Graydon (HCFA)
Dr. Gina Rabinovich (NIAID)
Dr. David Trump (DOD)

Liaison Representatives
Dr. Pierce Gardner (ACP)
Dr. Neal Halsey (AAP)
Dr. Rudolph Jackson (NMA)
Dr. Samuel Katz (IDSA)
Dr. Victor Marchessault (NACI)
Dr. Paul McKinney (ATPM)
Dr. Yvonne McHugh (BIO)
Dr. Ignacio Ortega (NVCM)
Dr. George Peter (NVAC)
Dr. Larry Pickering (AAP)
Dr. William Schaffner (AHA)
Dr. Jane Siegal (HICPAC)
Dr. Mary Tierney (AAHP)
Dr. Thomas Vernon (PhARMA)
Dr. David Wilson (AMA)
Dr. Richard Zimmerman (AAFP)

Executive Secretary
Dr. Dixie Snider

Office of the General Counsel
Mr. Kevin Malone

EPO
Chris VanBeneden

NCHSTP
Glen Nowark

National Center for Infectious Diseases
Allison Aiello
Dr. Miriam Atler
Dr. Beth Bell
Dr. Joseph Bresee
Dr. Lynette Brammer
Dr. Carolyn Bridges
Dr. David Dennis
Dr. Keiji Fukuda
Dr. Roger Glass
Dr. Ned Hayes
Rita Helfand
Dr. Hector Izurieta
Dr. Rima Khabbaz
Rob Lyerla
Dr. Hal Mangolis
Dr. William Martone
Dr. Eric Mast
Dr. Alison Mawle
Dr. Martin Meltzer
Dr. David Shaw
Bill Thompson

National Immunization Program
Dr. William Atkinson
Dr. Fran Averoff
Joe Beaver
Morinere Bernard
Dr. Roger Bernier
Dr. Bob Chen
Dr. Jose Cordeo
Dr. Steve Cochi
Dr. Jennifer Danielson
Maria Danward
Ms. Roz Dewart
Dr. Don Ekwuenme
Dr. Gary Euler
Dr. Suzy Feikema
Dr. John Glasser

National Immunization Program Cont.
Dr. Karin Galil
Dr. Dalya Guris
Dr. Beth Hibbs
Dr. Penina Haber
Dr. S. Humiston
Dr. Sonja Hutchins
Dr. Tamara Kicera
Dr. Duane Kilgos
Dr. Maureen Kolasa
Piotr Kramarz
Mary Lambert
Dr. Kimberly Lane
Dr. John Livengood
Dr. Ed Maes
Dr. Mary McCauley
Dr. Rebecca Martin
Gina Mootiey
Dr. Trudy Murphy
Glen Nowak
Dianne Quarterman-Ochoa
Dr. Walt Orenstein
Bette Pollard
Susan Reef
Dr. Ben Schwartz
Dr. Jane Seward
Dr. John Singleton
Dr. Vishnu-Priya Sneller
Robert Snyden
Elizabeth Spears
Heidi Steele
Dr. Ray Strikas
Cecelia Thompson
Dr. Fran Walker
Michael Washington
Dr. Bruce Weniger
Dr. Bob Wentworth
Amy Paul-Ward
Dr. Melinda Wharton
Jessie Wing
Skip Wolfe
E. Yacovone
Lynn Zanardi
Laura Zimmerman Swain

National Vaccine INFO CTR
Michael Belkin

OD
Charlis Thompson

Other Government Attendees
Dr. Karen Midthun, FDA

Others Present
Wendy Adams, Aviron
Lynn Bahta, IAC
Michelle Bailey
Michael Belbruir, NVIC
Douglas Bell, Wyeth Lederle
Karen Biscardi, PMC
Susan Brantley, Ortho Pharmaceutical
Jillian Carleon, Conn & Wolfe
Dan Casto, Merck Vaccine Div.
Jill Chamberlain, Vaccine Bulletin
Christina Chan, Merck
Keith Chirgwin, M.D., Merck
Troy Couch, Wyeth, Lederle Vaccines
Chris Courtois, SmithKline Beechman
Dack Dalrymple, Bailey & Dalrymple
Bill Darnall, Merck
Cheryl Diday
Bill Hayes Dorff, Wyeth Lederle
Jacquer Drucker
Gundula Dunne, CDC Student
Maria Favarito, Collus Wolfe
David Fedson, Pasteur Merieux
Barbara Loe Fischer, NVIC
Karen Fobchner, Lyme Disease Foundation
Cynthia Fowler, RW Johnson PRI
Yvonne Fuller, NMA
Joe Gaugi, QSI
Bruce Gellin, IDSA
Anne Gershon, M.D., Columbia University
Ruth Gilmme, GA Immunization Prog.

Others Present – Cont.

Kerry Gilzene, SmithKline
Alan Goolet, Biochem
Elizabeth Goss, Fox, Bennet & Turner
Jennifer Gottlieb, C & W Health Care
Eddie Gray, SmithKline Beecham
Jesse Greene, SC Dept. Health
Jeff Hackman, PMC
Jennifer Harvey, ASTHO
J.S. Harward, SmithKline Beecham
Richard Haupt, Pediatric Assoc. of MI.
Bill Hausdroff, Wyeth-Lederle
Joanne Hayward, Merck & Co.
Carol Hewett, Law Offices
Carol Hoban, DHR
Charles Holmes, U of Iowa
Sandra Holmes, Aviron
Phil Horne
Phil Hosbach, PMC
John Hollister, Aviron
Bita Honarvar, Pediatric News-Freelance
Barbara Howe, SmithKline Beecham
Kristen Huamani, C& W
Sue Hull
Young Hur, Korea of Health & Welfare
Clifton Irby, Christian Science Comm
Rich Keenan, Wyeth Lederle
Andrea Kesack, SmithKline
Alan Kimura, SmithKline Beecham
A.N. Krishney, SmithKline Beecham
Charolette Kroft, SmithKline Beecham
Barb Kuter, Merck Research Labs
Myron Levin, Univ. of Colorado Health
Scott Litherland, Parallax Commuc.
Sharon Ludwig, US Coast Guard
Jose-Luis Diaz
William Martone, NFID
Kathryn Meinrs, Johnson & Johnson
Peggy Monkus, GA Immunization Prog.
Andrea Morgan, Medua Pharma
Gary Noble M.D., Johnson & Johnson
Randy Pierson, IPAV
Peter Paradiso, Wyeth-Lederle
Robert Pietrusko, SmithKline Beecham
Eileen Plante, Merck
Stanley Plotkin, PMC
Jane Quinn, Merck
Sioshion Quinn, SmithKline Beecham
Carlos Quintanilla, GIP
Cassandra Richardson, Infectious Diseases
Gina Robinson, NIH
Croff Rogers, Merck & Co.
Fred Ruben, Pasteur Merieux Connaught
Florian Schodel, Evax
David Schofield, SmithKline Beecham
Kristine Severyn, Vaccine Policy Institute
Robert Sharrar, Merck & Co.
Frederic Shaw, Hepatitis Control Report
Judith Shindman, Pasteur Merieux Con.
Alan Sievert, Dekalb County Board of Hea.
Natalie Smith, CDHS
Jaco Smit, Pasteur Merieux Con.
Dale Spriggs, Bio Chem Pharma
Nick Spring, Merck
Stacy Stuerke, Merck Vaccine Division
Peter Tobar, Wyeth Vaccines
Miriam E. Tucker, Pediatric News
James Veazey, Biochem
Peter Vigliarlo, Cooney-Waters
Anne Walsh, SmithKline
Vandersmisger Walter, SKB
Beth Waters, Cooney-Waters
B. Watson, Phila Dept. of Public Health
Deborah Wexler, IAC
Laura York, Wyeth Lederle
John Zahradik, Pasteur Merieux
John Zhang
Willie Zimmerman, VET

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Advisory Committee on Immunization Practices
February 17-18, 1999

FEBRUARY 17, 1999

The Centers for Disease Control and Prevention convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on February 17-18, 1999 at the Atlanta Marriott North Central Hotel in Atlanta, Georgia. Chair Dr. John Modlin called the meeting to order at 8:33 a.m. 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.

The members introduced themselves and stated their potential conflicts of interest. The members without conflicts were:

- David Fleming, M.D., State Epidemiologist of Oregon Health Division
- Mimi Glode, M.D., pediatric infectious disease physician, University of Colorado
- Charles M. Helms, M.D., Ph.D., University of Iowa
- David Johnson, M.D., Michigan State Health Officer, Department of Community Health
- Bonnie Word, M.D., pediatric infectious disease physician, Central New Jersey

Those members with conflicts of interest may participate in discussions, but may not introduce, second, or vote on Vaccines for Children Program resolutions. Disclosure of conflicts is only required of voting members, but ex-officio and liaison members were also encouraged to disclose any conflicts. The members reporting potential conflicts of interest were:

- Richard Clover; M.D., University of Louisville: he and his department received honoraria and/or grants from Merck and Company, Pasteur-Merrieux Connaught, and SmithKline Beecham.
- Marie Griffin, M.D., Vanderbilt University Department of Preventive Medicine: she is Chair of Merck's Endpoint Monitoring Committee, which is not vaccine-related.
- Fernando Guerra, M.D., Director of Health, San Antonio, Texas: his department has done vaccine studies for Merck, SmithKline Beecham, and North American Vaccine, and he has consulted for Pasteur-Merrieux Connaught.
- Chinh Le, M.D., Chief, Infectious Disease Division, Kaiser Permanente Northern California: Kaiser conducts research studies with Merck, Wyeth Lederle, and SmithKline Beecham, and North American Vaccine. He has worked with Pasteur-Merrieux Connaught, and owns stock in Merck.
- John Modlin, M.D., Chair: owns stock in Merck.
- Paul Offit, M.D., Chief of Infectious Disease at Children's Hospital, Philadelphia: he co-holds a patent and consults in the development of a rotavirus vaccine by Merck.

The ex-officio and liaison members in attendance were:

- Rob Breiman, M.D., National Vaccine Program Office (NVPO)
- William Egan, M.D., Food and Drug Administration (FDA)
- Geoffrey Evans, M.D., Health Resources and Services Administration (HRSA), National Vaccine Injury Compensation Program
- Pierce Gardner, M.D., American College of Physicians (ACP)
- Randy Graydon, Health Care Financing Administration (HCFA)
- Neal Halsey. M.D., American Academy of Pediatrics (AAP)
- Rudolph Jackson, M.D., National Medical Association (NMA)

- Sam Katz, M.D., Infectious Disease Society of America (IDSA)
- Victor Marchessault, M.D., Canadian National Advisory Committee on Immunization
- Paul McKinney, Association for Teachers of Preventive Medicine (ATPM)
- Yvonne McHugh, M.D., Biotechnology Industry Organization (BIO)
- George Peter, M.D., National Vaccine Advisory Committee (NVAC)
- Larry Pickering, M.D., Red Book, American Academy of Pediatrics (AAP)
- Regina Rabinovich, M.D., National Institutes of Health (NIH), National Institute for Allergies and Infectious Diseases (NIAID)
- William Schaffner, M.D., American Hospital Association (AHA)
- Jane Siegel, M.D., Hospital Infection Control Practices Advisory Committee (HICPAC)
- Mary Tierney, M.D., American Association of Health Plans liaison (AAHP)
- David Trump, M.D., Department of Defense (DoD)
- Thomas Vernon, Pharmaceutical Research and Manufacturers of America (PHARMA)
- David Wilson, M.D., American Medical Association (AMA)
- Richard Zimmerman, M.D., American Academy of Family Physicians (AAFP)
- Ignacio Ortega, M.D., National Vaccination Council of Mexico

CDC staff present included:

- John Livengood, M.D., Epidemiology and Surveillance Division, National Immunization Program (NIP), CDC
- Alison Mawle, M.D., National Center for Infectious Diseases (NCID), CDC
- Walter Orenstein, M.D., NIP

Opening Comments

ACIP Executive Secretary Dr. Dixie Snider welcomed the attenders. He announced that the next ACIP meetings are scheduled on June 16-17 and October 20-21. He noted that the ACIP charter allows the Executive Secretary to designate ex-officio members to vote when less than a quorum of members can vote due to conflict of interest. Public comment would be received from those who had signed up to do so at specific points in the agenda. While the ACIP Chair attempts to allow open comments, Dr. Snider asked that they be brief. Dr. Modlin noted that a document had been distributed to the members on the government's rules of financial disclosure. He requested that this be reviewed and responses given to Ms. Gloria Kovach. He noted that the ACIP recommendations on rabies had been published and were available at this meeting, as well as Notices to Readers with updates on the DTP and hepatitis B vaccines.

Agency Updates

Food and Drug Administration (FDA)

Dr. William Egan, the Acting Director of FDA's Office of Vaccine Research and Review, announced the retirement of Dr. Carolyn Hardegree after a long and distinguished career. Dr. Norman Baylor is the Acting Deputy Director; the permanent Director will be recruited soon.

In the last year, the Office of Vaccine Research formed internal workgroups to discuss how to approach/address vaccine issues, including HIV and DNA vaccines, use of cell substrates and adventitious agents, and bioterrorism. An increased lab emphasis has occurred in the last year on cell substrates, adventitious agents, and TSE agents, all related to vaccine safety. FDA is are considering the use of tumor cell lines as cell substrates for viral vaccines (particularly for HIV vaccine), and expanded use of continuous cell lines for live viral vaccines.

Non-tumor cell lines are not yet available. A co-sponsored workshop with NIH and the National Vaccine Program is planned in fall, and an updated combination "Points to Consider" vaccine document is likely.

In other areas, FDA approved the LYMErix™ vaccine developed by Smith-Kline Beecham Biologicals on August 31, 1998. FDA commended Pasteur-Merieux Connaught for their good handling of the recent Tripedia™ vaccine recall due to subpotent content (posing no safety issues), as well as the CDC/ACIP for their recommendations. Finally, Dr. Egan reported renewed interest in the consequence of SV-40 contamination of the polio (1950-1960s) vaccine, which is now associated with tumors. Media attention was spurred by a recent article by Janet Butelle and John Lemicky in the *NCI Journal.* FDA and the WHO are both receiving calls on this.

National Immunization Program (NIP)

Dr. Walter Orenstein reported the *provisional disease reporting data from 1998.* He recalled the 1988 measles resurgence, in which >55,000 cases occurred over three years, producing >11,000 hospitalizations and >100 deaths. Little more than 100 cases were reported in 1998, an all -time low. An outbreak in Alaska has spurred a more aggressive pursuit of the two-dose schedule there. A slight rise in rubella occurred in 1998, still primarily among adults/Hispanic immigrants. NIP is working with Mexico/Latin America to incorporate rubella into their immunization programs, a drive supported by the Pan American Health Organization's Technical Advisory Committee. Pertussis cases were level in 1998, about half in those aged ≥10 years. There were no cases of wild virus polio in 1998, nor indigenously acquired cases since 1979. There was one confirmed vaccine-associated paralytic polio case in 1998, and three others are under investigation.

Introducing the President's budget recommendations, Dr. Orenstein explained that there are four funding sources for vaccine purchase: the Vaccines for Children (VFC) entitlement program (guided by ACIP resolutions and representing about 35% of the market), the federal discretionary 317 grant program (used by state and local health departments to cover children not eligible for the VFC–it captures 15% of the market); state/locally-funded programs (8%); and the private sector (43%).

The President's budget for infrastructure (e.g., surveillance) will remain unchanged from the FY99 budget. The 317 program budget received increases, including: 1) $60 million additional for vaccine purchase. This should fund in FY2000 the ACIP-recommended routine use of rotavirus vaccine, and catch-up for all children aged 12 months-18 years for varicella (10% coverage) and for hepatitis B (25% coverage) catchup; 2) $17 million additional for polio eradication, raising CDC's contribution to global polio eradication to $80 million; and 3) $15 million additional to strengthen CDC's extramural prevention research program. Project partnering is planned with managed care, academic health centers, and others. Of this, $750,000 will be given annually to NIP for each of three years to fund investigator-initiated cooperative research on controlling diseases recently made vaccine preventable. External peer review for awards is planned. An April RFA will be issued, with applications due in July, and awards are expected by September. An additional $450,000 for one year was given to NIP for surveillance research in managed care settings.

National Vaccine Compensation Program (NVCP)

Dr. Geoffrey Evans reported that only about 10 claims per month had been received since the last meeting. A small number of pre-1988 claims were dismissed due to the elapsed 1991 deadline for adjudication. Four claims related to varicella vaccine and none were for Hib alone. The program is adding coverage for rotavirus vaccine injury upon the publication of ACIP's recommendation in *MMWR*; the tax to cover this was effected in last October's budget bill. Nearly $1 billion overall has been paid in claims. With 95% of the pre-1988 program's claims complete, those for the post-1988 program are becoming predominant in adjudication and payment.

A planned General Accounting Office review of the National Vaccine Program Office and NVCP will address management/disbursement of compensation funds, claims review/processing, and collection/distribution of information on vaccine safety/injuries. Interviews are planned at CDC as well. The program welcomes this activity and will its report results later this year.

National Vaccine Program Office (NVPO)

Dr. Rob Breiman reported on the January meeting of the National Vaccine Advisory Committee (NVAC). The Vaccine Safety Action Plan developed by the Interagency Vaccine Safety Working Group was endorsed, which focuses on vaccine safety and communication issues. The workgroup encouraged collaboration with state/local health department and the private sector in its development, and ensuring that appropriate partners are involved to develop time lines and priorities in its implementation. Also recommended was implementation funding independent of current vaccine safety activities. Accelerated media attention to vaccine concerns, some unbalanced, was noted. The science of vaccine communication is a major part of NVAC's plan.

NVAC was updated on the ongoing development of immunization registries. Four hearings this past summer focused on the related privacy, technical, and resource issues. A report is pending, which is hoped to lead to an action plan of registry implementation. This activity is led by Dr. Mary Hendricks, the former NACCHO President. In other areas, a workgroup on the Influenza Pandemic Preparedness Plan is in formation. Its experts will advise on critical policy issues to prepare for/respond to a pandemic. NVAC also submitted for publication a report on sustaining success in immunization coverage.

Finally, Dr. Breiman reported activity in the last nine months to re-examine global vaccine issues. This includes attention to needed changes in the 1990 Children's Vaccine initiative, which focused on introducing vaccines to developing countries and on ensuring adherence to vaccine standards globally. The World Bank, the Rockefeller Foundation, and UNICEF are exploring changes and coalitions. Identifying and addressing gaps is critical in this work, which cannot be done by any single agency involved in the global immunization components. ACIP comments were welcomed.

Public Comment

Dr. Kristine Severyn from the Vaccine Policy Institute of Dayton, Ohio, asked Dr. Orenstein to make his slides available. She also objected to jesting comments about confession, a sacrament of the Catholic church, made during the committee introductions and statements of conflict, particularly since this was Ash Wednesday. Dr. Modlin apologized on behalf of the committee for the unintended offense.

ACIP Work Group Reports

Adult Immunizations Workgroup

Dr. Richard Clover reported that the Adult Immunizations Workgroup is addressing strategies and methods to improve adult population vaccine rates (e.g., focusing on prison settings, migrant workers, etc.) and addressing special vaccine issues (e.g., use of acellular pertussis vaccine in adults). A lunch meeting on these issues was planned for at this meeting.

General Recommendations Workgroup

Dr. Chinh Le reported the General Recommendations Workgroup's multidisciplinary membership, which includes academia, the private sector, NIP, and committee members. Transferred staff member Dr. Jay Watson was replaced by Dr. John Livengood.

The Workgroup agreed with Einstein that "everything should be made as simple as possible, but no simpler." A long document should be avoided, and rather 1) succinctly provide practical guidelines and recommendations for vaccine administration, 2) discuss issues applying to vaccine information and administration; 3) provide background information and references which support current immunization practice; and 4) be targeted to such readers as teaching institutions, and individuals or clinics providing immunization.

Two options for revision were presented: 1) retain a single comprehensive monograph with as much useful information as possible. The disadvantage is that the material could be quickly outdated, but it could be modeled on the AAP's Red Book and revised every three years or so. Or, 2) a non-disease-specific "major" ACIP document on infrequently-revised topics could be issued which provide principles and recommendations, administration techniques including that of concurrent multiple vaccines, vaccine interchangeableness, spacing of vaccines and other immunobiologics; vaccine safety contraindications, reports of adverse effects, etc. This could be supplemented by a separate set of often-revised disease-specific documents detailing, for example, listings of products, manufacturers, immunization schedules, storage and handling, etc.

The committee's feedback was requested on the choice between a single monograph (Dr. Le's preference) or two documents, as well as specific additions and deletions. The latter included issues relating to deletion of discussion on passive immunization in immunoglobulin preparations and immunization among the immunocompromised hosts; transplantation; whether to merge or keep separate implementation standards for pediatric and adult immunization practice; and whether to pursue publication of national "harmonized" standards for vaccine administration. Other items inviting discussion after input from the CDC/NIP scientific consultation, such as accepting vaccination records from other countries, especially those from orphanages; spacing of live virus vaccines given non-concurrently, TB skin testing with TB or varicella vaccine; conflict in needle-length recommendations for intramuscular injection in adults; and jet injection. Other issues include whether to include implementation standards for pediatric and adult immunization practice (now separate) in the General Recommendation document; overlapping discussion and recommendations with other ACIP workgroups in progress such as on immunizations and standardization of decision rules for vaccination; and whether NIP staff can handle the work of publishing document revisions in a timely fashion.

Discussion
Dr. Halsey expressed some support to separate disease-specific recommendations, but thought these impossible to update annually due to the time and input required. As with the Red Book, he thought a general update to be possible every 3 years, with clear notification that electronic (*MMWR*) revisions update this paper document. Dr. Orenstein thought that catch-up schedules could be published annually as a third page to the annual published schedule recommendation.

Pneumococcal Workgroup
Dr. Johnson recalled the last meeting's report of a randomized controlled trial which demonstrated a 100% efficacy of a seven-valent conjugate vaccine against invasive diseases. Data from the ongoing analysis of vaccine effectiveness for otitis media and pneumonia is expected shortly. This pneumococcal vaccine is expected to be licensed late in 1999.

Dr. Chris Van Beneden introduced Dr. Peter Paradiso of Wyeth-Lederle, who provided further follow-up data on this trial. The data reflected children analyzed by full or partial immunization with the vaccine in an intent-to-treat analysis using both vaccine and non-vaccine serotypes. In the same study groups as the original trial (>38,000 children), Wyeth-Lederle found 32 cases in the fully-immunized (another vaccine) control group, and 8 cases in the partially-immunized (not full schedule) group. The conjugate vaccine was 100% effective. The non-vaccine serotypes split, with three cases in the PCV7 (7 serotypes) group and six in the controls.

The workgroup will developed and circulate to the ACIP members a draft statement in the next two months. With licensure expected this year, a final statement is hoped for by October. The proposed statement addresses: 1) epidemiology of pneumococcal disease in the U.S., including rising resistance and the importance of its unique serotypes; 2) the new conjugate vaccine's immunogenicity and efficacy studies in healthy pediatric (aged <2 years) U.S. populations; 3) available information of immunogenicity studies in other high-risk pediatric populations (HIV-positive and sickle-cell anemia patients and Native Americans, also addressing the importance of included serotypes); 4) vaccine safety; 5) vaccine administration (including simultaneous administration with other vaccines and perhaps combination vaccines); 6) possible administration in children aged >2 years (including catch-up vaccination); and 7) recommendations for high-risk groups where polysaccharide vaccine is already recommended (>5 years old).

Discussion
Dr. Gardner asked if the Pneumococcal Vaccine Workgroup only addressed the conjugate, noting the importance of addressing the safety of revaccination in the 23-valent polysaccharide vaccine. Dr. Van Beneden agreed, but confirmed that this short statement's (and workgroup's) current focus is on the conjugate vaccine.

Polio Workgroup
Dr. Paul Offit identified the members of the Polio Workgroup, which discussed the movement to an all-IPV schedule and the related issues and time lines. Two options were considered: 1) recommendation of an all-IPV schedule by January 1, 2000; or 2) recommendation of an all-IPV schedule by January 1, 2000 with the sequential schedule as an acceptable alternative for the transition year (beginning on that date) but not after January 1, 2001. The workgroup

recommended the second option.

Dr. Offit outlined the issues and time lines for resolution: 1) assurance of a stockpile of OPV for outbreak control (a collaboration of CDC, the FDA, and manufacturers) will be done by January 1, 2000; 2) preparation and distribution of an ACIP statement draft (the first will be done prior to October 1999, the second draft by February 2000, and final publication by July 2000); 3) prepare a vaccine information sheet reflecting the all-IPV recommendation by January 1, 2000, to be final by January 1, 2001; and 4) solicit input from community partners and public health officials (ongoing).

Discussion

Dr. Snider asked how the recommendation would be implemented on January 1 if not published until July. Dr. Offit expressed the workgroup's expectation that a short ACIP statement (3-4 pages) would be published in the *MMWR*. Dr. Johnson added that the immunization schedule would be harmonized to advise an all-IPV recommended but accepting a sequential schedule for the year 2000. Dr. Halsey said that this would be acceptable to the AAP.

Dr. Katz asked when combination vaccines including IPV could be expected. Dr. Le reported a Kaiser/SmithKline Beecham study on a DTaP-IPV-Hib-hep B combination. Dr. Guerra asked for an update on purchases of IPV and OPV. Dr. Rebecca Prevots reported IPV purchases up a little in 1998, but not dramatically, c. 30% of all polio doses purchased. That equates to about a three-fifths implementation of the sequential schedule.

Dr. Fleming was reluctant to mandate IPV by 2001 in all cases, and wanted more discussion of what circumstances would allow OPV as an acceptable alternative. Dr. Offit responded that the idea is to eliminate use of OPV in order to eliminate polio in the U.S., but exceptions would exist (e.g., if two doses of IPV are not assured prior to travel to endemic region). Dr. Zimmerman reported AAFP's similar discussions. They noted the burden to the practitioner to explain the advantages and disadvantages of both schedules and the need to stock both vaccines, when by the time today's newborn is 4-6 years old there would not be any OPV. For that reason, the AAFP recommended an all-IPV schedule with a footnote stating the sequential schedule as still acceptable. Dr. Clover support an all-IPV schedule as long as the WHO's OPV use for global eradication is respected. Dr. Barbara Watson of the Philadelphia health department noted that many small practices still use OPV. She advised quick information to the private sector if this recommendation is issued within 10 months. Dr. Modlin summarized that this was clearly the direction of the committee. The final details will be discussed in June.

Public Comment

Mr. Randy Pearson spoke on behalf of Mr. John Salamone and Informed Parents Against VAPP (IPAV). His son Gordon has VAPP and lives with a wheelchair, a ventilator, and 24-hour nursing care. IPAV is not anti-vaccine, but pro-safe vaccine. It is supportive of the move to all-IPV and encourages implementation of these new recommendations by the year 2000 so that VAPP is a disease of the past. He urged the committee to adopt the January 1, 2000 policy to avoid the risk of any more children with VAPP. Finally, he reported with sadness that Mr. Harvey Wilcox , who addressed the ACIP in June 1997, had lost his son to polio. He thanked the committee for its action on behalf of all children.

Statement on Prevention and Control of Influenza
Dr. Guerra introduced this topic, reporting several workgroup meetings held to fine-tune the statement.

Ms. Lynnette Brammer reported on the international influenza activity and vaccine strain selection for the 1999-2000 influenza season. She shared a graph of the influenza isolates reported by the laboratories of the WHO and the National Respiratory and Enteric Virus Surveillance System. Since Type A viruses have predominated in the U.S., most have been subtype H3N2; 20% of the reported viruses were influenza type B. Most of the A (H3N2) virus samples antigenically typed at CDC were similar to A/Sydney/ 5/97, which is included in the influenza vaccine. The limited number of H1N1 viruses this year are similar to A/Bayern /7/95. The H1N1 vaccine component this year is for A/Beijing 262/95 virus). It is antigenically distinct from A/Bayern but antibodies produced to Beijing viruses cover A/Bayern-like viruses. All of the B viruses isolated this year in the U.S. are have been B/Beijing/184/93-like, which is included in the vaccine.

Charted U.S. surveillance data from this season showed that influenza-like illness as reported by sentinel physicians has been above baseline values for three weeks. The number of state and territorial epidemiologists reporting either regional or widespread activity has also increased in recent weeks, but there has not yet been sustained excess mortality. Most European countries also reported widespread influenza, mostly Type A (H3N2), and mostly similar to A/Sydney. But influenza B (similar to B/Beijing/184/93) predominated in Belgium, the Netherlands, and Spain. Influenza Type A/H3N2 was also predominant in Asia (mostly similar to A/Sydney), but 11% of those viruses tested in CDC labs showed a reduction in titers against A/Sydney antibodies. Outbreaks of respiratory illness in Northern China prompted concern over a variant influenza virus, but samples tested at CDC were mostly A/Sydney-like. There are some outbreaks in Asia, mostly B/Beijing-like. Influenza B has two currently circulating lineages, B/Beijing and B/Victoria. The latter circulates only in Asia and has not been in the in U.S. since 1990.

Ms. Brammer outlined the vaccine strain selection process. On January 29, 1999, the FDA decided to retain the A/Beijing H1N1 component as the H1N1 vaccine component. They deferred a decision on A(H3N2) and B components until the WHO vaccine strain selection. The WHO voted this week to retain A/Sydney for the 2000 vaccine, and in a departure, left it to the individual countries to select either the B/Beijing or B/Shandong strain for their vaccine. FDA will make its final strain vaccine selection on March 11.

Studies of the Impact of Influenza on Children aged <5 years
Dr. Keiji Fukuda introduced two studies that were recently conducted to determine if influenza-related morbidity or mortality is increased among children aged <5 years. Dr. Marie Griffin discussed her study of influenza morbidity among children in Tennessee. The study population included low-risk children aged <15 years, all enrolled in Tennessee Medicaid from birth or at least for one year before study entry. None had high-risk conditions for which influenza vaccine is recommended, nor were institutionalized, disabled, or had a low birth weight.

The study reviewed 19 years of data on hospitalizations and physician visits. Their methodology used person time to calculate rates. The year was divided into a summer period,

a peri-influenza period, and an influenza season. The latter spanned about 2.2 months as was defined by Vanderbilt University's continuous viral surveillance system during the 19 years of this study. The typical pattern of hospitalizations for respiratory illness was a baseline rate in summer, a rise in the peri-influenza season, and a peak in influenza season. A line chart showing both CDC's mortality data and morbidity data from the Tennessee database showed a well-defined influenza season in 1977-78, but a less clear pattern in 1990-91.

The data for the low-risk Tennessee children showed hospitalization rates (per 100 children hospitalized) in 1974-1993 at about 1.5 times higher than the national rate for children aged <1 year for respiratory diagnoses. The rate for all cause hospitalizations was 32 per 100 children, as compared to the national rate of 7 per 100. However, the Tennessee rate also included children hospitalized multiple times.

The study methodology was to annually calculate the hospitalization rate during influenza season, subtract that in the peri-influenza season, and attribute the excess rate to influenza. They also explored the percentage attributable to influenza of the whole winter's excess rate of hospitalization for respiratory illness by subtracting the summer hospitalization rate for respiratory illness.

A bar chart of excess hospitalization rates for children aged <1 year showed 72 per 10,000 children; 32 of those were attributable to pneumonia and influenza only. The rate of influenza-related hospitalizations fall radically with advancing age: 10 per 10,000 in those aged 2 and 3, and 2-4 per 10,000 in those aged ≥4 years. The excess winter hospitalizations due to influenza were lower for very younger children, at 15-20% of total winter excess versus 20-30% for older children.

They used the same methodology of comparing influenza versus peri-influenza time periods for outpatient visits and antibiotic courses, and found these close to national rates. One correlation indicated that most older children who go to a physician receive an antibiotic. The study's data suggest that 10 to 20 percent of antibiotics in younger children are due to influenza, a correlation also found in other studies.

The limitations of the data include: 1) possible confounding by other winter viruses, especially RSV, which overlaps the influenza season and introduces a potential overestimate of 10-20%. 2) Baseline data for hospitalizations for young children were also more variable than for adults. 3) Very young children may be hospitalized for other types of conditions than influenza, such as sepsis syndrome or fever of unknown origin, so it is not certain that all influenza -related morbidity in very young children was captured.

Conclusions: influenza hospitalizations for "low-risk" children are very high for those aged <1 year (3-7/1000). They were also high for children aged <4: 1-2/1000 excess hospitalizations (similar to high-risk young adults). But other children aged >4 years were similar to low-risk adults (3-5/10,000). Influenza accounts for 15-30% of excess hospitalization. For outpatient care, influenza accounted for 6-14 excess treatments per 100 children and ≥30% of excess outpatient visits, 5-9 excess antibiotic courses per 100 children; and 10-30% of excess winter antibiotic use.

Dr. Hector Izurieta presented the preliminary findings from one study site of the impact of

influenza on rates of respiratory disease hospitalizations among children. The main hypothesis explored was whether healthy children aged 0-4 years are at higher risk of influenza-related hospitalization compared to healthy older children. The cohort included children aged 0-17-years, members of the Group Health Cooperative of Seattle (managed care group) either continuously enrolled for one year, or born within one year before the period of interest. High risk children were defined based on ACIP recommendations: the children had either been hospitalized, seen as outpatients, seen in emergency room for a high-risk condition, or had been prescribed medication.

The study periods were influenza periods defined as the successive weeks during the winter in which 10 percent or more of the isolates are influenza, and in which no other respiratory viruses were found in ≥10% of the submitted tests. A similar method defined the RSV season.

The two outcomes studied were acute lower respiratory disease hospitalizations using ICD9 codes for pneumonia, influenza, or acute bronchitis and all respiratory disease hospitalizations using ICD9 codes for all respiratory diseases except pneumoconiosis.. They calculate the rates of respiratory tract disease hospitalizations per 100,000 person-months by age, risk status (high- or non-high risk), and by period. Excess rates were calculated by subtracting the baseline rates from those of the specific influenza periods.

The data showed that most of the illness occurred in the first two years of life. The rates of lower respiratory disease hospitalizations in children aged <2 years were significantly higher than those for adolescents. When the analysis was focused on children aged <5 years, the rates of the specific influenza period were lower than the rates in the standard influenza period, which are lower than the RSV period. RSV was the main illness in children under 5.

The excess rates were calculated by estimating the rates during a specific influenza period minus the rates during the summer baseline. This analysis showed that the excess rates for children under 2 were significantly higher than zero, ranging 22 to 71 per 100,000. The excess rates for all respiratory disease hospitalizations for a specific influenza period among-high-risk children were similarly significant, between 16 and 85 per 100,000.

The study then compared excess rates of respiratory disease hospitalizations for children aged <5 years across studies regardless of risk status. Mallooly and Barker in a 1982 published study reported excess rates of influenza-related lower respiratory disease hospitalizations of 120 per 100,000 in a December-to-March influenza period during the 1968-69 pandemic year, and in the severe season of 1972-73. Glezen reported 155/100,000 in 1981-82, and 248/100,000 in 1982-82. In the Group Health Cooperative study, the estimated impact of influenza among all respiratory diseases using the standard definition of the influenza season was 123 per 100,000 persons; for all respiratory diseases, 76 per 100,000 persons; and for lower respiratory disease hospitalizations during the specific influenza season, 30 per 100,000.

Dr. Izurieta summarized that RSV is a confounder in the analysis of the risk of influenza-related hospitalizations among children aged <5 years. In these studies, the children under 2 years of age appear at higher risk for influenza- and RSV-related hospitalizations. However, further study site data are being collected to confirm these findings and assess their generalizability.

Discussion

Dr. Orenstein asked for details on the 11 children aged <2 years who were hospitalized for influenza. Dr. Izurieta reported these as lower respiratory infections, pneumonia, and bronchitis. Dr. Jackson noted that both Atlanta and Pittsburgh were flattened with influenza this winter, and asked the lag time and/or under-reporting of surveillance data to CDC. Dr. Brammer reported only a one-week lag. But CDC does not receive actual numbers of cases; only reports from state epidemiologists of their state/territory's activity, which may vary from state to state. Most are just indices to reflect increases in activity. Dr. Jackson asked about the use of rapid diagnostic tests, and Ms. Brammer reported no good information on how many are using them. One Year 2000 surveillance question for this spring addresses their availability in hospital/HMO settings. Two new antiviral testing kits were released this season, and were heavily marketed. Dr. Modlin recalled data mentioned by Dr. Paul Glezen that some very young infants (1-3 months) may have some passively acquired antibody to influenza. He hoped the related data would be parsed down even further.

Potential Changes to ACIP Influenza Recommendations

Dr. Keiji Fukuda summarized the evolving developments driving changes in the influenza recommendations: development of live attenuated influenza vaccine (LAIV), impending licensure of neuraminidase inhibitors, marketing of rapid detection kits; vaccine cost effectiveness studies; and unusual summer outbreaks.

In 1998-9, the Influenza Workgroup discussed: 1) the possible expansion of influenza recommendations, focusing on healthy children <5 year-old and healthy adults aged 50-64 years; 2) the potential role of new products (LAIV; antivirals including neuraminidase inhibitors); 3) Guillain-Barré Syndrome (GBS); and 4) summer outbreaks.

The workgroup assigned a top priority to expanding vaccine use in all high-risk groups aged <65 years, in whom vaccination coverage averages <30%. The current knowledge of barriers to vaccination in these groups needs to be summarized, and pilot projects done to find ways to surmount those barriers.

Dr. Fukuda summarized the workgroup's discussions by age groups.

- *Healthy children aged <5 years* are indicated by older data as a high-risk group for influenza-related complications. As described at this meeting, this is supported by recent unpublished studies, but these findings are inconclusive pending further analysis. Among the methods issues are how to separate influenza from RSV and the effects in high-risk versus healthy children.

  The workgroup discussed the issues likely to arise if vaccination was recommended for this group: 1) how many children and family contacts would be affected; 2) who would pay and where would they be vaccinated over a short period; 3) determining the recommendation's acceptability to parents/the pediatric community– would it lower the acceptability of other vaccines?); 4) determining the benefits/cost effectiveness of a long-term annual program; and 5) determining the long-term immunologic effects of annually vaccinating children. Additional CDC studies and analyses are planned among hospitals with HMO databases, as well as a cost effectiveness analysis.

- *Healthy children aged 5-18 years.* The workgroup's prevailing sentiment was that there is currently no compelling case to routinely vaccinate this age group of healthy children. Whether doing so could reduce the community spread of influenza is a topic of current research.

- *Healthy adults aged 18-49 years:* Again, no compelling data invite extending recommendations to this group now. But there are important issues related to cost effectiveness; for example, Dr. Kristin Nichols' study showed costs savings with vaccination of young healthy adults. A literature review and modeling done for a workgroup meeting showed variable results depending on the study, year, and circumstances. It is unknown if cost effectiveness would occur over an extended period.

- *Adults aged 50-64 years:* This group is of interest due to its increasing influenza-related mortality and morbidity and increasing prevalence of high-risk conditions. Age-specific analyses are planned. The logistical questions include the number affected by such recommendations, and possible coordination with pneumococcal recommendations.

Live attenuated influenza vaccine: The timing of this vaccine's licensure is uncertain, but unlikely for the 1999-2000 influenza season. There will be no ACIP recommendation until its licensure, but background work has begun for this document.

Antiviral agents: After some discussion, it was agreed to retain this in the ACIP document. However, the use of antivirals in controlling outbreaks is not well described for settings other than nursing homes. To distinguish Rimantadine from Amantadine, the document points out its lesser association with CNS side effects. Finally, a scheduled FDA meeting on neuraminidase inhibitors the following week was reported.

Proposed 1999 changes to the ACIP general influenza recommendation
Dr. Fukuda reviewed in detail the changes made to the ACIP's general recommendation on influenza prevention and control, as well as comments recently received. The recommendation's text:

1. Notes increased use by the elderly, but remaining lower use in Blacks and Hispanics and in high-risk groups aged >65 years.
2. Discusses additional vaccine benefits of cost saving and decreased antibiotic use. *Additional comments* advised indicating that inactivated vaccine is also associated with decreased antibiotic use, and mentioning that pneumococcal vaccine can be given simultaneously with influenza vaccine.
3. Assigns a top priority to increasing coverage in high-risk groups aged <65 years.
4. Makes no major changes in recommendations on vaccine use.
5. Is shortened in the pregnancy section.
6. Is unchanged in the vaccine safety section.
7. Contains altered recommendations on travelers to address the increased risk of influenza exposure among large international travel groups as well as in travel to the tropics and southern hemisphere. It advises travelers at high risk of influenza complications to consult a physician about influenza risk before traveling and about carrying antivirals with them. *Additional comments* found the wording too permissive, potentially causing confusion and perhaps stimulating unmeetable antiviral and vaccine demand. The discussion begins with all travelers and ends with only high-risk travelers. A focus only on high-risk travelers

was advised, with cruise ship/tourist outbreaks not expected to be a substantial annual problem.

8. Addressed needle length in discussing dosing route and timing of vaccination. *Additional comments* noted that this has remained unresolved for years; some think shorter needles inadequate. Most manufacturers at a recent PHARMA meeting expected no problem in going from a 5/8" to 1" needle. But doubt was expressed that side effects increased with subcutaneous injection with shorter needles; and 5/8" is a community standard. Using a longer needle in the elderly could cause subperiosteal deposition of vaccine, and unpublished data indicates equivalent titers from subcutaneous versus intramuscular injections; when they differ, intramuscular injection provides higher titers. Permissive recommendations were suggested for 5/8" and longer needles. Another comment suggested referencing vaccine "usually" available in September for the upcoming influenza season.
9. Divided discussion of effects and adverse reactions to those which are local/systemic and those related to GBS. *Additional comments:* This section created lots of controversy and involves the most liability issues for the manufacturers. Wording changes, which will be redistributed, included: a) mention of the lack of vaccine-associated GBS in the 18-44 age group (at low risk of severe influenza complications) in the 1992-94 influenza vaccine study. Dr. Orenstein noted that the permissive language poses different impacts to that group; but it is important to note no cases among 4 million doses. Dr. Robert Chen added, however, that note also is needed that data are unclear on age-specific risk. He advised including other studies' results as well. Other wording changes included, on page 9: "slightly more than one additional case of vaccine-associated GBS;" removing "were slightly elevated" before "not statistically significant"; on page 10: alternates to the text on no definitive data linking influenza to GBS of (a) "no definitive data proving or disproving this association" or (b) referencing "case reports of GBS following influenza vaccination, but no epidemiologic studies documenting such an association..."; replacing "may provoke GBS" with "is associated with;" and clarifying "that". Also no page 10, references were provided to support the paragraph about GBS' low incidence in the general population and anticipating a greater risk to those with GBS history. But it needs to be clearer that it is unknown if those with a GBS history are specifically at greater risk of GBS after influenza vaccination. The wording of recurrent GBS as "is expected" should be changed to "may be expected."
10. Provided background information on LAIVs. *Additional comments*: Caution was advised to not advertise a commercial product.
11. Discusses the potential expansion of groups for recommended vaccination. *Additional comments:* clarify "technical developments."
12. In antiviral agents, emphasizes their role as an adjunct to vaccine, and cites many experts' consideration of Rimantadine as safe and effective among children. *Additional comments:* Add to the referenced "strong consideration" for extending vaccination to this group "if the programmatic and economic consequences of such a recommendation are adequately addressed."
13. Added as section on the role of viral diagnosis, comparing three different kits.
14. Added a new section on antivirals. *Additional comments* from FDA's Center for Drug Research noted that new data are available on Rimantadine; no new studies are needed or being conducted. But "safe and effective" sounds like an ACIP seal of approval; replace it with "many experts consider Rimantadine acceptable (or useful) in the treatment of children." And, regarding evolving developments of antiviral agents, clarify that critical

studies are underway and that there is a need for re-evaluation of the role of neuraminidase inhibitors as prophylaxis and treatment when new data are available. Other wording changes may arise after FDA's February 24 meeting on a new product.

Dr. Fukuda requested comments by February 26; by March 5, draft #7 would be returned to the ACIP and other reviewers; draft #8 must be to *MMWR* on March 19 for an April 30 publication.

Discussion
Dr. Modlin congratulated the workgroup on this achievement and urged the members to provide comments to Dr. Fukuda. Although more changes are needed, they were expected to be minor, and a vote was needed on this day to allow publication. But Dr. Halsey demurred; since controversial issues remain, he disliked voting without further discussion. This would leave the final wording in the hands of only a few people. He hoped that next year, only the controversial issues would be offered to allow for discussion by the committee. Dr. Snider offered as an alternative to take a formal vote by a conference call after review of the next and subsequent drafts. Committee management would arrange that, including the necessary announcement of a public meeting in the Federal Register. Dr. Fukuda left his overheads to guide the committee on the issues of importance to discuss.

Varicella Prevention
Dr. Jane Seward provided a background to the varicella issues to be addressed. The vaccine was licensed March 17, 1995 and available to the private sector in May; ACIP recommendations were approved in June 1995 and published in 1996. The AAP recommendations were published in May 1995; and the federal vaccine contract was signed on May 10, 1996. The vaccine was available to the private sector in late 1996. As of December 31, 1998, 14.2 million doses had been distributed, 8.1 million in the private sector and 6.1 million in the public sector. The National Immunization Survey indicates that vaccine coverage in 1997 among children aged 19-35 months was 26%, with state and urban areas ranging from 4-43%. National coverage was up to 39% in the second quarter of 1998; the third quarter data will adjust the denominator to exclude children with prior disease.

Varicella vaccination barriers include: perception of the disease as too mild for vaccination; concerns about vaccine effectiveness/safety; persistence of immunity with a disease shift to adults where disease is more severe; and cost and availability (barriers mostly removed). State health departments also cite the absence of an ACIP recommendation for use in outbreak control.

Dr. Seward outlined three studies which provide reassuring estimates of vaccine effectiveness in the field. One was published in JAMA in 1997 and the other two were presented at the IDSA meeting in Nov., 1998. Two were of child care center outbreaks and one was a case-control study in a pediatric practitioner's offices in the New Haven area.

CDC is addressing these barriers. Data refute the perception of the disease as mild: the disease burden for the five years pre-licensure (1990-4) included 4 million cases/year, >90% in children (aged <20 years), resulting in 11,000 hospitalizations, 69% of them for children, and 105 deaths, 45% among children. The NIP data on deaths 1995/6 indicate that, considering deaths from diseases for which vaccines are routinely recommended in childhood, of the 105

vaccine-preventable deaths in children aged <20 years, the majority (76) were from varicella. Eleven of those deaths were in children aged <1 year. None were due to polio, diphtheria, tetanus, or mumps. In children aged 1-9 years, almost all deaths were due to varicella.

National surveillance for varicella deaths has been in place since late 1997; and nationally reported to CDC since January 1999. Cases of three related adult deaths were outlined among healthy parents exposed to their children' varicella. One adult on prednisone contracted it from an unvaccinated child in her family-run child care center. Three cases in children in 1998 were also outlined.

Proposed ACIP Recommendation Language

Requirements for Child Care and School Entry

The National Health Interview Survey (NHIS) provides age-specific incidence for varicella, which clearly show that incidence is highest in the pre-school and early elementary school-aged children. A bar chart clearly demonstrated the rising incidence to age six (age of school entry), and dramatic drop thereafter. Another showed the higher incidence in child care settings. An outbreak was summarized in a small Boston child care center where of 14 children, 12 were susceptible, and the attack rate was 100%. Two were hospitalized with invasive Group A Streptococcus complications. An outcome of this outbreak was increased demand for vaccine due to the media attention surrounding the outbreak. Massachusetts has passed an immunization requirement for child care entry (August 1998 implementation) and school entry (to be implemented in September 1999).

The Healthy People 2010 goals for varicella are to have >90% coverage in 2010 among children aged 19-35 months, and >95% coverage at school entry. This undoubtedly will require state requirements for child care and school entry.

The Council of State and Territorial Epidemiologists (CSTE) issued a position statement in 1998 calling for all states to begin preparing child care and school vaccine requirements by 1999. The AAP Committee on Infectious Disease is considering endorsing this in their revised statement. State immunization programs indicate that an ACIP recommendation helps them to develop requirements. Six states now have such requirements in place, although not all have been implemented, and eight have requirements in process.

Proposed recommendation: "ACIP recommends that all states implement a requirement that children entering licensed child care facilities and elementary schools have received varicella vaccine or have evidence of immunity to varicella. Evidence of immunity should consist of a physician diagnosis of varicella, a reliable history of varicella, or serological evidence of immunity. In addition, all states should consider implementing a requirement that children entering middle school (or junior high) have received varicella vaccine or have evidence of immunity to varicella."

Discussion

Dr. Halsey appreciated the statement's aims to remove barriers to physicians regarding vaccine use. The AAP will reaffirm some of the controversial issues regarding vaccinating children in households with a pregnant woman or immunocompromised individual, etc. They had not discussed modification of statement language about physician evidence/certification of

varicella history because that evidence is weak, but they have emphasized physician-diagnosed varicella.

Dr. Johnson commented that most states with child care/school entry varicella requirements accept parental history as adequate proof of immunity/disease. In Michigan, they concluded that since many clinical practitioners do not have children come in for a chicken pox diagnosis, requiring that certification would create more problems than it solved. They probably will gradually implement this requirement as was done for measles, requiring vaccination/serological proof as the disease becomes more infrequent.

Dr. Zimmerman raised the liability issues related to retrospective diagnosis by a physician for a new patient. Dr. Orenstein was comfortable with the language as stated, citing the measles and mumps recommendations as a precedent: physician-diagnosis is acceptable evidence; without it, or in the presence of doubt, recommend vaccination. Dr. Glode agreed; requiring physician history would require a clinical appointment and burden the physician community.

Dr. Modlin suggested substituting a "signed parental statement," to nods around the table. Dr. Guerra reported just that done in San Antonio, coupled with criteria to help inexperienced parents avoid misdiagnosis of something mimicking varicella, such as scabies or flea bites. Upon assurance that such other conditions were considered, they accept the parent's (or experienced daycare worker's) ascertainment of chickenpox. Dr. Seward also noted that physicians face the same decision in deciding whether to vaccinate a child based on history.

Dr. Fleming reported Oregon's experience that promoting varicella vaccination to resistant physicians was facilitated by focusing on adolescent/middle school immunization, to prevent people passing through school unvaccinated or exposed, and ensuring that the top end of the age scale would be vaccinated. He hoped that "school entry" would not be interpreted as only the primary grades. Dr. Seward noted, however, that this is not in the measles statement and that many states are implementing adolescent requirements. She asked if such specificity was needed. However, Dr. Modlin thought that since the states are asking for this, it should be specific. In that case, Dr. Fleming suggested text to specify "children attending school," rather than school entry, if not "adolescent requirement." Dr. Clover disagreed, preferring to state any entry into school. Particularly considering the migration between states, he would not restrict the entry statement to middle school.

Dr. Orenstein favored the more practical graduated implementation for measles, which began with K-1 rather than K-12. Dr. Johnson agreed. Michigan would update the history or vaccinate as needed all children entering kindergarten or a school district for the first time. He would hesitate to have ACIP recommend for all grades, although he agreed to the importance of addressing the middle school student. He suggested, rather than addressing students "entering licensed child care centers and...", he suggested those "attending" them, to give more flexibility.

But Dr. Orenstein noted that "school attendance" generally means K-12. Catch-up is already recommended to age 18; this change would specifically ensure immunization at one or two points in time. He suggested adding "middle school" to licensed child care and elementary schools. Dr. Fleming agreed; if the state was approached this piecemeal, this would encourage the middle school requirement first. Dr. Peter advised a two-step approach,

recommending a requirement for school entry as in the original draft and a second paragraph to encourage states to consider vaccinations for middle school. And, since the focus is on reliable history, he suggested substituting "reliable" for "parental" and leaving the interpretation to the program.

Dr. Fleming proposed giving middle school equal weight and placement with elementary school, rather than adding second paragraph. Dr. Griffin agreed, since middle school is the most important cohort to keep from reaching adulthood without immunity. But Dr. Orenstein observed that the greatest prevalence of morbidity is in school entry, and felt that separating them emphasizes the rationale supporting middle school immunization as a priority. Dr. Johnson noted that many states don't have a middle school assessment, so providing equal weight to kindergarten entry would be important, but he supported separate statements. The text of the recommendation was revised overnight for a vote on the following morning.
Decision: Deferred

Use of Vaccine for Outbreak Control
Dr. Seward drew the members' attention to a distributed handout which summarized the extensive available literature on the use of vaccine. She noted that the absence of an ACIP recommendation hinders use of the varicella vaccine for outbreak control/post-exposure prophylaxis. In its own statement revision, the AAP's Committee on Infectious Diseases is considering a stronger statement supporting post-exposure use.

The live attenuated Japanese varicella vaccine (Oka/Biken), licensed in 1974, demonstrated 70-100% effectiveness if administered within 5 days of exposure, 100% if administered within <3 days, using doses lower, similar to, and higher than the U.S.-licensed Oka/Merck vaccine.

The strongest data come from household exposures. In two controlled trials in Japan, the vaccine was given to seronegative healthy siblings exposed in a household. In the first study, none of the 18 children developed varicella (vaccine efficacy [VE] of 100%) compared with all the unvaccinated controls. In the second study, two of 34 vaccinated children developed a mild rash; again, there was a 100% attack in the unvaccinated siblings. The efficacy was 71%, but some vaccine was delivered in 300-600 platforming units (PFU), and effectiveness was not reported by vaccine dose. Nonetheless, it clearly was very effective in preventing moderate and severe disease. It is extensively and effectively used in Japanese hospitals to prevent disease from post-hospital exposure in both healthy and high-risk children.

Data from another Japanese study of timing and dose (300-15,000 PFU), for those both with- and without varicella symptoms was demonstrated on a scattergram. Of those with 300-600 PFU doses, 610 children developed mild rash (10 vesicles); and all with >600 PFUs were protected from varicella. After five days, the three children with doses of 1500-4000 PFUs all developed clinical varicella. Another chart showed the lower dosage to be as effective as the Merck vaccine's 1350-10,000 PFU doses. The Japanese concluded that the Oka/Biken vaccine was highly effective and recommended it for post-exposure prophylaxis, especially in hospital settings.

A small study (Salzman) published in *Pediatric Infectious Disease Journal* in 1998 reported vaccine administered to 10 siblings. Five of the ten developed a mild rash compared with historical controls who would have had an 87% attack rate (for an unvaccinated control group), but

the rash was not tested for vaccine-relatedness.

Comparisons of two homeless shelter outbreaks in winter in Philadelphia also supported vaccine use. Vaccine use in one shelter (Dr. Barbara Watson) resulted in only a 3-week outbreak of five cases and a 6-week shutdown to new admissions. Two varicella cases in a mother and infant exposed 52 susceptible children aged <13 years. Vaccination and disease histories were checked and vaccine was administered 36 hours post-exposure. Two weeks later, two cases with 15 lesions each emerged in two siblings, and one varicella case (300-500 lesions) in an unvaccinated child with an erroneous history. VE was 95% to prevent all disease and 100% to prevent severe diseases. On the other hand, non-use in another large shelter of 400 people resulted in a 6 month-shutdown. One varicella case exposed 134 children aged <13 years with undetermined susceptibility, resulting in 63 cases. Data from two outbreaks in child care centers was mathematically modelled. These outbreaks lasted 12-15 weeks. The modelled data predicted that 98% of cases could have been prevented with vaccination 0-2 days after the start of the outbreak. Even if a vaccination clinic were offered at 28-30 days, 87% of cases would still have been prevented.

CDC also has assisted with many adult outbreaks, recommending vaccine use for outbreak control for every one, and the military has published reports of vaccine use to control outbreaks.

Proposed text (similar to the measles outbreak control statement): "Varicella outbreaks in child care, school, and family shelter settings, with a high proportion of susceptible children, may last for 3-6 months. Varicella vaccine may shorten outbreaks by preventing or modifying disease among persons already exposed and by preventing cases among persons not yet exposed. Local and state health departments should consider use of varicella vaccine for outbreak control either by advising exposed susceptible persons to contact their regular health care provider for vaccination or through offering vaccination through the health department. Staff of the National Immunization Program, CDC, are available to assist health departments in developing an outbreak control strategy."

Discussion

Dr. Fleming thought that state and local health departments would ask if people receiving post-exposure vaccine should be considered susceptible regarding re-entry to child care and school settings. Dr. Orenstein favored allowed re-entry, as done with measles, because new generation of disease is unlikely within an immunized setting. Barring them would essentially punish them for seeking vaccination.

Dr. Fleming asked about exposed health care providers. Dr. Watson recalled that issue as arising when the vaccine was licensed; the hospital infection control committee was unwilling to allow re-entry to those immunized back. But with four years of occupational data, they are now only barred from high-risk settings such as the oncology ward. And as seen in Philadelphia, keeping shelters closed for a lengthy time is not feasible. In the 6-week outbreak, the children were kept from school; but they did not develop disease, so the subsequent shelters' children have gone back to school with no further spread. When Dr. Egan asked whether the adults in Philadelphia were followed to administer a second dose, she confirmed that as now a standard practice; none developed disease.

Dr. Trump noted that the wording discusses populations of healthy susceptible children, but it could be interpreted as applying to similar adults (e.g., college students). Dr. Livengood suggested inserting a general statement that "varicella outbreaks, in *certain settings: (e.g., child care, schools, other institutional settings)* may last for 3-6 months." He also suggested a recommendation that local/state health departments at least send a letter to parents to contact their health care provider, even if they do not actually deliver the vaccine.

VOTE on recommendation regarding use of vaccine for outbreak control in a supplementary varicella statement: *"Varicella outbreaks in certain settings: (e.g., child care, schools, other institutional settings) may last for 3-6 months. Varicella vaccine may shorten outbreaks by preventing or modifying diseases among a proportion of persons already exposed and by preventing cases among persons not yet exposed. Local and state health departments should consider use of varicella vaccine for outbreak control either by advising exposed susceptible persons to contact their regular health care provider for vaccination or by offering vaccination through the health department. Staff of the National Immunization Program, CDC, are available to assist health departments in developing an outbreak control strategy:"*

Only five ACIP members had no conflict with Merck, requiring the votes of the ex-officio members if they so chose; they were not obligated to do so. The five eligible ex-officio members were Drs. Evans, Rabinovich, Trump, Egan, Breiman (absent for this vote), and Mr. Graydon.

In Favor:	Glode, Fleming, Word, Helms, Johnson, Trump, Graydon, Egan, Rabinovich, Evans
Opposed:	None
Abstained:	Griffin, Clover, Guerra, Offit, Le, Modlin
Decision:	**Passed**

Use of Vaccine Among Persons Exposed to Varicella

Proposed text: "Exposure to varicella is not a contraindication to vaccination. Varicella vaccine, if administered within 72 hours of and possibly up to 120 hours following varicella exposures, may prevent or significantly modify disease. If exposure to varicella does not cause infection, post-exposure vaccination with varicella vaccine should induce protection against subsequent exposure. If the exposure results in infection, no evidence indicates that administration of varicella vaccine during the presymptomatic or prodromal stage of illness increases the risk for vaccine-associated adverse events."

Discussion

Dr. Offit found the data up to 72 hours to be convincing but asked about the efficacy up to days 4 and 5. Dr. Seward reported a good amount of data indicating that dose on days 4 and 5 would be effective, but more data would be useful by day or on the period after day 5. Dr. Le suggested language to recommend the varicella vaccine for susceptible populations within 72-120 hours. A first sentence of "Varicella vaccine is recommended for use in susceptible persons following exposure to varicella" could help avoid missed vaccination opportunities.

Dr. Halsey raised the difference between continuous household sibling contact (for which the

data indicate probable protectiveness for up to 96 hours post-exposure) and social contact exposures (e.g., at a party with a known specific time of exposure). He wondered if the recommendation should account for the 24-hour infectious period prior to rash onset. He also advised a cautionary note in the statement that a child vaccinated near the five-day border could develop disease, and to recommend reaffirming the child's exposure to avoid misperceptions if vaccine-caused chicken pox. Such anticipatory guidance should be given particularly for a rapid onset case. Dr. Watson, however, noted that the Vaccination Information Statement for parents clarifies that, and thought it unnecessary to address. Dr. Snider thought that Dr. Halsey's points could be included in an *MMWR* article.

Dr. Helms felt that for consistency if the vaccine use is recommended under these conditions, it should also be recommended under outbreak control. In that case, Dr. Guerra wondered if use of antivirals with exposures >120 hours should be advised. Dr. Modlin acknowledged that this would parallel the influenza statement addressing chemoprophylaxis. It could be considered in the next varicella update.

Dr. Siegel advised including some text in the *MMWR* article about patients exposed in health care facilities as vaccine candidates, if not otherwise contraindicated, because this is an important infection control issue. Dr. Glode proposed adding the issue of VZ16 prophylaxis in the statement's discussion, but with clarity that this does not replace VZ16.

VOTE on recommendation regarding use of vaccine among persons exposed to varicella for outbreak control: *"Varicella vaccine is recommended for use in susceptible persons following exposure to varicella. Exposure to varicella is not a contraindication to vaccination. Varicella vaccine, if administered within 72 hours of and possibly up to 120 hours following varicella exposures, may prevent or significantly modify disease. If exposure to varicella does not cause infection, post-exposure vaccination with varicella vaccine should induce protection against subsequent exposure. If the exposure results in infection, no evidence indicates that administration of varicella vaccine during the presymptomatic or prodromal stage of illness increases the risk for vaccine-associated adverse events."*

Conflicts:	Merck. ex-officio members were asked to vote.
In favor:	Glode: Fleming, Johnson, Helms, Word, Evans, Rabinovich, Egan, Graydon, Trump
Opposed:	None
Abstained:	Clover, Guerra, Offit, Le, Modlin
Decision:	**Passed**

Dr. Modlin asked if the ACIP should issue a specific recommendation for this vaccine's use in outbreak control. Dr. Fleming opposed that, since other activities probably would have to be dropped by health departments to effect that, and only 30% of children are currently vaccinated. He preferred text that is supportive and permissive as opposed to mandatory.

Dr. Offit asked if the distinction between "is recommended" and "should be considered" is based on data supporting efficacy. He wondered if it should also consider cost and, for example, modify a recommendation if cost is prohibitive. Dr. Modlin agreed that this is an important problem, but recommended tabling this for informal conversation or another agenda.

Dr. Snider noted that such a decision should be part of ACIP's policy/procedures document. To date, the ACIP had not tried to get as specific as, for example, the U.S. Preventive Services Task Force, since the ACIP considers more than just the science to recommend (i.e., economic, social, and legal issues).

Varicella Vaccine Use in Children With HIV/AIDS

Dr . Seward introduced Dr. Ann Gershon and Dr. Myron Levin, both Professors of Pediatrics at Columbia University and the University of Colorado, respectively. They presented data on studies among children with leukemia in the 1980s and among children with HIV in the 1990s. The children with leukemia were in remission and were receiving maintenance chemotherapy when immunized. For leukemic children, vaccine side effects were high (approximately 40-50% developed rash and fever) but these children have much poorer T cell function than asymptomatic children with HIV infection. Based on the study which they reported, in which they they were impressed with the vaccine's safety in a subset of HIV-positive children, they hope for a recommendation to provide it to other HIV-infected children.

The HIV-infected children in their studies were immunized in the pediatric ACTG program. Dr. Anne Gershon presented data suggesting a greater severity of chicken pox in children with leukemia than in those with HIV. Among a group of 49 children followed in New York, pneumonia mortality in children with underlying cancer (mostly leukemia) was 9%, versus none in those with HIV. She noted that early reports were among hospitalized HIV-infected children, and therefore were biased by the presence of more severe disease.

Safety data on vaccinees with leukemia and immunocompromised children differ. Studies of three different lots of vaccine used in the 1980s (Merck lot 867, a consistency lot, and a production lot, all with the same PFUs) produced a post-vaccine rash (about one month post-vaccination) in 26% of the lot 867 group, 62% of the consistency lot group, and 47% of the production lot group. Those with >100 lesions were 26%, 22%, and 17% respectively. They were treated with acyclovir. The children were given two doses of vaccine, which was found 86% efficacious after household exposure. They developed rash from the vaccine, some with enough lesions to be treated with acyclovir and with enough lesions to be considered chicken pox.

Chicken pox is more severe in HIV-positive children than in those who are healthy. A startling frequency of zoster development in seen in those children with HIV, particularly in those with low CD4 levels at chicken pox onset. Of those with <15% CD4 cells on contracting chicken pox, up to 80% developed zoster within two years, some of them developing chronic zoster; but in those with >15% CD4 count, only 6% developed zoster. Therefore, the interest in immunizing children with HIV targets zoster as well chicken pox. Immunized children with leukemia also had a significantly lower incidence of zoster than naturally-infected children.

Dr. Myron Levin then reported on the NIH/NIAID safety/immunogenicity study of immunization of 41 children with HIV in ACTG 265. The children were aged 1-8 years, with no evidence of having had chicken pox and identified as mildly affected by CDC category A1 or N1. They received two doses of commercial vaccine separated by three months (the schedule used for the leukemic children). They were evaluated for local and systemic reactions after each dose; the CD4 count at baseline and monthly; the HIV plasma level at baseline and at weeks 4, 12, 16, and 28; VZV antibody was measured by LPA at baseline and 8-weeks post-dose; and the

children were followed after varicella exposure.

These immunized children had fewer local and systemic reactions (the latter included everything: otitis media, fever, rash, etc.) than immunized leukemic children. The systemic reactions declined between the two doses. The main systemic reaction was fever (20% of children had fever after the first dose, half of those having fever >103°), but only 5% had fever after the second dose. Vaccine-related skin lesions were rare and those seen were local, a different result than seen in leukemic children. There were no serious events and none changed their CDC clinical categories.

Changes in the CD4 counts and plasma HIV RNA levels were not significant at 4 or 8 works post-dose, but their CD4 counts did change at 16-20 weeks. However, this could be due to the natural history of HIV progression in children with high viral loads.

The antibody response was 53% after one dose; 60% after dose 2. This was lower than in leukemic children. Cell mediated immunity ,as measured by lymphocyte proliferation, increased from 65% to 83% between doses 1 and 2. They observed the same phenomenon seen by Dr. Gershon in leukemic children: those history- and antibody-negative had false-positive baseline LPAs, demonstrating the same response as those with negative LPA at baselines. Ultimately, 80% developed cell-mediated immunity after vaccine regardless of study entry category. This was demonstrated on a 2x4 table.

Dr. Levin summarized that antibody and cellular immune response were not closely correlated, but more importantly, neither the CD4 count nor HIV viral load correlated with seroconversion in 86% of vaccinees after one dose, and in 88% after two. However, they found that viral load was important. After dose one, there was a correlation of HIV viral load prior to the first dose with a positive LPA afterward, but less of a correlation after the second dose.

The exposure outcomes were followed in nine children with 7 playmate/classmate exposures and one household exposure. Of those, two children received VZ16, and none developed chicken pox. One additional child, with no history of a varicella exposure, developed mild varicella.

The conclusions were that varicella vaccine is safe and immunogenic in children mildly affected by HIV infection. The protocol includes follow-up for the next three years for vaccine persistence and efficacy. They also are extending the study to children with more advanced disease (clinical Stage B or immunologic Stage 2) to test reconstitution.

Proposed text: "Varicella virus vaccine should not be administered to persons who have primary immunodeficiency, including cellular immunodeficiency, hypogammaglobulinemia, and dysgammaglobulinemia. Children infected with HIV may be at increased risk of morbidity from varicella and herpes zoster. Limited data on vaccination of 41 HIV-infected children indicate that the vaccine is immunogenic and effective. No severe adverse effects to vaccination were observed in this group. Therefore, weighing potential risks and benefits, varicella virus vaccine should be considered for HIV-infected children with a CD4 percent >25%. Routine screening for HIV before vaccination is not recommended. The use of the varicella vaccine in HIV-infected children is being investigated further."

Discussion
Dr. Halsey reported AAP's plan to review all their live viral guidelines for the immunosuppressed, some of whom (children with selective IgA deficiency, subclass IgG deficiency) have no problem with these viral infections and can be vaccinated. However, dysgammaglobulinemia groups them all together; he suggested re-examining that language. He also advised caution in going beyond the package insert, particularly since these two studies are small, although good. More studies are needed, and the limitations of the data must be stated. He favored text that vaccination "is recommended" over "is considered."

Dr. Robert Sharrar of Merck knew of no data specifically on vaccine use among children with hypo- and dysgammaglobulinemia. Dr. Katz suggested approaching this as was done with VAPP. Potential humoral immunodeficiency probably would not have been diagnosed if vaccine is administered early; whole the cellular-immunodeficient child would have been ill prior to age one. He suggested simply stating "cellular deficiencies." Dr. Levin suggested changing the test to "children with CDC Class I level of disease." Dr. Pickering suggested including common variable immunodeficiency under cellular humoral deficiency, since children with that can react to live viral vaccines.

Dr. Orenstein acknowledged the committee's expertise here, but thought this issue to be sufficiently generic that, rather than rewrite the varicella text, it be addressed in the general recommendations. Dr. Halsey suggested addressing "children whose underlying conditions predispose them to more severe disease." The AAP's recommendation will probably suggest consultation with an expert such as an immunologist. Dr. Modlin stated that common variable immunodeficiency is a T-cell immunodeficiency and should be included, but x-linked agammaglobulinemia is not and should not be included. He thought the statement to be on reasonably firm ground based on expert opinion. Dr. Offit disliked using the term "cellular immunodeficiency," observing that B-cells are cells. He suggested tabling this recommendation, to general agreement.
Decision: Tabled

Public Comment
Mr. Michael Belkin, Director of the Hepatitis B Project of the National Vaccine Information Center, noted that VAERS data indicate a threefold rate of reported severe adverse reactions in 1996 as reported disease cases in the 0-14 age group. Of the 2424 adverse events reported 1990-1998 in children aged <14 years who only received hepatitis B vaccine, there were 1209 serious events and 73 deaths – 50% of the children <14 years who received only hepatitis B vaccine. He was astonished that the scientists of this committee would disregard or cover up data on the severity and number of adverse reactions to this vaccine.

Mr. Belkin felt that a benefit risk analysis of the hepatitis B vaccine for the average American infant must conclude that VAERS shows the real-world risk of death or injury to a newborn infant, greater than the remote chance of contracting this primarily blood-transmitted disease. His 5-week old daughter, Lila Rose, had died within 16 hours of receiving this vaccine, which was given due to ACIP's 1991 universal vaccination policy. At her death, Lila had four of the eight highest reported symptoms in the VAERS hepatitis B adverse reaction data. Mr. Belkin holds all those who promulgated this policy of mandated newborn vaccination to be negligent and personally responsible for her death. He charged that, because CDC refuses to acknowledge this large number of adverse reactions, misled hospitals and doctors continue to

administer the vaccine and then deny the connection to effects. To continue that denial is negligent, unethical, and a crime against American children.

Hepatitis B Recommendation

Dr. Hal Margolis noted that since the hepatitis B statement's revision in 1996, new vaccine formulations and recommendations had emerged. Incorporating these into the updated ACIP document, which had been distributed, would make it more useful to the practitioner. He invited the members comments, particularly as regards the document's user-friendliness. He also noted the limited information provided on the combined hepatitis B-Hib conjugate vaccine, which was left to be discussed in the full statement.

Discussion

On discussion, the members offered the following edits:

- Provide more detail in the summary of what the new recommendations are, or refer to the pages with new information (Fleming).
- Clarify whether all children or only those at high risk are targeted; provide separate infection risk rather than that adjusted for age/ethnicity; extend the section on vaccine safety (Griffin)
- Emphasize the need for vigilance as to concentrations of 5 μg or 10 μg to avoid under immunization (Guerra).
- Clarify where "care provider" means "family"; clarify advice to begin immunization whether or not completion is assured, and to vaccinate adolescents at any visit with a goal of completion by age 11-12 (Le).
- Delete "catch-up" from the section title of Vaccination of Children at High Risk of Infection (page 55) and move it to Vaccination of Groups at Increased Risk (page 56); translate that back to the summary; fully integrate recommendation for vaccination of all children throughout the text (Vernon).
- Clarify/strengthen the case for immunization: the goal of transmission elimination within age groups (Orenstein); also cite the expected mortality of hepatitis B infection (Snider).
- Mention the WHO work on infant immunization, emphasize that this is the first anti-cancer vaccine, and parallel this to polio eradication (Schaffner).
- Examine the tables for consistency and clarify that other schedules can be used (Halsey); add a subsection to that effect, rather than addressing this under Interrupted Schedules; and add to the rationale the goals for 2010 when available (Peter).
- Ensure consistency on dose intervals and duration of protection (Orenstein).
- Add that those with chronic hepatitis C with ongoing risk factors should be vaccinated (Griffin).
- Be consistent that the duration of protection is 15 years (Vernon).

Some percentage risks, not yet in the text distributed, were supplied to the ACIP: an average 30% risk of percutaneous exposure to blood; risks to sexual and nonsexual household contacts were in an upper bound of about 60%, but the lower bound was not available at this meeting; nonsexual contact risk is about 30%. Dr. Vernon noted the difference cited in transmissibility from household contacts in highly endemic areas (page 20) versus acute hepatitis B (page 48). Dr. Margolis confirmed the difference between chronic carriers and acute hepatitis B; the recommendation has reflected that since 1981. Most children adopted from an endemic country are chronic cases. He would like to add as an important component in the 2010 goals to put antigen-positive children into the category of non-sexual household

contacts.

Dr. Karen Midthun, of the FDA, noted that Table 1 included Comvax™ administration to infants of hepatitis B surface antigen-positive mothers, while the label indicates it for surface antigen-negative mothers. She asked how the label's schedule should be addressed. Dr. Margolis reported that some areas (Alaska, the Pacific) are considering the combination vaccine to finish the schedule with that later dose, rather than at 6 months. The issue of interference is only inferred where, for example, Pedvax/Hib™ vaccine was used with hepatitis B vaccine in a post-exposure setting (Alaska). In population data, Hib disease and hepatitis B are virtually eliminated when Pedvax™ is used. So while this is not on the package inset, CDC acknowledges that some high endemic areas prefer to use this to facilitate immunization.

Dr. Egan asked why public safety workers were singled out for immunization even though the text notes that their hepatitis rates parallel the population's when adjusted for race/gender. Dr. Margolis reported this as provided for education; OSHA guidelines drive immunization for those exposed. Dr. Egan then asked about a seeming contradiction of VAERS reports on anaphylaxis versus other studies. Dr. Margolis responded that the reports are from different countries; reporting system differences may be why the data, which appear valid, are contradictory.

Dr. Egan asked if data can be referenced to support the text on repeating a 3-dose series for infants who are incorrectly vaccinated. Dr. Margolis reported this as inserted to help states coordinate minimum intervals with school entry laws. But Dr. Halsey commented that AAP would not call for a repeated full schedule; at least two doses would be counted; and probably only one more additional dose would be needed. Dr. Orenstein noted that this would be discussed on the following day, but agreed that consistency is needed. The General Recommendations Workgroup advised repetition if the interval between dose 1 and 2 is <25 days, and that between dose 2-3 is <7 weeks; otherwise, it would be acceptable. Dr. Shödel suggested allowing alternatives, such as testing for antibody or revaccinating, since hepatitis B has an established seroprotective level.

Dr. Severyn asked, if the vaccine was licensed in 1990, where the 15-year data was coming from? Dr. Margolis responded, as is discussed in the section on long-term vaccine efficacy, that the 15-year data comes from vaccine trials in cohort studies using plasma vaccine. These data are presumed applicable to recombinant vaccine. The 10-year data follow-up from early trials is now being published. The long-term efficacy data is mixed for both plasma and recombinant vaccines.

Hepatitis B Vaccines and Rare Adverse Events

Dr. Chen introduced the topic of vaccine safety, which he thought may have been unnecessarily polarized and controversial . The safety standards applicable to pre-licensure work includes laboratory, animal, and human studies (Phases I-III). The advantages of these trials are that they allow detailed follow-up, and randomized, placebo-controls permit easy assessment of their causality. But the disadvantages include poorly detected reactions due to the events' rarity, delayed onset, and occurrence within subpopulations, and that there is no standard case definition for "safety."

Therefore, post licensure surveillance is needed when a vaccine is used in the millions.

Traditional tools include passive surveillance (spontaneous reporting system), as with VAERS and ad hoc-controlled epidemiologic studies. New tools include Phase IV trials "linked " to licensure of a new vaccine, pre-organized large-linked databases (LLDB) in HMOs, enhancement of passive surveillance, and potential disease registries.

Hepatitis B vaccine was first extensively used in Asia and Africa. The data of the first 3 years after hepatitis B vaccine licensure (150,000 doses used) in the U.S. included some serious reactions, but only the GBS outcome was greater than expected (a relative ratio of 1.2-2.8; adjusted to 0.3-0.6 cases/100,000 vaccinees). Under-reporting may also have lowered this ratio; however, postmarketing surveillance for adverse effects has generally not been conducted. .

More active surveillance among Alaskan natives of the plasma-derived vaccine showed no elevated risk for GBS. But given GBS' rarity, this study might not have had sufficient statistical power. They used self-report and a database search to study two serious outcomes: GBS and transverse myelitis. There were 39 reports of adverse reactions, for which rates by age groups were compared. No elevated risk emerged from GBS analysis.

The Institute of Medicine's 1991 and 1994 literature reviews found the scientific evidence inadequate for any conclusion on causal relation between hepatitis B vaccine and several adverse events. The gaps/limitations cited included that the data were limited in type and limited research capacity. In 1996, Niu et al reviewed the VAERS data on recombinant hepatitis B vaccination of neonates and infants. This analysis showed no unexpected adverse effects in neonates and infants given this vaccine despite at least 12 million doses administered.

Shortly after VAERS was implemented in 1991, it received a Wisconsin physician's report of four nurses who he evaluated with demyelination disorder after hepatitis B vaccine. CDC created three case definitions (to compensate for the lack of a baseline rate): inflammatory events, paralytic events, and Janssen's definition of grouped categories. For these three categories, hepatitis B initially appeared to have a higher reporting rate than other vaccines (Td, influenza, MMR, OPV). But because hepatitis B vaccine was recommended for health care workers, adjustment was needed to account for possible health care workers' higher reporting rate to adverse event systems. When the apparently high reporting rates for hepatitis B vaccine was adjusted for the nuisance events, the reported ratio dropped to the 1-2 range, so this VAERS signal was not pursued. VAERS data for 1996-7 were similarly analyzed, with similar trends. Reporting rates for three "nuisance" adverse events were also high for hepatitis B vaccine compared to other vaccines.

A 1998 publication summarized case reports of hepatitis B vaccine adverse events across the world. Dr. Chen specifically described and compared two case to illustrate how, when examined more closely to review the listed symptoms individually, dissimilarities in complaints emerged that overcame the initial reported apparent similarities of fatigue and memory loss.

VAERS data show a large number of disability reports post-hepatitis B vaccination, 80% of them from females. But about two-thirds of health care workers are female, and similarly higher proportions are reported after vaccination for influenza and MMR. Dr. Chen stated the need to study persons with disabilities, perhaps working backward to construct a case

definition. He showed a chart of the VAERS data from 1991-98 in ages 25-65. The similarities and differences across these categories of disability need to be better understood.

However, without a unique laboratory result or clinical syndrome, public health has to rely in epidemiologic study to explore a causal link. The problem is that VAERS reports only address those who have been vaccinated and shown an outcome; there are no data on comparison groups. There are few applicable studies to conclusively explore whether these demyelinations are vaccine adverse events. But Dr. Chen outlined three, all unpublished (French Ministry of Health; the U.K.; SmithKline Beecham HMO setting), all of which found no statistically significant results. The Vaccine Safety Datalink hopes to have some results in the next year; and the Harvard Nurses cohort study should produce results in the next six months. In France, a case crossover design is exploring whether exacerbations of multiple sclerosis relate to some vaccination.

A study by CDC/Kaiser in California is also investigating Immunization and infant death. This study was difficult to organize, requiring identification of all deaths within the counties where HMO members reside. But HMO files do not specify attrition by death or other cause; ascertainment must be done from the counties and matched. They are matching two controls to each case by data of birth, and will examine the history of vaccination in recent periods. Preliminary analysis is underway, using birth certificate and geocoded census data, on neonatal versus post-neonatal periods.

Dr. Chen reviewed the French decision to suspend routine adolescent hepatitis B vaccination. Routine infant hepatitis B vaccination has also dropped by more that 70%. A number of influencing factors relate to this that may not parallel other settings. An intensive hepatitis B campaign in France since 1993 vaccinated two-thirds of the adult and half of all the population. They have a strong pharmacovigilance, but are weak in pharmacoepidemiology to examine whether these events are causally related. France's "CDC" is new, with sparse longitudinal data on hepatitis B disease incidence. The context of this issue's public, media, and court reaction also relates to the previous HIV blood contamination scandal which greatly affected the French perception. So, when the two hepatitis B studies presented could not "rule out" an association, even though they were not statistically significant, vaccination was suspended in schools. Routine adolescent immunization is still recommended but it is now done by individual physicians. The WHO's Viral Hepatitis Prevention Board reviewed the same study results and found that the vaccination had important benefits beyond the theoretical potential risks.

The problem is that the presence of relative risks of 1.0-2.0 suggests several possibilities: a real association but an underpowered study; or the presence of some confounding factor or bias which was not adjusted for. Some information emerging from the genetic literature indicate that 5-10% of primary hepatitis B vaccinees do not seroconvert, but the mechanism was unclear. Recent studies characterizing these by HLA categories indicate a gap in the T-cell recognition repertoire, with a molecular mechanism spurring the non-response. On the safety side, the Pope et al study reviewed a case series of chronic inflammatory polyarthritis with unknown etiology developed after hepatitis B vaccination. They found an HLA Class II in 9 of the 11 cases expressing a rheumatoid arthritis-shared motif. Given the frequency of the latter in the healthy population, they suspect other factors to be involved. The five-year follow-up showed two of the 11 still with persistent inflammatory arthritis.

Dr. Chen summarized that 1) the increase in hepatitis B vaccination worldwide produced an increase in both causal and coincidental adverse effects along with the increased numbers of those vaccinated without problems; 2) no "unique" hepatitis B adverse effect syndrome has yet been identified; 3) epidemiologic studies are needed on each alleged adverse event (e.g., demyelination, infant death, GBS, etc.), the best etiologic study possible, which will be resource intensive. Several studies on demyelination are underway and one on infant death. 4) There is a female predominance among disabled vaccinees, perhaps indicating an "unmasking" of genetic susceptibility. This is likely to be a complex interaction. 5) It is unknown if routine pre-vaccination screening will ever be possible or practical. But the GBS/influenza experience underscores the need to be open-minded. 6) Large epidemiologic studies are needed to clarify these questions, but there are no stable resources for such. 7) In the meantime, the vaccine risk communication will remain challenging.

Dr. Modlin thanked Dr. Chen, urged the members to provide Dr. Margolis with their comments, and hoped to have a final vote on this at the June meeting.

Public Comment

Barbara Alexander Mullarkey, of the Illinois Vaccine Awareness Coalition, asked Dr. Chen's finding of the Illinois nurses' report to VAERS of 15 health care workers who developed multiple sclerosis after hepatitis B vaccination. She also asked why Merck monitored among healthy adults and children in their clinical studies for 4-5 days. Dr. Chen responded that the nurses' report came from Wisconsin and reflected an expected prevalence. The peak age of multiple sclerosis in females is in age 20-40 years, the predominant age of health care workers who also are mostly female. Only a controlled epidemiologic study (underway) would show an increased risk. Dr. Barbara Howe of SmithKlein Beecham, responded that 5-10 days of follow-up is standard in studies of recombinant as well as inactivated vaccine.

Revised Recommendation for Vaccination of Children Against Hepatitis A

Dr. Glode outlined the membership of the Hepatitis A Workgroup. Dr. Beth Bell first raised the need for expanded recommendations for hepatitis A at the June 1998 ACIP meeting. The workgroup formed in August 1998 and held conference calls in September and October. The first draft of revised recommendations was presented to ACIP in October. Two more conference calls occurred in December 1998 and January 1999, resulting in changes reviewed by the workgroup and sent to the ACIP members.

The issues and questions addressed by the workgroup were: 1) recommending an increase in the populations targeted for routine immunization with hepatitis A vaccine as an incremental step toward eventual universal immunization; 2) crafting the statement to allow flexibility in terms of strategies for immunizing children; 3) deciding how permissive the statement should be about offering the vaccine to any one at any age residing in a community with a rate of <10/100,000; and 4) discussion of how to encourage more research to develop an infant vaccine and to address the long-term immunogenicity/efficacy of a single dose.

Dr. Beth Bell defined as the most important overall strategy an incremental implementation of routine hepatitis A vaccination. To do so, Phase I involved routine vaccination of children living in "high rate" communities (e.g., Alaskan natives and Native Americans living on reservations); Phase II involves routine vaccination of children living in states/communities with consistently elevated rates; and Phase III will involve the routine vaccination of infants nationwide.

The rationale for this strategy rests on several points: 1) the current strategy is unlikely to produce an overall sustained reduction of hepatitis A incidence because the current focus on control of hepatitis A outbreaks in intermediate rate communities has been difficult to implement and rarely results in sustained routine vaccination; 2) routine vaccination is most likely to result in a sustained reduction of rates; 3) lack of a vaccine for infant use is a barrier to universal vaccination. The proposed recommendation would focus resources in the areas most likely to produce a benefit, and its focus on routine vaccination is likely to reduce overall incidence over time. 4) The epidemiology of hepatitis A indicates that specific states and counties have consistently elevated hepatitis A rates. These areas are geographically clustered, have the majority of reported cases nationwide, and have epidemiologic patterns that predict persistently elevated rates.

The January 25, 1999 draft of the recommendation to the ACIP offered two recommendations: 1) "In states where the average hepatitis A rate during 1987-97 was at least 20/100,000 population (i.e., approximately 2 times than the national average) (Table 1), and counties or communities where the average annual hepatitis A rate during 1987-97 was at least 20/100,000 population, routine hepatitis A vaccination of children is recommended;" and 2) "In states where the average hepatitis A rate during 1987-97 was at least 10/100,000 population (i.e., approximately the national average) (Table 2), and counties or communities where the average annual hepatitis A rate during 1987-97 was at least 10/100,000 population but less than 20/100,000 population, routine hepatitis A vaccination of children may be considered." Eleven states are applicable to the first recommendation; six to the second.

The workgroup felt that this incremental strategy prepares for an eventual recommendation for universal vaccination. It provides for flexibility in implementation (one or more single age cohorts or selected settings such as child day care), and reflects the direction already being taken in many of these states.

Discussion

Dr. Modlin thanked the workgroup for their very thoughtful process. Dr. Livengood asked for an estimate of how many specific areas would likely be applicable to this recommendation. Dr. Bell shared a U.S. map showing, other than entire states, some areas in Texas, Oklahoma, and Florida. The clustering is marked. Dr. Snider asked if an *MMWR* article was preferred, or to incorporate these recommendations into the larger hepatitis A recommendations.

Dr. Orenstein felt that as now written, the statement makes an inadequate case for routine vaccination, but its information should be disseminated. Routine immunization of children prompts a whole series of issues, such as children traveling to a high-rate area. The health burden/impact must be conveyed in this statement even more than numbers of cases. This will also help to address the rising resistance to vaccines based on safety fears, and help to overcome barriers. Dr. Pickering supported the stated inclusion of benefits to children. Since the children may not be as ill as older individuals, physicians will need to be convinced of the vaccine's value.

Dr. Orenstein suggested an ACIP vote to direct the workgroup in preparing a statement more vigorously making the case for routine vaccination, and not to publish a recommendation before the statement. Since 60% of the vaccinations nationally were delivered by private practitioners, they and managed care will have to be convinced by good data. However, Dr.

Margolis raised the need for guidance by those states already pursuing this, and the time needed to develop a statement. Dr. Guerra agreed, noting the need to guide fund allocations to target specific counties.

Dr. Modlin suggested writing an *MMWR* article while the statement is updated. Dr. Fleming thought that possible, but thought the workgroup did not expect a complete hepatitis A statement update before releasing this information. Dr. Snider expected that the further rationale and statistical argument desired by Dr. Orenstein could be done in the time needed to develop an *MMWR* article, while the statement update is begun. It was concluded that such an article would be written and that a new statement would not be needed to proceed with the new recommendation.

Dr. Le asked for the AAP's opinion, agreeing that the bulk of immunization will fall on private practitioners. He also asked if the lack of an infant vaccine really poses a barrier. He noted that the Canadian vaccine for use at age one is based on the same SmithKline Beecham data that permits age two administration in the U.S. Dr. Egan noted that this related to the safety data cited on licensure.

Dr. Halsey reported the AAP's perception of this as a public health initiative. While they would welcome this a schedule amenable to routine visits, studies are needed to effect that; they would not support additional visits. Their policy calls for vaccination of children in high-risk communities, leaving the risk level determination to the states.

Dr. Livengood commented on the absence of cost effectiveness analysis, and that the presentation indicated only a few related assumptions of cost effectiveness. He asked why this process so differed from the requirements of, for example, rotavirus vaccine. Dr. Bell reported that analysis in development, but also noted that the assumptions used in the meantime are very conservative. Dr. Livengood remarked that the incremental approach being used has helped to make people more comfortable with moving forward with this recommendation.

Dr. Snider urged that as much data as possible be included on mortality and morbidity for the less-informed and media audiences, to better foster an immediate understanding. Dr. Margolis, however, noted that this had not been done in the past, indicating a needed policy decision by ACIP to guide future recommendation development. In the past, the usual *MMWR* Notice to Reader simply referred back to an existing major statement's sections.

Dr. Wilson was unconvinced that routine hepatitis A vaccination is necessary now. Just having a safe vaccine does not mean it must be delivered to every child, which is implied in the goal of universal immunization. Dr. Livengood agreed; the incremental steps might be supportable with *MMWR* articles, but a new statement is necessary to endorse an elimination strategy which, in his opinion, was the only reason to effect a universal immunization program. Dr. Evans also noted that this vaccine is not covered by the NVCP. As states implement this policy, ACIP leadership will be needed. Dr. Glode noted that the recommendation is challenged, not from the standpoint of health and economic burden, but from the differing perspectives of children's health burden versus that of preventing disease in adult cohorts. The epidemiology of those two cases differs; but this can be addressed.

VOTE on the two recommendations on Prevention of Hepatitis A through Active Immunization: *"In states where the average hepatitis A rate during 1987-97 was at least 20/100,000 population (i.e., approximately 2 times than the national average) (Table 1), and counties or communities where the average annual hepatitis A rate during 1987-97 was at least 20/100,000 population, routine hepatitis A vaccination of children is recommended;" and 2) "In states where the average hepatitis A rate during 1987-97 was at least 10/100,000 population (i.e., approximately the national average) (Table 2), and counties or communities where the average annual hepatitis A rate during 1987-97 was at least 10/100,000 population but less than 20/100,000 population, routine hepatitis A vaccination of children may be considered."*

Conflicts: Merck and SmithKline Beecham; ex-officio members were asked to vote.
In favor: Glode, Fleming, Johnson, Helms, Word, Evans, Rabinovich, Graydon, Trump
Opposed: None
Abstained: Clover, Guerra, Offit, Le, Modlin, Egan, Griffin
Decision: Passed

With no further comment, the meeting adjourned 5:45 p.m.

FEBRUARY 18, 1999

Unfinished Business

Varicella vaccine requirements for child care and school entry

Dr. Jane Seward presented the language on *Varicella vaccine requirements for child care and school entry*, as suggested on the previous day.

Proposed recommendation: "ACIP recommends that all states implement a requirement that children entering licensed child care and elementary schools have received varicella vaccine or have other evidence of immunity to varicella. Evidence of immunity should consist of a physician diagnosis of varicella, a reliable history of varicella, varicella vaccination, or serological evidence of immunity. In addition, all states should consider implementing a requirement that children entering middle school or junior high have received varicella vaccine or have evidence of immunity to varicella."

Discussion

Dr. Guerra commented that limiting the recommendation to child care centers risks missing many unlicensed settings, which he acknowledged are hard to monitor. Dr. Pickering agreed, and suggested instead the term "child care facilities." There was some debate over adding "parental" back in to "reliable" history, but also noted that some children will not have a parent to provide that information. This will be addressed in the statement text. Dr. Fleming advised clearly including in the text the issue about why immunization later in school age is important to avoid passing through unimmunized children.

Vote on Recommendation: *"ACIP recommends that all states implement a requirement that children entering child care facilities and elementary schools have received varicella vaccine or have other evidence of immunity to varicella. Evidence of immunity should consist of a physician diagnosis of varicella, a reliable history of varicella, varicella vaccination, or*

serological evidence of immunity.

"In addition, all states should consider implementing a requirement that children entering middle school (or junior high) have received varicella vaccine or have other evidence of immunity to varicella."

Conflicts: As above; ex-officio members were asked to vote
In Favor: Glode, Fleming, Johnson, Helms, Word, Trump, Graydon, Egan
Opposed: None
Abstained: Clover, Griffin, Guerra, Offit, Le, Modlin
Decision: Passed

Use of Varicella Vaccine Among Those With Altered Immunity
Dr. Karin Galil introduced the proposed language on altered immunity. As suggested on the previous day, language was inserted to include primary T-cell immunodeficiency and deleting the other terms, and included children with CDC Class I disease.

Proposed recommendation: "Varicella virus vaccine should not be administered to persons who have primary T-cell immunodeficiency. Children infected with HIV may be at increased risk of morbidity from varicella and herpes zoster. Limited data on vaccination of 41 HIV-infected children indicate that the vaccine is immunogenic and effective. No severe adverse effects to vaccination were observed in this group. Therefore, weighing potential risks and benefits, varicella virus vaccine should be considered for HIV-infected children in CDC Class I with CD4% >25%. Routine screening for HIV before vaccination is not recommended. The use of varicella virus vaccine in HIV-infected children is being investigated further."

Discussion
Dr. Katz suggested altering the CD4 count to ≥25% and dropping "primary" T-cell immunodeficiency.

VOTE on recommendation on varicella use among those with altered immunity
"Varicella virus vaccine should not be administered to persons who have T-cell immunodeficiency. Children infected with HIV may be at increased risk of morbidity from varicella and herpes zoster. Limited data on vaccination of 41 HIV-infected children indicate that the vaccine is immunogenic and effective. No severe adverse effects to vaccination were observed in this group. Therefore, weighing potential risks and benefits, varicella virus vaccine should be considered for HIV-infected children in CDC Class I with CD4% ≥25%. Routine screening for HIV before vaccination is not recommended. The use of varicella virus vaccine in HIV-infected children is being investigated further."

Conflicts: As above; ex-officio members were asked to vote.
In Favor: Glode, Fleming, Johnson, Helms, Word, Graydon, Rabinovich, Evans
Opposed: No
Abstained: Egan, Guerra, Offit, Le, Griffin, Clover, Modlin
Decision: Passed

Varicella Immunization Among Adults at High Risk of Exposure

Dr. Galil noted that the ACIP statement recommended vaccination for adults (aged >13 years) in close contact with high-risk persons, but only advised it to be considered for adults who are themselves at high risk of exposure. CDC's experience is that these adults have not been vaccinated; in all adult outbreaks in closed settings on which CDC worked, no institutional screening/vaccination had been done. Dr. Galil shared a chart of the facilities with outbreaks. Of adult deaths in 1998-9, seven were from varicella deaths, four of them in healthy parents (three fathers and one mother).

To address this, Dr. Seward provided the wording for persons aged >13 years: "Vaccination is recommended for susceptible persons in the following groups who are at high risk of exposure: nonpregnant women of childbearing age and men living in households with pregnant women or young children..."

Presentation of Navy Data
Dr. David Trump reported the Navy's experience of a significant historical disease burden from varicella, which was also seen in other military services. All Naval recruits (45,000/year) are trained at the Great Lakes, Illinois, boot camp. In 1987, there were 758 varicella hospital admissions per year (19.7/1000 person years). This declined in 1998 to 2.4/1000 person years. But concern over closed settings (such as the 1989 shipboard 11% attack rate) prompted a varicella prevention program. All recruits are given a rapid serological test for varicella immunity on their first processing day and those who are seronegative receive two vaccine doses over 10 weeks.

The rapid ELISA test identified 7.2% of recruits as seronegative (susceptible) to varicella. An early use of "history of chicken pox" was found not to be a good predictor of serologic status, and no association between serological status and age/gender was found. Susceptible recruits were more likely to be Asian or African-American. There were geographic differences, but these were not statistically significant. In the two years (1997-98) of the vaccine program, 30 Navy recruits have developed varicella; 24 had received one dose of varicella vaccine. Sixteen were exposed prior to arrival and became ill; and eight succumbed >21 days after arrival. Six were unvaccinated; three had seropositive titers presumed to be laboratory errors and three seronegative titers were missed at in-processing. There were no cases in those who received two vaccine doses, and no reports of serious adverse events.

The varicella prevention program's benefits in boot camp, shipboard, and other critical settings include prevention of severe mortality and morbidity, the provisions of data helpful to public health, and proven cost effectiveness at Great Lakes from avoided hospitalizations/lost time to training. The Navy's experiences indicate that there is still a significant population of young susceptible adults. Until infant/childhood vaccine provides better coverage, the Navy will continue their program.

Discussion
Dr. Plotkin found these data to support an emphasis in age groups older than young children and a stronger recommendation on adolescent vaccination. He suggested adding it to the list of vaccines recommended for adolescents without a history of varicella. Dr. Orenstein thought that already done through VFC recommendations. Dr. Seward noted that the statement includes varicella as recommended for catch-up at the adolescent visit among children aged <13. Dr. Modlin suggested the statement raise the age from 13 to 18.

Dr. Schaffner noted that the way outbreaks are handled is variable, and specifically, varicella vaccine use among hospital personnel has been modest. He advocated beefing up the statement to make it more forceful and directive, such as by reconsidering how they are considered immunized in the text. In effect, the statement it now considers them as potentially not immune and suggests that on an exposure they might be considered susceptible. His found this approach lacking; someone vaccinated but not considered immune defeats the whole purpose of immunization. Finally, he asked what behavior the text on men in households with pregnant women/young children was intended to motivate. He did not expecting it to increase immunization. Dr. Seward said that this was included to educate that healthy parents are susceptible. Dr. Schaffner appreciated that, but urged that it be linked to a very vigorous educational program, or it will be missed even by vaccine advocates. Dr. Fleming suggested that, as done with the original varicella statement, HICPAC take up the issue of health care workers with ACIP. Dr. Siegel agreed.

VOTE on the recommendation on varicella immunization among adults at high risk of exposure: *"Vaccination is recommended for susceptible persons in the following groups who are at high risk of exposure: nonpregnant women of childbearing age and men living in households with pregnant women or young children..."*

Conflicts:	Merck; ex-officio members were asked to vote.
In Favor:	Glode, Fleming, Johnson, Helms, Word, Graydon, Egan, Rabinovich, Evans, Breiman, Trump
Opposed:	None
Abstained:	Clover, Griffin, Modlin, Le, Offit, Guerra
Decision:	**Passed**

Post Licensure Varicella Vaccine Safety and Efficacy

Dr. Gina Mootrey noted that the information on recent VAERS data and suggested ACIP recommendation wording changes were in the ACIP's meeting packets. The recommendations were advisory to the committee of updates in the scientific information, and did not substantially change the recommendations.

Transmission of vaccine virus

A paragraph would be added to state: "Since licensure of the vaccine, transmission of the vaccine virus has been documented by PCR analysis on three occasions. A 12-month old toddler transmitted the vaccine virus to his pregnant mother. Following an elective abortion, the fetal tissue tested negative by PCR for varicella vaccine virus. At the time of vaccination, the child was being treated for eczema with a potent topical steroid. The other documented cases involved transmission from a healthy one year-old male to his healthy 4.5-month old sibling, and from a heathy 1 year-old male to his father. Secondary transmission has not been documented in the absence of a rash post-vaccination."

Discussion

Dr. Glode suggested added that "following the last two transmissions both the secondary cases were mild in nature." Dr. Siegel suggested saying "although transmission of vaccine virus has been documented, the consequences are mild and less severe than transmission of wild-type virus and therefore would not be a contraindication to using the vaccine."

Dr. Clover expressed concern that this text might be interpreted as a recommendation to abort at risk of exposure. Dr. Modlin responded that the intent was educational, but Dr. Gardner agreed that is was unclear. Dr. Zimmerman asked if the varicella registry had any information of inadvertent vaccine administration during pregnancy. It that experience is similar to the rubella registry, then similar language to that in the MMR document can be used. Dr. Sharrar reported that Merck's registry has about 400 women who received vaccine in pregnancy, with no congenital anomalies. But the numbers are small and it is unknown if the women were really susceptible at vaccination, which prevents any generalized statement. He thought the abortion decision was made by the woman, not her health care provider. He would tend to emphasize that all the individuals with secondary transmission had a vesicular rash from household contact.

Dr. Vernon suggested saying "when the mother chose an abortion, the fetal tissue was tested and found to be negative." Dr. Clover proposed "although not indicated, an abortion was performed" and "the mother elected to terminate the pregnancy."

VOTE on recommendation on post licensure vaccine safety and efficacy: "Since licensure of the vaccine, transmission of the vaccine virus has been documented by PCR analysis on three occasions. A 12-month old toddler transmitted the vaccine virus to his pregnant mother. The mother elected to terminate the pregnancy. The fetal tissue tested negative by PCR for varicella vaccine virus. At the time of vaccination, the child was being treated for eczema with a potent topical steroid. The other documented cases involved transmission from a healthy one year-old male to his healthy 45 month-old sibling, and from a heathy 1 year-old male to his father. Secondary transmission has not been documented in the absence of a rash post-vaccination."

Conflicts:	Merck – ex-officio members were asked to vote.
In Favor:	Glode, Fleming, Johnson, Helms, Word, Trump, Graydon, Breiman, Egan, Evans, Rabinovich
Opposed:	None
Abstained:	Griffin, Clover, Guerra, Offit, Le, Modlin
Decision:	**Passed**

Dr. Le requested that the varicella team return to discuss varicella vaccine as a treatment for zoster in adults. It may be time to recommend on the cost benefit of that. Dr. Modlin reported that Dr. Levin has studied that. Hard data are still distant, but an update would be good. Dr. Vernon reported that the Virginia assembly had voted unanimously to adopt varicella requirements for school attendance; and five other states with published regulations now in the review period have no apparent opposition to those requirements.

Recommendation for Lyme Disease

Dr. Fleming noted that Lyme disease poses a similar but even greater challenge than hepatitis A in geographic distribution. This has been addressed in some depth since the last meeting. A vaccine was licensed, and a recommendation is needed. There is no total agreement on the key issues, but a fairly good consensus was achieved on most issues, and he believed the recommendations to be sound.

Dr. David Dennis reported a great deal of public health effort to define/address Lyme disease since it was described 20-25 years ago. About 90% of Lyme disease cases are reported in 10

states and about 150 counties therein. Since surveillance began in 1982, 120,000 cases have been reported, reflecting a slow geographic expansion and increased zoonotic intensity in well-known foci. The prevention strategy focuses on geography and human activity, since humans are incidental hosts due to intrusion into this complex natural enzootic cycle.

The workgroup discussed the issues related to the two vaccines being tested in Phase III and agreed to limit recommendations to LYMErix,™ which was licensed in December. A Notice to Readers was published in *MMWR* three weeks earlier describing the vaccine, trials, efficacy/safety and epidemiologic framework of its use and utility in the U.S. Some of the LYMErix™ label language was incorporated into the proposed Lyme disease recommendation's statement, including revised data on its safety and efficacy (50% VE in year 1, 80% VE in year 2). The recommendations address vaccine use in children and in persons aged >70 years; use in pregnancy; vaccine schedule and boosters; persons with a previous Lyme disease history; and use by travelers. ACIP guidance was requested if the latter should be only for travel to high risk areas. CDC finalized the risk-based indication for immunization based on geographic and activities exposure factors.

Dr. Ned Hayes thanked the committee for their input to data and reviewed the changes in detail.

Persons at high risk were defined as those who reside, work or recreate in areas of high or moderate risk during Lyme disease transmission season **and** engage in activities (recreation, property maintenance, occupational, and leisure) that result in frequent or prolonged exposures to tick-infested habitat. Two levels of risk are described (based on geography and activity). This text replaced previous wording about visitors to these areas.

Vaccine use in children takes language from the label (should not be administered to individuals outside the ages of 15-70), clarified vaccine use in those older; simplified the recommendation on vaccine use in pregnancy, and added FDA-suggested language to recommend reporting to the pregnancy registry if vaccine is administered to a pregnant woman. The **vaccine schedule** section was simplified, including spacing/time of administration suitable to the transmission season and a simplified booster section according to the product label. **Simultaneous administration** with other vaccines was liberalized from ACIP input. The statement was clarified about vaccine use among persons with immunodeficiency, and guidance was provided on persons with previous Lyme disease history (the reference to "resistant Lyme disease" on page 17 will be changed to "resistant arthritis"). A map will represent an approximation of Lyme disease risk distribution and clearly state that this may change with vector distribution.

Recommendation on travelers to areas of high or moderate risk: "Because of the limited time of exposure, travelers to endemic areas are generally expected to be at lower risk of Lyme disease than those who permanently reside in endemic areas. The desirability of vaccination for travelers to areas of high or moderate risk during Lyme disease transmission season depends on the anticipated frequency and duration of their exposure to tick infested habitat. Vaccination *should be considered* for travelers to high or moderate risk areas if frequent or prolonged exposure to tick habitat is anticipated. Vaccination must begin at least one year before the anticipated exposure to ensure optimal protection. All travelers to high or moderate risk areas should practice personal protection measures as described earlier, and seek prompt

diagnosis and treatment if signs or symptoms of Lyme disease develop."

Discussion
Dr. Hayes asked if this should be modified to areas of just high risk rather than high or moderate risk.

On discussion, the members offered the following edits:

- Replace "ideally" rather than "must" vaccinate one year in advance, or point out that protection from two doses is adequate, but optimal from three (Halsey). Or state that optimal protection requires administration one year before the anticipated exposure, however, about 50% of persons are protected by two doses (Modlin). Note that optimal protection is achieved with the recommended 3-dose schedule to not complicate matters when a 6-month schedule is approved (Peter). Or, draft two sentences, one to point out protection from two doses and one on optimal 3 doses.
- Insert "is not recommended for those aged <15 years at this time." This could provide guidance to a physician seeing a 16 year-traveler and 14 year-old sibling going to camp, while being clear that this vaccine should not be administration to those aged <15 years due to concerns about toxicity (Peter).
- Delete the "is not recommended" sentence for those aged >70. This is excessive care. (Plotkin) Be clear that the label only says the vaccine is not approved for those over 70, making its use off-label, but those over 70 were not included in the trials (Peter). Point out the data only indicated reduced efficacy, not safety (both trials had some evidence of reduced efficacy in older individuals); it is not tested and therefore not recommended for those aged >70 (Halsey). Dr. Parenti reported an internal analysis done by SmithKline Beecham not finding a safety issue in those >60; but assessing efficacy for that age group was not in the protocol.
- Clarify that this recommendation is for domestic travel only (Roz Stewart).
- Drop the semi-qualitative "moderate" risk for travelers, since that risk is too variable across the country; let the physicians decide. There is no need to require LYMErix™ for a day outing in Vermont or the Napa Valley.
- Add a section on the trials' demographic makeup (Trump), clarifying that those with inflammatory conditions/carditis and immunodeficiency were excluded from the trials (Pickering). Dr. Parenti reported that the trials' tended to exclude those already with swollen joints, one of the efficacy endpoints (e.g., rheumatoid arthritis, but not common osteoarthritis). This will allow guidance for those groups most likely to pose questions to vaccine administration, while keeping the guidance short.
- Migrant workers may be addressed by the "reside, work, or recreate" text; a more specific sentence would be submitted (Guerra).
- Define "frequent or prolonged" to provide guidance for the field (Atkinson).
- Cite studies in progress on a shorter schedule than the current 0,1,12, and reinsert available data supporting a shorter schedule to avoid the need to update if a label data change is published soon after this recommendation.

In other comments, Dr. Snider issued a plea to the pharmaceutical companies to be more liberal about including those aged >70 years in the trials, to provide data to help such committees as the ACIP advise on the vaccines, especially as the population's median age rises. Dr. Schaffner noted that older age groups were not studied for other vaccines either, and that including this specific information in the recommendation differs from other vaccine

recommendations. He suggested instead that the details of the trials be presented in the front of the statement. Dr. Fleming appreciated that input, but preferred to advise on this off-label use to help health care providers.

Public Comment

Dr. Dennis Parenti of SmithKline Beecham thanked the committee for their hard work on the recommendations. While SmithKline Beecham disagrees with some points, they agreed to disagree and move forward. SmithKline Beecham will continue to work on alternate dose schedules, booster strategy and pediatric indications. When complete, they also will present their improved pharmacoeconomic models to the committee.

Ms. Karen Forschner, of the Lyme Disease Foundation, asked for a delay on the Lyme disease vaccine recommendation pending a 30-60 days scientific comment period. She objected that, although an ACIP vote places a vaccine under state Medicaid coverage, this recommendation was generated "in secret;" up to two weeks earlier, it was unavailable as a "do not cite/do not reference" document. Before the vote, it should be released for comment by scientists with different perspectives who are published in peer-reviewed journals. The statement excludes such aspects as disease prevalence in the south; issues of congenital and new newborn death despite treatment; and fails to reference an article in *Infectious Diseases of the Newborn,* published fatalities, the 30% seronegative rate published by Stonybrook, or diverse opinion on treatment issues. With licensure and package labeling in place, there would be no harm to await that scientific feedback which is different from the information that the ACIP had been provided.

Dr. Modlin thanked Ms. Forschner for her comments, but noted the driving forces to address Lyme Disease on this day: the recommendations can be altered up to their publication even after the ACIP approval, a new vaccine has been licensed and marketed, and the committee could not address this again until June. The members felt it important to proceed.

Discussion of Lyme Disease General Recommendations and Policy

Dr. Offit noted the differences between Red Book recommendations (based on safety and efficacy) and the ACIP's (including affordability at the federal, state, and local level). While both are good, this also risks confusion the field's interpretation of recommendations. That is, interpreting ACIP's "should be" by Red Book standards would lead to a conclusion that the data on efficacy is somewhat less than that of a "is recommended" intervention. And, since the states' resource decisions are aided by ACIP recommendations, he felt that the standard's bar should be set higher. He suggested perhaps sub-stratifying the Lyme disease recommendation, for example, to recommend vaccine for high-risk behavior in a moderate-risk area.

Dr. Livengood agreed that a health department probably would place more resources behind a "recommended" vaccine. But in this case, Lyme's great focality probably ensures that local information will be used in deciding about vaccine use. He commented that the ACIP could proceed as with the hepatitis A recommendation, which uses two risk levels based on prevalence to advise "is recommended" and "may be considered." However, Dr. Offit remained unsure that physicians understand the distinctions between ACIP and Red Book approaches.

Dr. Le thought the draft's recommendation was appropriate to the existing knowledge. He

noted the vaccine's newness, its likely need for frequent booster doses, and in his opinion, the real potential for immunopathogenesis of a clinical Lyme disease not responsive to antibiotics. He felt that two years of data was insufficient to comfortably support a potential three doses in two years; long-term effects are unknown. The wording of the ACIP recommendation also can help alleviate the manufacturer's market pressure on the physician advising the patient. Dr. Fleming reported an informal poll of state health department staff who favored the "should be considered" text. Dr. Griffin stated that discussion is needed to codify ACIP's meaning of "should be" and "is" recommended.

VOTE on recommendation on Lyme disease general recommendations and policy. The committee voted on the statement recommendations as presented by the workgroup, with the recognition that the statement is incomplete and will require other modifications. The members will review the revised draft and comment to Dr. Fleming within four weeks. The final draft will be recirculated, but the full committee did not expect to have to revisit it.

Conflicts:	SmithKline Beecham and Pasteur-Merieux Connaught (since the Pasteur-Merieux Connaught vaccine is in development)
In Favor:	Griffin, Glode, Fleming, Offit, Johnson, Helms, Word, Modlin.
Opposed:	None
Abstained:	Clover, Guerra, Le
Decision:	**Passed**

Rotavirus Issues for Use in Premature Children

Dr. Chuck Vitek reported that the rotavirus statement is in review by the *MMWR* editors and should be ready to publish by the end of March. Dr. Modlin summarized that the statement was approved in June 1998. Since then, concern was expressed over the policy on premature infants and on children with diarrheal disease at immunization. Differences between ACIP and AAP policy for those children risks confusion in the field, so the workgroup suggested changes in a conference call during the previous week.

Currently, routine administration is recommended for all full-term infants (>37 weeks of gestation) with three oral doses of rotavirus vaccine at ages 2, 4, and 6 months. The precautions statement addresses premature infants (<37 weeks) citing limited data that they are at increased risk of hospitalization from diarrheal disease in their first year of life. Data are insufficient to fully establish the safety/efficacy of rotavirus vaccine in these infants, but some experts believe the benefits to outweigh the theoretical risks. The lower level of maternal antibody to rotaviruses in these infants might increase the rate of severity of fever. Physicians are advised to consider the risks and benefits of vaccination of premature infants against rotavirus. A section under adverse events gives a very brief summary of the data on 23 infants included in the licensure trials who were ≤35 weeks of gestation.

The workgroup offered two options to address vaccine use among these premature infants:

1. Retain the current version with available data incorporated, and stating under precautions that premature infants can be vaccinated if they are ≥6 weeks old, leaving the nursery/not hospitalized, and clinically stable. Limited data indicate that premature infants are at increased risk of hospitalization from diarrheal disease in their first year of life, but data are insufficient to fully establish the safety/efficacy of the rotavirus vaccine.
2. Change to a recommendation similar to option #1, but under precautions, state that ACIP

supports immunization of premature infants if they are ≥6 weeks old, leaving the nursery/not hospitalized, and clinically stable. The cautionary language is retained regarding the potential for increased adverse events, citing limited data. (This was preferred by the workgroup).

Discussion
Dr. Glode felt strongly that she would only feel comfortable changing the recommendation if a large clinical trial provided data. Dr. Rabinovich reported that studies are underway, but recognized that the small cited study of 23 infants is important for public health recommendations. NIAID hopes to have a study in planning submitted by this summer.

Dr. Guerra asked about data on infants with prior rotavirus infection before the age recommended for vaccination. Dr Modlin reported little available data, but expected that they would be at risk of additional rotavirus infection. And, in response to a question by Dr. Johnson, Dr. Modlin reported similarly limited data suggesting premature infants' slight increase in relative risk of hospitalization due to diarrhea in their first year.

Dr. Atkinson expressed concern that non-physician health care providers forced to consider risk and benefit, as advised in the current version, probably will interpret this as advice not to vaccinate. Physicians will need to screen for prematurity, and there could be uneven application of the recommendation prior to VFC approval. Dr. Offit supported the workgroup's recommendation. Premature infants are likely to be at least as at-risk in their first year of moderate- or severe disease as are healthy full term babies. Those potentially at risk for reaction to the first dose are those infants with a very low degree of passively-acquired antibody. Transfer starts at 32 weeks and rises in the period to 37 weeks. Dr. Offits felt that the benefit from protecting infants outweighed the potential risk.

Dr. Egan felt that until the additional needed data are in hand, this vaccine's use should not be encouraged in that population. However, Dr. Pickering noted that AAP supports rotavirus immunization for premature infants. This is a susceptible group for diarrheal disease and with mortality often attributable to RV, although no clear data support that. He hoped that the ACIP would mirror the AAP recommendation to avoid confusion in the field.

VOTE on to modify the rotavirus recommendation to accept the workgroup's preferred language on premature infants.
Routine Administration: "ACIP recommends routine immunization for all infants with three oral doses of rotavirus vaccine at ages 2, 4, 6 month. Because natural rotavirus infections occur early in life, RRV-TV should be incorporated into the routine childhood immunization schedule. The first dose should be administered at age 2 months, and the second and third doses administered at age 4 months and 6 months, respectively."

Precautions: "Limited data suggest that premature infants are at increased risk of hospitalization from diarrhea during their first year of life. The ACIP supports immunization of prematurely born infants if they are 1) at least 6 weeks old, 2) leaving the nursery or are no longer hospitalized, and 3) clinically stable.

"However, the number of premature infants studied in clinical trials is insufficient to confidently establish the safety and efficacy of RRV-TV for all premature infants. The lower level of

maternal antibody to rotaviruses present in very low birth weight premature infants could theoretically increase the risk of fever following rotavirus vaccine. Until further data are available, the ACIP believes that the benefits of RRV-TV immunization of premature infants outweigh the theoretical risks."

Adverse events: "... Only limited data on premature infants given RRV-TV are available. Of 23 who were ≤35 weeks of gestation who received RRV-TV, 1 developed fever (38.6 C) on day 2 and 2 developed diarrhea (days 2 and 5 and days 6 and 12 after immunization...)"

Conflicts: Wyeth-Lederle
In Favor: Griffin, Fleming, Clover, Guerra, Offit, Johnson, Helms, Word, Modlin
Opposed: Glode
Abstained: Le
Decision: Passed

Conflict with AAP regarding recommendation on infants with ongoing diarrhea
This language would change the statement to recommend against vaccination of infants with diarrhea, state a contraindication for infants with concurrent gastrointestinal disease rather than just those with moderate to severe vomiting (as now stated), and states a precaution for infants with pre-existing chronic gastrointestinal disease. The workgroup considered this an efficacy rather than safety issue. The wording is intended to match the Red Book committee's contraindication of rotavirus immunization among infants with diarrhea.

Vote on recommendation on infants with ongoing diarrhea, as modified:
Contraindications: *"RRV-TV has not been studied in infants with concurrent gastrointestinal disease. While RRV-TV is likely to be safe for infants with gastrointestinal disease, it is theoretically possible that immunogenicity and efficacy may be compromised. By analogy, infants given oral poliovirus vaccine (OPV) during an acute diarrheal illness have been shown to have diminished poliovirus antibody responses to OPV. Therefore, RRV-TV should be withheld from infants with acute, moderate-to-severe vomiting or diarrhea. Vaccination of infants with mild, self-limited gastrointestinal illness may be warranted if deferral of vaccination is likely to result in a significant delay in vaccination of the infant against rotavirus. Otherwise, infants with diarrhea should be vaccinated as soon as the condition resolves."*

Precautions: *"Infants with pre-existing chronic gastrointestinal diseases such as congenital malabsorption syndromes, Hirshsprung's disease, short gut syndrome, or persistent vomiting of unknown cause, may potentially benefit from immunization, although the safety and efficacy of RRV-TV for these infants is unknown."*

Conflicts: Wyeth-Lederle
In Favor: Fleming, Griffin, Glode, Clover, Word, Helms, Johnson, Offit, Guerra, Modlin
Opposed: None
Abstained: Le
Decision: Passed

Vaccines for Children (VFC) Program

Mr. Dean Mason, Chief, Program Support Branch, Immunization Services Division, NIP, provided a progress report on the VFC program and CDC's future contracting plans for vaccine purchase.

Background: The VFC program was created by the 1993 Omnibus Budget Reconciliation Act and operationalized in October 1994. All 50 states now participate and 61 of the 64 immunization projects (excluding Pacific islands without Medicaid programs). VFC's rationale is to 1) ensure funding for a national vaccine purchase and supply through states for VFC-eligible children in accordance with ACIP guidelines, 2) to address vaccination barriers (including vaccine costs and inadequate health insurance), and 3) to ensure equal access to vaccinations. Eligibility involves children age ≤18 years who are Medicaid eligible, Alaska Native or American Indian, and the underinsured (when insurance does not include vaccinations as a covered benefit) when served by federally qualified health centers. The VFC's policy is to maximize cooperation between the public and private health care sectors and to minimize paperwork to encourage widespread provider participation.

1998 was the first year since the VFC program began in which there was a reduction in the number of enrolled provider sites. Enrollment decreased by about 690 from the all-time high of 45,505 enrolled for 1997. The cumulative VFC budget totals $1.2 billion for its first five years. Operational costs (enrollment, monitoring, vaccine storage and distribution) have been constant at about $24-29 million annually, or 9% of the total annual cost. The 1998 budget was $417.8 million, with vaccine purchases of $388.2 million. HCFA provides funds to CDC to fund VFC awards to the 61 grantees. The program is very successful, widely supported and with good penetration in the public/private health communities. The 1997 National Immunization Survey indicated that 75% of children receiving at least one immunization did so from a VFC provider.

Current issues include: The elimination of VFC coverage for children eligible for the Children's Health Insurance Program (CHIP) in some states where CHIP is not managed by Medicaid. Legislation has been prepared that may change that policy. Health departments are again experiencing referrals for vaccinations from some managed care plans, the very activity the VFC sought to eliminate. Other issues include significant cuts in the 317 program (the basic program for infrastructure since 1974) and difficult state funding decisions on vaccine purchase/supply with the new vaccine recommendations.

As encouraged in the Omnibus Reconciliation Act, CDC in 1995 began guaranteeing a market share to all vaccine manufacturers based on high and low bids, as opposed to the previous award of a contract to the lowest bidder. In 1997, pilot contracts were issued for DTaP and hepatitis B (adolescent) vaccine. This pilot guaranteed all vaccine manufacturers access to the market while allowing competition to determine the market share. The evaluation included assessment of each company's market share, vaccine purchase trends, purchases by funding source, the government's cost savings, and positive/negative features of this strategy. The findings were generally positive. It allows vaccine brand consistency for purchasers, it simplifies contract administration with fewer contracts to negotiate, and reduces the government's risk due to the low minimum guarantee purchase amounts. The downside was that the states came under increased market pressure (including inappropriate inducements) to buy products, there was some confusion on purchases with increasingly complex schedules,

and the potential of stocking more vaccines raised the possibility of greater loss.

The pilot contracts will be expanded in future to consolidate vaccine contracts through five vaccine manufacturers (Merck, SmithKline, North American Vaccine, Pasteur-Merieux Connaught, and Wyeth Lederle). The consolidated contracts will cover multiple products. About April 1, 1999, a 12-month contract will be instituted with a price which can be changed every four months or twice a year. At those times, products can be added if they are new combinations of existing vaccines produced by another company. Vaccines not covered in the consolidated contracts include adult vaccines, new vaccines, or vaccines for which the contracts have been in place for <6 months. CDC will extend those contracts to August 1, 1999 or until minimum purchase guarantees have been met.

Discussion
Dr. Tierney reported that AAHP had received reports of VFC confidentiality requirements frustrating registry data collection, and hoped for a collaborative approach with CDC to resolve this. Dr. Zimmerman reported an AAFP survey which found that those receiving free vaccine supplies vaccinate earlier. Dr. Le asked about government contract discounts. As the largest purchaser (the VFC vaccine market share is about 60%, although only 5% for the adult influenza vaccine), the government benefits from discounts, some artificially created by vaccine price caps adjusted to inflation. However, the downside is that there is no return policy for expired or unused products.

Dr. Guerra applauded the VFC program as one of the very important collaborative efforts of public health and the private sector which allows broadened capacity, especially for those populations without ready access to health care. It has raised immunization levels. He asked about collaboration with the WIC Infant Immunization Initiative, but Mr. Mason reported this as WIC-driven. Dr. Orenstein added that this subject is so important that Congress required states to spend at least 10% of their 317 funds for infrastructure to link with WIC unless they can prove that this work is done without needing those funds. Many children in WIC are also VFC-eligible.

Dr. Helms asked why the providers dropped by 3000. Mr. Mason responded that the states reported this number as being more representative of the most accurate reporting figure, and does not represent a backlash or concern about the VFC program. The program was expected to level off and, since some providers do not serve VFC-eligible children, the program never expected a 90-100% participation rate. It may also relate to managed care mergers, although in theory VFC enrolls provider sites, so managed care is a big participant in VFC.

Dr. Katz asked about the fees charged for administering vaccine. Mr. Mason reported that HCFA sets appropriate maximum costs that are state-specific. This varies from New York's $18/dose fee to a $5-10/dose fee in other states. If this is not a Medicaid charge, then the cost is between the physician and parent, as long as it does not exceed the administration cap. Dr. Severyn asked the hospitals' reimbursement charge for vaccine at birth. Mr. Mason reported a national range of about $10 to $18 per dose. Dr. Orenstein added that a distinction is needed between the price cap and what is reimbursed. The latter is lower, about $6-12 per dose, depending on the state. The price for the uninsured child is set by agreement, but it cannot exceed the state's maximum cap. Mr. Mason noted that many managed care and private

insurance companies do not separate out administration from vaccine service charges, and Dr. Severyn added that many insurance companies will not divulge their vaccine charges.

Votes to Consolidate VFC Resolutions

Dr. Livengood reported that the hepatitis B resolution had been withdrawn due to several errors therein. It will be reintroduced in June.

Pneumococcal Vaccine

Resolution 2/99-1: Repeals and replaces VFC resolutions 6/94-3 and 6/94-11. The purpose of this resolution is to consolidate all previous resolutions pertaining to pneumococcal polysaccharide vaccine into a single resolution. This resolution does not make any substantive changes to any previous resolution, except to clarify the recommended pneumococcal vaccine schedule and dosage intervals. Schedule: "One dose of pneumococcal vaccine is recommended for children and adolescents who are at least 2 years of age and at high risk, as listed under Eligible Groups. For children who are immunocompromised or who have functional or anatomic splenia: If the child is aged >10 years, a single revaccination is recommended if ≥5 years have elapsed after the previous dose; if the child is ≤ 10 years, a single revaccination is recommended 3 years after the previous dose. Intervals: minimum age for the first dose: 2 years; minimum interval from dose 1 to 2 (where applicable): 3-5 years.

Discussion

Dr. Snider noted that these are the elements required for a VFC vote, taken from the general recommendations. Dr. Modlin emphasized that nothing conflicts with the statement. Dr. Snider acknowledged that it is not uncommon to raise other policy issues within VFC votes, but when that is done, the issue needs to be placed in the original recommendation as well; the two must match. The basic purpose of the VFC vote is to make insurance coverage consistent with ACIP recommendations.

Dr. Glode suggested that the contraindication of "acute, moderate or severe illnesses with or without fever" be left at "acute, moderate or severe illness." Dr. McHugh suggested saying "hypersensitivity" rather than "allergy," but Dr. Livengood reported "allergy" used consistently in these recommendations. Perhaps in future this could be systematically reviewed. Dr. Vernon advised dropping the redundant sentence on catch-up vaccination.

Dr. Guerra asked if children with chronically recurrent otitis who are regular attendees at child care would qualify for VFC coverage. Dr. Halsey knew of related studies (e.g., by G. Kline) but the data are insufficient to support supplying the polysaccharide vaccine now. Dr. Breiman recalled an earlier ACIP review and judgement that the data were too conflicting for a recommendation.

Vote on Resolution on Pneumococcal Vaccine: to approve the pneumococcal vaccine recommendation with two modifications: 1) remove the redundant sentence on catch-up vaccination and 2) drop "with or without fever" from "acute, moderate or severe illnesses with or without fever."

Conflicts:	Merck and Wyeth-Lederle; the ex-officio members were asked to vote.
In Favor:	Glode, Fleming, Word, Helms, Johnson, Trump, Graydon, Breiman, Egan and Evans

Opposed: None
Abstained: Guerra, Offit, Le, Modlin, Griffin
Decision: Passed

Diphtheria, Tetanus and Pertussis Vaccine
Resolution 2/99-2: Repeals and replaces VFC resolutions 2/94-2, 2/94-3, 2/94-8, 2/94-17, 6/94-5, 6/94-6, 6/94-18, 6/96-2, 2/97-1, 2/97-2, and 6/97-4. The purpose of this resolution is to consolidate all of the previous resolutions pertaining to diphtheria, tetanus, and pertussis vaccines into a single resolution. This resolution does not make any substantive changes to any of those previous resolutions, except to: 1) add a DTaP vaccine preference (expressed by ACIP several years ago) and 2) clarify vaccine contraindications and precautions by separating them out, not done in previous resolutions.

Discussion
Dr. Livengood noted that the second footnote will read "elapsed," not "lapsed". The first footnote under dosing is consistent with ACIP policy, preferring 15-18 months but allowing vaccination at 12 months. The dosage intervals do not reference a fifth dose for some vaccines because they are not licensed for such.

Dr. Halsey recalled previous ACIP discussion that four month intervals are acceptable and a wish to not be rigid about the six-month minimum interval. Dr. Livengood noted that this is consistent with the published statement, but discussion on this afternoon may require revision of minimum intervals in all VFC recommendations. Dr. Modlin noted that this vote must be on exact wording consistent with the statement. Dr. Snider hoped to find the simplest way to change the minimum intervals without having to bring all the resolutions back for vote. He also noted that "acute" needed to be added to "moderate or severe illnesses," and Dr. Johnson pointed out that "on or after" to the fourth birthday needed to be added on page 2.

Vote on resolution on diphtheria, tetanus and pertussis vaccine: to approve the diphtheria, tetanus and pertussis vaccine recommendation with the two modifications noted above.

Conflicts: PMC, SmithKline Beecham, Wyeth-Lederle, and North American Vaccine
In Favor: Griffin, Fleming, Offit, Johnson, Helms, Word, Modlin
Opposed: None
Abstain: Guerra, Le, Clover
Absent: Glode
Decision: Passed

Haemophilus influenzae type B Vaccine
Resolution 2/99-3: Repeals and replaces VFC resolutions 2/94-5, 2/94-6, 6/94-10 and 6/94-14.
The purpose of this resolution is to consolidate all of the previous resolutions pertaining to *Haemophilus influenzae* type B vaccine into a single resolution. This resolution does not make any substantive changes to any of those previous resolutions, except to clarify catch-up vaccination (recommends Hib vaccine for all children through 5 years of age. A schedule is provided if Hib vaccination is not initiated by 6 months of age), and to clarify issues of interchangeableness (allows use of combined hep B/Hib vaccine when any components of the combination are indicated and if other components are not contraindicated; or the separate Hib

and hepatitis B vaccines may be used). "Acute" also will be added under contraindications to "moderate or severe" illness.

Discussion
Dr. Vernon suggested parenthetically providing the brand name after the formulation, adding into text that the use of brand names is not an endorsement, as done in the hepatitis A statement.

Vote on *Haemophilus influenzae* type B vaccine

Conflicts:	Merck, Wyeth-Lederle, Pasteur-Merieux Connaught, and SmithKline Beecham. The ex-officio members were asked to vote.
In Favor:	Fleming, Word, Helms, Johnson, Graydon, Trump, Evans
Opposed:	None
Abstain:	Clover, Griffin, Guerra, Offit, Le, Modlin, Egan
Absent:	Rabinovich, Breiman
Decision:	**Passed**

Hepatitis A Vaccine
Resolution 2/99-4: Repeals and replaces VFC resolutions 6/95-2, 6/95-3, and 6/96-1. The purpose of this resolution is to consolidate all of the previous resolutions pertaining to hepatitis A vaccine into a single resolution. This resolution does not make any substantive changes to any of those previous resolutions, except to:

1) Add to the list of eligible groups aged 2-18 years "Persons traveling to countries that have high or intermediate endemicity of infection" and " Persons in states, and communities or counties where the average annual hepatitis A rate during 1987-1997 was at least 10/100,000 population." It also clarifies that children living in highly endemic communities includes children of migrant workers.
2) Clarify the minimum interval (6 months from dose 1 to dose 2)
3) Add contraindications (allergy to vaccine components, acute, moderate or severe illnesses with or without fever; history of hypersensitivity reactions to alum or the preservative 2-phenoxy ethanol) and precautions (pregnancy) to the administration of hepatitis A vaccine.

Discussion
Dr. Pickering noted that contraindications "are;" more than one is listed. He also requested clarification of the statement that "persons with chronic liver disease should receive this immunization" because people with surface antigen for hepatitis B and those who are hepatitis C-positive do not necessarily have chronic liver disease, and they are most in danger of this virus. Dr. Livengood agreed to insert text referencing "susceptible persons with chronic liver disease including those infected with hepatitis A or hepatitis C". Dr. Guerra also hoped to include reference to the many adolescent parents who satisfy the requirement for immunization and who are within VFC coverage guidelines. Dr. Livengood agreed to insert "all persons 2-18 years of age meeting the following conditions" above the delineated risk groups.

Dr. Margolis noted, however, that the risk of fulminant or acute liver failure is among children with chronic liver HBV disease, which does not include all those who are surface antigen positive. This is similar to those with HCV, although a higher proportion of those with HCV have liver disease. He preferred to keep the focus on chronic liver disease than surface antigen positivity. Dr. Snider commented that a way would have to be found to track a two-

way recommendation. Dr. Modlin agreed; the hepatitis A statement may have to be revisited to do so. He requested a vote on this text consistent with the current statement now, and addressing this later.

Vote on Hepatitis A vaccine:
Conflicts: SmithKline Beecham, Merck
In Favor: Fleming, Word, Helms, Johnson, Trump, Evans, Rabinovich, Graydon
Opposed: None
Abstained: Guerra, Griffin, Offit, Le, Modlin, Clover
Absent: Glode, Egan and Breiman
Decision: Passed

Standardization of Decision Rules for Vaccination
Workgroup Chair Dr. Guerra noted that this topic evolved from discussions about the decisions needed for computer programmers to computerize the ACIP recommendations. After the October meeting, consensus was reached on eight of ten related recommendations. But it became apparent that the two remaining ones involved issues greater than those of computer schedules. They involved important decision rules to connect the human element so important to immunization programs with the decision rules needed to provide consistency. He outlined the members of the workgroup, who brought broad perspectives to bear on these questions, and he thanked the CDC staff for guiding them through a very complicated discussion. He hoped that after a trial implementation in the next few months, this document could be re-reviewed in the summer meeting and then finalized in the fall.

Dr. Roger Bernier provided the details. He began by noting that a lack of clarity and consistency resulted from recommendations developed individually rather than comprehensively. For example, confusion exists on the meaning of "minimum age" and "minimum interval." They are used variously as a minimum cut-off or as an alternative/accelerated schedule as applied to age and interval. ACIP also has provided little guidance (except for MMR) on the consequences of violating those minimums, resulting in 33 different ACIP recommendations related to ages and intervals (11 different recommendations for age and 22 for intervals).

An important element of the workgroup's discussions was the reality that schedules are based on competing values and priorities (safety, efficacy, cost, missed opportunities, practicality and convenience, flexibility, quality control/enforcement of recommendations, etc.) This issue goes beyond data; it's about balance and clarity. The workgroup tried to avoid the term "minimum" as much as possible.

Dr. Bernier clarified that on this day, total agreement on the tables was not the object as much as buy-in on the concept. He then presented a charted framework of an approach developed by the workgroup, with three examples of application.[1]

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[1] 1) General case for any recommended age at vaccination or any recommended interval between doses; 2) Recommended aged at vaccination for the first dose of DTP; 3) Recommended interval between early DTP doses.

The framework's progression was represented on a chart by the colored segments of two lines. These two lines represented the reality that each ACIP recommendation addresses two schedules: the routinely recommended age or interval of vaccination and an accelerated age or interval. Both of them involve four different time periods: *unacceptable practice* (too early–marked in red), *sub-optimal practice* (early–yellow), *"best" practice* (on time–dark green), and *acceptable practice* (late–light green). These also present four critical decision points, which were marked by vertical arrows: 1) age to repeat (ATR) or interval to repeat (ITR); 2) accelerated age or interval to vaccinate; 3) recommended age or interval to vaccinate; and 4) age or interval to recall. Ideally, ACIP would recommend on all four time periods. DTP was charted as an example.

Dr. Bernier noted several advantages of this framework: 1) it standardizes best and acceptable practice for programs, computer algorithms, etc. while still providing limited time zone flexibility; 2) it makes the schedule more parent- and provider-friendly with increasingly complex schedules; and 3) it gives clear standards for handling violations (repeat dose: yes/no). The disadvantages are that: 1) it offers more options (although previous recommendation "disconnects" essentially created their own sub-optimal practice zone); 2) it has less flexibility than a carte blanche override capability to the algorithm; and 3) there is a potential for more suboptimal doses to be administered.

Dr. Bernier outlined the projected time line if the ACIP accepts this concept of four points in time to frame each recommendation's age and interval components. The members' comments will be incorporated in the next 30 days. That "version 1.0" will then be circulated for 3-6 months (with remaining issues highlighted) for review and comment by providers, programmers, program staff, and other advisory bodies. At the October meeting, the final "version 2.0" will be provided of ACIP's immunization recommendations.

To illustrate the use of this concept, the staff also applied it to the recommended childhood immunization schedule. A table (Attachment 1) applied it to the 11 age and 22 interval recommendations issued over time by the ACIP. The original recommended ages/intervals were retained as possible; where not, a new value for the ATR/ITR (shown in bold on the table) was created with the help of experts. A one-month grace period was added to the recommended age/interval to define the recall time. The last column of the table summarized the competing values contributing to that recommendation's ATR/ITR, to convey how these were weighed and balanced.

Discussion

In discussion, great support was voiced for this concept. Specific comments expected it to aid consistent practice, quality assurance and auditing. It will help managed care in reporting on HEDIS and other indicators. And, in states addressing the medically underserved including Medicaid, it allows practitioners flexibility to vaccinate when the child is in without violating the rules. Some who have already used this concept in decision rules found it to relieve the process. It allows easier linking to the CASA audits, which allow assessment of the rates of compliance across practice groups (HEDIS standards, managed care organizations, etc.). Dr. Johnson reported comments and support from ASTHO in a conference call.

Dr. Fleming expressed a minor concern that a yellow zone should not be created if not warranted (e.g., MMR and varicella) to avoid weakening the standard. Similarly, Dr. Le asked

for clarity that the green zone is not really "acceptable" prospectively, although it may be retrospectively. A different word would be preferable. Dr. Clover advised clarity on when the 30 day grace period for recall begins (30 days after the recommended age; e.g., at 19 months for an 18-month recommendation). Dr. Johnson advised entitling these draft recommendations the "ACIP standardization process" to indicate its essential difference from computerization issues. Dr. Zimmerman suggested consideration of a graphic cross-hatching rather than colored zones (except perhaps for the immunization schedule) to avoid the problems in copying or faxing color charts.

Dr. Snider noted that the accelerated schedule really encompasses two different constructs: an accelerated schedule to address outbreaks, and then an implied accelerated schedule of minimum acceptable ages. Dr. Halsey suggested a single line schedule, so that all the antigens given at the same time (especially at the 2, 4, 6 intervals) would have the same cut points. However, he was troubled that the presented schedule had different time periods specified for Hib, IPV, and DTaP. Dr. Bernier reported that as considered. A common ATR was set for all vaccines received at 12 months, but there were exceptions such as polio at 7 weeks. He requested that such inconsistencies be highlighted in the review, offering both alternative values and the priorities which lead to that suggestion.

Dr. Vernon asked if communication plans include color charts for each vaccine or incorporation into an overall table as shared at this meeting. Different charts and tables may be needed for different intervals; for example, the age of the third dose of hepatitis B vaccine depends on the age at which the first dose is given. Dr. Bernier reported this not yet discussed with graphics and communication experts. All suggestions were welcomed. Dr. Livengood suggested at least a color chart of the vaccine schedule.

Discussion of Immunization Schedule Tables

Ms. Suzy Feikema reviewed the table (Attachment 1) of the recommended childhood immunization schedule, particularly the proposed new values (which are bolded). She first noted that MMR was made consistent with varicella and the Hib booster dose at 11½ months. She asked if consistency is important such that, for example, all those vaccines recommended at 12 months have common ATR. Dr. Bernier reported most disagreement on this point among the workgroup. State laws might require an exception for MMR. The question was whether to circulate the table as it exists, or to change it with ASTHO's comments and drop a yellow zone for MMR.

Dr. Halsey reported limited data indicating a difference of about 4 percentage points in seroconversion rates for children immunized at 12 months versus 15 months; a trend, but a small sample and not statistically significant. But the titers also were lower at 12 months, indicating still a trace presence of passively acquired maternal antibody. With increasingly few naturally infected women, the recommended age could likely go to 9½ months, but there are no data yet for that conclusion. Another study showed no difference at 10 or 12 versus 15 months. He suggested a data review before making any decisions. Dr. Modlin summarized that no yellow zone seemed advisable for MMR now, with 12 months as a cutoff.

Ms. Feikema suggested that when the committee crafts its recommendations, it might consider leaving a gap between the recommended age range and the absolute cutoff. Dr. Katz commented that measles data has been used as the flagship because there are no

comparable data on mumps or rubella. However, Dr. Plotkin noted that unlike measles, mumps and rubella aren't problems below 12 months, and data show good response even down to 10 months. Ms. Feikema agreed and shared evidence to support that; for measles, seroconversion improves with age.

Dr. Fleming advised attention to what is practical. Advising one year is easier than 50 weeks, and its benefit outweighs the two-week gap. But Dr. Clover clarified that the point is to address children arriving at 51 weeks, to be able to vaccinate them with MMR. Dr. Fleming understood, but pointed out that whatever line is chosen, the same question arises; in this case, it would just arise at 49 weeks plus one day.

Dr. Zimmerman asked why the ATR for DTaP-4 was set at 43 weeks. Ms. Feikema could not explain that (the number was provided to her); It might be a safety concern connected to extra doses of DTP. But she added that the staff is not wedded to these numbers.

Dr. Bernier outlined several issues for the committee to consider in preparing version 1.0: 1) the interval spacing for live vaccine; 2) timing of repeated doses (last, or last valid); and 3) changes in vaccine recommendation based on time of evaluation (i.e., could there be an "age beyond which to only count doses" rather than by age or months?). The members' comments were requested by March 30.

Maintaining Public Confidence in Vaccines; Risk Communication Efforts

Dr. Sam Katz introduced the Infectious Disease Society of America's Vaccine Initiative Program. IDSA and the Pediatric Infectious Disease Society joined to suggest an effort focused on teachers of infectious diseases to help dispel misinformation about immunizations. In September 1997, their collaboration was begun. He and Dr. Louis Sullivan serve as Co-Chairs for the program, which is headquartered at Vanderbilt University. It is guided by an Executive Committee. It seeks the most positive and effective way to learn the concerns of the public, particularly among parents and parents-to-be, and to determine their perceptions of immunization. Ironically, the field's success is in some ways its problem, in that many young parents are unaware of the diseases now controlled. The media sometimes seizes on aberrant stories and disregards the success stories such as the success of *Haemophilus influenza* B vaccine. The program also appreciates the importance of educating state legislators, since in some states they affect the implementation of ACIP recommendations.

Dr. Bruce Gellin, the Vaccine Initiative's staff director, reported the project's recent receipt of grant support from the R.W. Johnson Foundation. This reflects their acknowledgment of the need for an improved communication and education about immunization issues by an independent voice. The Initiative is not allowed to accept funding from government, industry, etc.

Dr. Gellin agreed that the field is the victim of its own success. Like problems such as TB that seem to go away but resurge, concerns about safety issues bubble up regularly in the media and practitioners' offices. They are not likely to be reduced, and in fact are like to increase with the vaccines in development. He stressed that the answer is not just information, but communication; they are not synonymous. So, the Initiative consulted communication specialists.

Importantly, these concerns translate into behaviors, such as the French hepatitis B example already provided. As another example, Dr. Gellin provided a copy from a Scottish publication that demonstrated a downturn in MMR immunization with negative media coverage of vaccine adverse effects, and a video of a recent 20/20 story.

To assess the latter's impact, the Initiative conducted focus groups with parents of young children. The preliminary findings showed that most participants found the story scary as parents, and were confused by it. It heightened previously-held vague fears about vaccine safety. Most did not feel well informed after the story, and left with additional unanswered questions about vaccine safety. Some felt the story was purposely skewed, showing serious reactions but not people with effects from hepatitis B disease. Almost all would seek more information. The information sources cited included the Internet, parents, and magazines, but pediatricians seemed to be the most credible source. CDC focus groups a year earlier found similar results: the parents want information from providers, who want it from the government. Education on the whole range of issues is needed in a communication strategy to distill all the information into a communicable form.

The Initiative is planning a national survey in consultation with other groups doing similar work, and they have reactivated the Immunization News Service (http://www.idsociety.org). They are also conducting a media training effort as part of the communication strategy, to help practitioners answer parents' questions. This includes training on speaking to the media and training potential spokespersons. The challenge is to speak clearly without sacrificing the science.

Maintaining Public Confidence in Vaccines

Dr. Chen introduced the topic of risk communication. As background, he noted that the National Childhood Vaccine Injury Act of 1976 required the conveyance of vaccine risk/benefit information (Vaccine Information Sheet). In 1995, CDC developed a question-and-answer brochure on common vaccine misconceptions and updated the Parents' Guide to Childhood Immunization. CDC's risk management plan for vaccine safety includes VAERS as a hypothesis generator, and the Vaccine Safety Datalink (VSD) to test the hypotheses. But risk communication is needed to disseminate those results, and vaccine development is needed to ensure new safer vaccines.

Ms. Beth Hibbs described the NIP's Vaccine Risk and Communication (VARICO) activity. Its goal is to better communicate vaccine benefits to the public, providing information in a timely manner. Partnership is key in doing so. Since there is little risk communication theory specific to vaccine issues, they engaged Dr. Ann Bostrom to address this. In 1997, an IOM risk communication workshop called for such risk communication to be a dynamic process pursuing informed decision making about vaccine risks/benefits, quantifying vaccine uncertainty as much as possible, with vaccine safety research key to building public confidence.

CDC explores behavioral science for clues to sources of bias, and to help relate common perceptions of risk to vaccine issues (e.g., perception of individual control as less risk than system control, which relates to school entry vaccination requirements; natural versus man-made, familiar vs. exotic, etc.).

The NIP is analyzing peoples' different beliefs about vaccine through several methods: focus

groups, surveys, media response/interpretation to scientific articles, monitoring of Hotline calls and Web page hits, and by attending meetings. The Training and Education Branch's focus groups have indicated that people would like to receive information earlier than during the physician's visit. Recurrent themes of concern about vaccine safety include chronic disease, autoimmune conditions and neurological disorders, and vaccine additives and contaminants. Similarly, the vaccine safety risk communication in media focus seems cyclical; for example, the hot topic of fetal tissue in vaccines that circulated two years earlier arose again this past summer.

To analyze the impact of the recent Friday night 20/20 report on hepatitis B vaccine, the VARICO activity asked the NIP Hotline to analyze their calls. The calls increased from the following Monday to Thursday, then dropped to normal level. About 30% of the increase related directly to the 20/20 show. Of those, 39% were worried and wanted information; 34% knew someone or personally had an illness mentioned on the program; 20% were health care providers looking for parent information, and 6% gave miscellaneous opinions on the program. The NIP Web pages on hepatitis B had 1146 hits the first four days after the broadcast. Only two requests for media interviews followed. There are some concerns about hepatitis B vaccine now being introduced into state legislation, with challenges emerging to new rule making in some states.

Other VARICO research includes evaluation of public perceptions of vaccine risks, examination of the impact of potential loss of confidence in vaccines, and education and training. The latter includes materials development, presentations at conferences and workshops, Vaccine Safety Web page, Hotline staff training, and a recent satellite broadcast on vaccine safety and risk communication which is now on videotape.

Other work to evaluate public perceptions of vaccine risks includes the ATPM/LSU provider/public focus groups on vaccine information; VIS focus groups; an NIP Hotline survey over the next 6 months of callers' concerns, which will be used to update the booklet addressing common misconceptions; and examination of the potential impact of loss of confidence in vaccines (including the impact of the anti-whole-cell pertussis movement in foreign countries and the individual and societal risk of measles from health consequences of religious and philosophical exemptions [Alsmon, in press]).

Future needs include identifying common beliefs in different population segments, researching specific risk communication approaches, improving risk-benefit materials (including defining uncertainty and rare risks); identifying new and strengthening existing partnerships; improving public information and education systems; and maintaining, improving, and promoting public information systems.

Discussion

Dr. Offit noted that ACIP's primary role is to interpret the scientific data and advise CDC, but expressed interest in pursuing a broader strategy of educating people about the vaccines' success. Dr. Snider noted CDC's progress in this regard, from a reactive stance just a few years ago to a proactive Office of Communications with media relations and communication strategists. The individuals CDC Centers, Institutes, and Offices' expertise is also building, including the NIP and NCID. How the committee wants to interact with that is open to discussion, and could be a future agenda item.

However, he also noted the ACIP's important role in this effort, advising the Assistant Secretary of Health/CDC Director. It provides a foundation for the education effort to ensure that the rationales, scientific information, etc., support its recommendations, and by requesting additional needed information and analyses. He would be loath for the ACIP to take on additional communication activities if they divert the committee from those essential tasks.

Dr. Modlin agreed to those primary tasks, but also noted the influence of the committee as a whole in increasing circles, which should be taken advantage of. Dr. Pickering raised the recent development by the "Canadian ACIP" of an information sheet, and Dr. Le noted that no evaluation has been done of the VIS' effectiveness. Dr. Word reported New Jersey's well-received mailing of a newsletter to all AAP members to educate them about the hepatitis B, IPV/OPV, etc. vaccine controversies. Dr. Vernon advised the others to cruise the Internet for a revealing education on the very negative opinions of vaccines.

Dr. Snider cautioned the committee members that they are special federal employees while at the meeting, but not elsewhere. When communicating about vaccine issues, he urged them to be clear that they are speaking as an expert in the field, not as a representative of the ACIP. Dr. Modlin advised the members to review the relevant ACIP policies and procedures.

Dr. Evans reported FDA's work with the ATPM to help residents/nurses, students, etc. more effectively teach and communicate the vaccine risks and benefits. That is only sporadically done today. One element is to achieve a decision making partnership in a society with so many different mandates. He stated that honesty with the public is also needed that science and the ACIP don't have all the answers. Trust is the major point, and he foresaw lots of related work ahead.

Dr. Breiman commented that NVAC's Subcommittee on Vaccine Safety and Communication is also exploring the infant field of risk communication, and encouraged coordination of this work with NVAC and other groups so engaged. Dr. Peter commended Dr. Offit's own book ("What Every Parent Should Know About Vaccines") for parents and consumers, as an excellent resource.

Electronic Updating of ACIP Reports

For Dr. John Ward, who was prevented from attending by an agenda miscommunication, Dr. Snider summarized the operative question regarding the electronic updating of ACIP reports: is the ACIP and CDC ready to use the electronic medium as a primary versus secondary (current status) medium to issue and update the recommendations? He suggested that a workgroup be formed to examine the related advantages and disadvantages, and if found advantageous, to propose how to go about that. Dr. Halsey encouraged movement in that direction, reporting the AAP's recent expedited information dissemination by electronic posting to its members. Dr. Modlin requested those interested in this workgroup to so inform him.

Public Comment

Ms. Mullarkey asked several questions, beginning with the statement by Former FDA Commissioner David Kessler that only 1% of serious reactions are reported to the FDA. She asked how ACIP could assure 90% reporting of serious reactions; how to ensure penalty to physicians, nurses, and pharmacists who don't report serious adverse effects; what studies show the safety effect of simultaneous injection of many vaccines; and how hepatitis B or

chicken pox vaccine could be approved without: 1) studies of animal reproduction or reproductive capacity, 2) unknown duration of vaccine protective effect and the need for booster dose; 3) Merck's minimal 4-5 days of monitoring among healthy adults and children in the hepatitis B clinical trials, 4) no evaluation of the varicella vaccine for cancer-causing or mutagenic potential or for fertility impairment; and 5) what is the rationale for including monosodium glutamate in chicken pox and other vaccines? She also expressed concern about the ACIP members' conflict of interest.

Mr. Belkin called on CDC to release within 30 days: 1) all pre- and post-licensure scientific data used by ACIP to justify the policy of universal hepatitis B vaccination of all newborn infants <2 months old; 2) basic science research data on the biological mechanism of hepatitis B vaccine injury/death, including the case-controlled monitoring studies of infants, the number and ages of the infants enrolled, and the time periods of follow-up for vaccine adverse events including deaths, which were used by ACIP to prove the vaccines' safety to newborns; 3) release by CDC and FDA of all scientific studies done to justify raising the Recombivax™ hepatitis B newborn dose from 2.5 μg to 5 μg; and 4) a detailed explanation of the statistical technique used by Dr. Chen to adjust the data in his hepatitis B and demyelination charts presented on the previous day, which reduced the rate from ten times that of other vaccines to below them, including references from statistical textbooks supporting the legitimacy of the statistical methods used. This request was also being filed under the Freedom of Information Act.

With no further comment, the meeting adjourned at 3:32 p.m.

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

John F. Modlin, M.D., Chair

17 Jun 99

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CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

Records of the Meeting Held on

February 17-18, 1999

Atlanta Marriott North Central Hotel
Atlanta, Georgia

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Atlanta Marriott North Central - Atlanta, Georgia
February 17-18, 1999

February 17, 1999

Agenda Item		Purpose/Action	Presider/Presenter(s)
8:45	Welcome		Dr. J. Modlin (Chair, ACIP) Dr. D. Snider (CDC, OD)
9:15	Updates	Information	
	Food and Drug Administration		Dr. Wm. Egan (FDA)
	National Immunization Program		Dr. W. Orenstein (NIP, OD)
	Vaccine Injury Compensation Program		Dr. G. Evans (HRSA)
	National Vaccine Program		Dr. R. Breiman (OD, NVPO)
9:45	Working Group Updates		
	General Recommendations	Information	Dr. C. Le (Kaiser-Permanente)
	Pneumococcal Vaccine	Information	Dr. C. van Beneden (NCID, DMBD) Dr. D. Johnson (MI Dept. of Health)
	Polio	Information	Dr. P. Offit (Children's Hospital)
	Timeline to implement further changes in the polio schedule	Discussion	Dr. R. Prevots (NIP, ESD)
	BREAK		
11:00	Prevention and Control of Influenza Recommendation	Information	Ms. L. Brammer (NCID, DVRD)
	World & U.S. Surveillance Data	Discussion	Dr. K. Fukuda (NCID,DVRD)
	1999-2000 Vaccine/Neuraminadase Inhibitor Update	Decision	Dr. M. Griffin (Vanderbilt Univ.)
	Influenza-Related Morbidity in Young Children		Dr. H. Izurieta (NCID,DVRD)
	1999 Influenza Vaccine Guidelines		
12:30	**LUNCH**		
1:30	Prevention of Varicella	Information	Dr. K. Galil (NIP, ESD)
	Should ACIP recommendations for vaccine requirements for day care and school entry be strengthened?	Discussion Decision	Dr. A. Gershon (Columbia Univ.) Dr. M. Levin (Univ. Colorado)
	Should varicella vaccine be recommended for outbreak control?		Dr. G. Mootrey (NIP, ESD) Dr. J. Seward (NIP, ESD)
	Update on varicella safety and efficacy		Dr. D. Trump (DOD)
	Should varicella vaccine be recommended for use in children with HIV/AIDS?		
	Should ACIP recommendations for adults be strengthened?		
3:00	**BREAK**		
3:30	Hepatitis B Recommendation	Discussion	Dr. R. Chen (NIP, ESD)
	Update on recommendation status	Decision	Dr. H. Margolis (NCID, DVRD)

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
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5:00	**Revised Recommendation for Vaccination of Children Against Hepatitis A** Discussion on change agreed upon at the October 1998 meeting and approval of draft recommendation	Discussion Decision	Dr. B. Bell (NCID, DVRD)

5:45 Adjourn

February 18, 1999

8:00	**Unresolved Issues from the Previous Day**	Discussion	Dr. J. Modlin (Dartmouth Med. School)
8:30	**Recommendation for Lyme Disease Vaccine** Discussion of the revised statement Approval of the Lyme disease vaccine recommendation	Discussion Decision	Dr. D. Dennis (NCID, DVBID) Dr. D. Fleming (Oregon Hlth. Div.) Dr. N. Hayes (NCID, DVBID)
10:00	**Rotavirus** Re-address issues around use in premature children	Discussion Decision	Dr. J. Modlin (Dartmouth) Dr. C. Vitek (NIP, ESD)

10:30 BREAK

	Vaccines for Children Program Update on general principles of VFC Finish consolidating resolutions	Information Discussion VFC Vote	Dr. J. Livengood (NIP, ESD) Mr. D. Mason (NIP, OD)

12:30 LUNCH

1:30	**Standardization of Decision Rules for Vaccination** Draft recommendations	Information	Dr. R. Bernier (NIP,OD) Ms. S. Feikema (NIP, DMD) Dr. F. Guerra (San Antonio Hlth. Dept.) Dr. E. Maes (NIP, DMD)
2:30	**Electronic Updating of ACIP Reports and Recommendations**	Information	Dr. J. Ward (EPO, OD)
3:00	**Maintaining Public Confidence in Vaccines** NIP's Vaccine Risk Communication Efforts IDSA/PIDS Vaccine Initiative What role should ACIP/CDC play in dispelling myths and misinformation about vaccines?	Information Discussion	Dr. R. Chen (NIP, ESD) Dr. B. Gellin (IDSA) Ms. B. Hibbs (NIP, ESD) Dr. S. Katz (Duke University)

3:30 Public Comment

3:45 ADJOURN

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