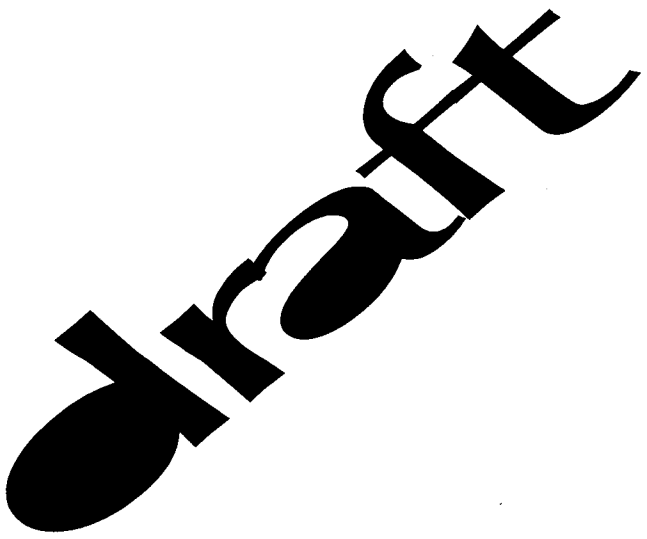
CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL IMMUNIZATION PROGRAM

RECORD OF THE MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

OCTOBER 16-17, 2002



Atlanta Marriott Century Center Hotel

Atlanta, Georgia

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ATTENDANCE

ACIP Members

Robert B. Belshe, M.D.
Guthrie S. Birkhead, MD, MPH
Dennis A. Brooks, MD, MPH
Jaime DeSeda, MD
Celine I. Hanson, MD
Myron J. Levin, MD
John F. Modlin, MD
Paul R. Offit, MD
Margaret B. Rennels, MD
Lucy S. Tompkins, MD, PhD
Bonnie M. Word, MD
Richard Zimmerman, MD

Ex-Officio Members

Centers for Disease Control and Prevention

Alison Mawle, MD, NCID
Walter Orenstein, MD, NIP
Dixie Snyder, MD (ACIP Executive Secretary)
Melinda Wharton, MD, NIP

Other Federal Agencies

Thomas Balbier, Health Research and Services Administration (HRSA)/National Vaccine Injury Compensation Program (NVICP)
Bruce Gellin, Director Designate, National Vaccine Program Office (NVPO)
Amy Groom, Indian Health Services (IHS)
Benjamin Diniega, Department of Defense (DOD)
Geoffrey Evans, National Vaccine Injury Compensation Program (NVICP)
Randolph Graydon, Center for Medicare and Medicaid Services (CMS)
Carole Heilman, National Institute for Allergy and Infectious Diseases (NIAID)
Karen Midthun Food and Drug Administration (FDA)
Kristin Nichol, Department of Veterans' Affairs (DVA)

Liaison Representatives

Jon Abramson, American Academy of Pediatrics (AAP), Committee on Infectious Diseases (COID)
Stephan Foster, American Pharmaceutical Association
Eric France, American Association of Health Plans (AAHP)
Carlos Franco, National Immunization Council, Mexico
Samuel Katz, Infectious Disease Society of America (IDSA)
Victor Marchessault, National Advisory Committee on Immunization, Ontario, Canada
David Neumann, National Coalition for Adult Immunization (NCAI)
Kathleen Neuzil, American College of Physicians (ACP)
Georges Peter, National Vaccine Advisory Committee (NVAC)
William Shaffner, Infectious Disease Society of America (IDSA) and Guide for Adult Immunization
Jane Siegel, Hospital Infections Control and Prevention Advisory Committee (HICPAC)

Agency Staff

Department of Health and Human Services (DHHS)
William Hall, DHHS, Washington, D.C.
D.A. Henderson, M.D., DHHS, Washington, D.C.
Andrew Patzman, Washington, D.C.

Agency for Toxic Substances and Disease Registry (ATSDR): Naomi Bock

Centers for Disease Control and Prevention (CDC)

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP): Ken Rose

National Center for HIV, STD, and TB Prevention (NCHSTP): C. Scott Danos, Charles Vitek

National Center for Infectious Diseases (NCID)

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David Bell
Craig Borkowf
Caroline Bridges
Lynette Brammer
Martin Cetron
Soju Chang
Myrna D.Charles
Joanne Cono
Nancy Cox
Roz Dewart
Aaron Fleischauer
Keiji Fukuda
Rafael Harpaz
Scott Harper
Alan Janssen
Nino Khetsuriani
James LeDuc
Harriette Lynch
Alison Mawle
Martin Meltzer
Ann Moen
Erin Murray
Ida Onorato
Michelle Pearson
Angie Peck
Joe Posid
Alicia Postema
Lisa Rotz
Don Sharp
Stefanie Steele
Tim Uyeki

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHPP: Kathleen Y. McDuffie

National Institute for Occupational Safety and Health N(IOSH:) Scott Deitchman

National Immunization Program (NIP):

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W. Atkinson
Carolyn Bachino
Michele Bailey
Barbara Bardenheier
Roger Bernier
Kris Bisgard
Karen Broder
Linda Brown
Molly J. Buehn
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Laura Franzke
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Bob Keegan
Vanda Kelley
Allison Kennedy
Alena Khromava
Wanda King
Laurie A. Johnson
Sharon Katz
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Brock Lamont
Larry LaRue
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Joan C. Lipton
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Brian Pascual
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Ben Schwartz
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National Institutes of Health (NIH): Linda Lambert

National Pharmaceutical Stockpile (NPS): Robert Snyder

National Vaccine Program Office (NVPO): Steve Sepe, Gregory Wallace

Office of the CDC Director: Larry Anderson, Sharon KD Hoskins, Von Roebuck

Office of General Counsel: Kevin Malone

Department of Defense (DOD): R.D. Bradshaw, Charles Hoke, John D. Grabenstein, Scott Spratt

Department of Veterans' Affairs (DVA): Carter Mecher, David Rimland

Food and Drug Administration (FDA): Karen Goldenthal, Cynthia Kleppinger, Richard Markoff, Douglas Pratt, Jenny Riemenschneider, Dorothy Scott, Barbara Styrt, Dorothy Waurose.

National Institutes of Health (NIH): *NIAID:* Sarah Landry, Barbara Mulach; Gary Wallach, CDC/NIH, Research Triangle Park, NC

Members of the public or presenters to the committee in attendance were:
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Girtika Ahlija, ABC News
Steve Allred, getaflushot.com, Portland, OR
Larry Altman, New York Times, NYC, NY
B.F., Anthony, Biologics Consulting Group, Great Falls, VA
Carmen Arrijia, Immunization Initiatives, AAP
Susan Atlas, Cooney Waters Group, NYC, NY
Lynn Bahta, MN Department of Health
Michele R. Bailey, American Social Health/CDC NIP, Research Triangle Park, NC
Denise Baker, NBC News, Atlanta, GA
Joe Beaver, TN Department of Health
Bryan Bechtel, Infectious Diseases in Children, Thorofare, NJ
Soubeyran Benoit, Aventis Pasteur
Joan Benson, Merck & Co., Inc.
Paul Blum, Acambis
Peter Bootsma, Royal Netherlands Embassy, Washington, D.C.
Dr. Luciana Borio, Johns Hopkins University
Judy Bowden, Fayetteville, GA
Greg Bowman, CNN, Atlanta, GA
Andrew Bowser, freelance medical writer, Brooklyn, NY
Willis Boyd, WXIA TV, Atlanta, GA
Patti Boyle, Aventis Pasteur
Judy Brady, Henry Schein Company
Noelle Broadnax, NE Health District, Athens, GA
David Brown, Washington Post, Washington, D.C.
Kimberly Brown, People Magazine
Sgt. H.P. Brown, DeKalb County Police Department
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Diana Davis, WSB TV
Jeffrey P. Davis, NVAC/Wisconsin Division of Public Health, Madison, WI
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Luther Deweese, Athens, GA
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Ferre Dollar, CNN
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Will Edwards, Bloomberg Business News, Atlanta, GA
Kris Ehresmann, Minnesota Department of Health, Minneapolis, MN
Craig Engesser, Wyeth, St. Davids, PA
Judith English, APIC, Washington, D.C.
Gary Evans, Hospital Infection Control, Atlanta, GA
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Steven Foster, American Pharmaceutical Association
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Sheila Friedlander, University of San Diego, CA
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Jeffrey Fu, Merck
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Kenneth Guito, Aventis
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Claire Hannan, Association of State and Territorial Health Officers (ASTHO)
Catherine Harris, ICP Report

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Kim Haupt, Merck & Co., Inc.
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Joe Hirsch, Fox News Channel
Todd Hofmeister, Holland & Knight LLP, Atlanta, GA
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Philip Hosbach, Aventis Pasteur
Barbara Howe, GSK
Dominic Iacuzio, Roche Labs
Melonie Jackson, Georgia Chapter, AAP
Michael Jester, NBC, Atlanta, GA
Virginia Johnson, DVC, Frederick, MD
Jan Jubilee, United Press International
Jay Karjewski, ABC News
Jim Kauffman, CNN
Claudio Kelly, Merck Vaccine Division
Peter Khoury, Baxter BioScience
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Dr. Arlene King, Health Canada
Deborah Kleijne, National Institute of Public Health, Bilthoven, Netherlands
Jim Knowles, NBC News, Atlanta, GA
Dr. J. Michael Lane, Atlanta, GA
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Michele Marill, Hospital Employee Health
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Angela Moore, Children's Healthcare of Atlanta, Atlanta, GA
Wayne Morges, Baxter Healthcare, Columbia, MD

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Peter Paris, Cooney Waters Group, NYC, NY
Ebony C. Parker, R.N., Douglasville, GA
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Stacy Stuerke, Merck
Dr. L. J. Tan, American Medical Association
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John Zahradnik, Aventis Pasteur
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CENTERS FOR DISEASE CONTROL AND PREVENTION
NATIONAL IMMUNIZATION PROGRAM
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MINUTES OF THE MEETING
OCTOBER 16-17, 2002

OCTOBER 16, 2002

A meeting of the Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention's (CDC) National Immunization Program (NIP) at the Atlanta Marriott Century Center Hotel in Atlanta, Georgia, on October 16-17, 2002. The meeting agenda (posted on CDC's Website, http://www.cdc.gov/nip/) principally addressed the use of smallpox vaccine, but also addressed the influenza vaccine recommendation and the 2003 recommended childhood immunization and catch-up schedules. The meeting was convened by ACIP Chairmen Dr. John Modlin at 8:30 a.m.

Those present are listed on the attached sheets.

OPENING COMMENTS

ACIP Executive Secretary Dr. Dixie Snider made several announcements:

- ACIP members whose terms have expired but are serving until they are replaced are Drs Word, Offit, and Rennels.
- He congratulated former ACIP member Dr. Natalie Smith, NIP's Deputy Director.
- He requested that updated CVs from all the members be sent by mail or e-mail to Ms. Gloria Kovach by November 15.
- The ACIP home page is: www.cdc.gov/nip/acip.
- The 2003 ACIP meetings will be held on February 26-27, June 18-19, and October 15-16, with the locations to be announced.
- He requested, with two unfilled member seats and Mr. Salamone's absence, that the members be attentive to maintaining a quorum for this meeting. If a quorum of eight members is not eligible to vote on a motion due to conflicts of interest, the Executive Secretary is deputized to appoint the liaisons as voting members. Finally, he announced that public comment is enabled at ACIP meetings by randomly selecting the names of those who sign up to speak.
- He provided workgroup updates:
    - HBV vaccine will be available in the next couple of years. A workgroup to formulate relevant recommendations is chaired by Dr. Lucy Tompkins.
    - Dr. Celine Hanson is the new Chair of the General Recommendations Workgroup. Dr. Wharton reported activity in the form of conference calls to address the vaccine storage issue raised at the last meeting. An update was to be provided at this meeting.

YELLOW FEVER

2002 Yellow Fever ACIP Recommendation, Immunization of Infants
Dr. Modlin provided the background to this topic. The ACIP had recommended on yellow fever vaccination in February 2002, but infant immunization was still at question.

Dr. Midthun reported that the vaccine's indication approved by the FDA for use in those aged ≥9 months, and WHO data from yellow fever endemic countries indicate vaccination at no younger than 6 months. Use among younger infants (to 4 months) was discussed but is not supported by data as yet.

Dr. Martin Cetron, Deputy Director of the National Center for Infectious Diseases' (NCID) Division of Global Migration and Quarantine, outlined the options related to revising the recommendation to allow vaccination to ≥6 months:

1. Retain the recommendation of the 1990 statement for vaccine use in those aged ≥9 months and add permissive use when necessary at 5, 6, 7, and 8 months.
2. Consistent with the new package insert, recommend no usage in those aged <9 months.
3. Recommend a consensus approach consistent with the WHO's practice to permit use at ages 6-8 months in areas at high risk of transmission.

Data are few from areas with good surveillance that address children aged <9 months, but those available were presented.

- Yellow fever is a neurotropic disease diagnosed by isolation of the vaccine virus from CSF. The early (1952-1955) literature on infants aged <12 months report post vaccinial encephalitis clustered (14 of 16 cases) in those aged ≤4 months. VAERS reports of the 1990s indicate ~10 cases scattered in age. In view of permissive use in areas without good surveillance, the challenge is to know the denominator.
- Vaccine use age distribution, U.S.: A study of 13 civilian (military use was not included) travel clinics including 5000 vaccinees over a year indicated vaccine use mostly in adult clinics, with 15 cases found from 1952-55 and 10 cases from 1990-2002. The pediatric percentage is uncertain, but manufacturer production figures provide a crude denominator. The prominent clustering seen in the early years, before use in infants was not advised, has not been seen in later years.
- There is no vigorous surveillance for encephalitis, but outbreak data include:
    - Gambia: attack rate incidence of 30% and a 1:5 or 1:10 attack rate in cases of high transmission risk.
    - Texas fishers, half protected and half not protected by their own choice, produced one fatal case among the seven who were unprotected.
    - An attack rate of 1:1000-1:5000 was documented in a two-week excursion to endemic area.
    - The incidence of post-vaccine encephalitis may be 1:1 million to 10 million.

Discussion included:

- Few doses have been given world wide to those aged 0-4 months, and the WHO policy recommends administration to 6 months, not ≤4 months.
- *Are there more data on diagnosis?* In those with less severe disease, most recover without sequella. Two fatalities occurred from 1952-2002, one in a child and one case from Thailand in a person unknowingly positive for HIV. There is no evidence of a temporal association or of any CSF findings in the literature. Only one case found the yellow fever isolate in CSF, which had reverted to the wild-type virus.
- *How is the current vaccine similar/different to those in the past?* These vaccines are 99.9% homologous at the nucleotide level.
- The presentation made the denominator clearer about the doses given, but the statement does not address this other than to note the absence of rates. An added sentence was advised to note the assumption that few cases occurred worldwide in children aged ≥4 years, but the ACIP estimates the rates to be higher. The contraindications also perhaps should say "may be" more susceptible, since there are no data to show they are more so.

Dr. Tompkins **moved to accept Option 3**. The motion was seconded by Dr. Brooks and Dr. Abramson reported AAP's agreement.

Vote:

Conflicts:	with Aventis: Drs. Belshe and Rennels
In favor:	Word, Zimmerman, Levin, Offit, Brooks, Tompkins, Modlin, Birkhead
Opposed:	None
Abstained:	Rennels, Belshe

The motion passed.

SMALLPOX

Background. Dr. Modlin summarized that the smallpox vaccination program plan has been vetted through CDC and forwarded for approval to DHHS and the highest levels of government. No definitive decision has yet been made, but the administration is considering expanding on the ACIP's October 2002 recommendations, to include immunization of larger number of health care workers than recommended in order to have more acute care hospital facilities with immune staff.

The media reported three options as discussed: 1) focusing on the health care providers caring for the first patients. This could include up to 50% (i.e., 2500) of hospitals in the U.S., with 200 staff in each (to total 500,000 staff); 2) open vaccination to all health care workers clearly at high risk and all first responders (10-11 million); and 3) have vaccination open to the general public. This meeting's focus is to examine the first option and what implementation would be needed.

The joint Smallpox Workgroup of the ACIP, the National Vaccine Advisory Committee (NVAC) and the Healthcare Infections Control Practices Advisory Committee (HICPAC)

has been active since the June ACIP meeting. CDC anticipated some decisions to be made as to whether further actions by this group should be vetted to the public, and if there should be a joint ACIP/NVAC statement. Dr. Snider expressed CDC's wish for an ACIP/NVAC/HICPAC support of the recommendations made. Discussions are ongoing on how best to accomplish that.

Smallpox Vaccine Production

Mr. John A. Becher, R.Ph., of the NCID, reported on the current smallpox vaccine products: Wyeth's Dryvax,® the Acam1000® and Acam2000® products, and the Aventis-Pasteur (AvP) vaccine. Fifteen million doses of undiluted Dryvax® is available (75 million diluted 1:5); 54 million doses of the Acambis vaccinia vaccine (Acam1000) are contracted to be produced in MRC5 cells; and 155 million doses of the Acambis vaccinia vaccine in vero cells (Acam2000) are to be produced for a one-time purchase. There are 85 million doses of the AvP vaccine produced in the mid-1950s, equating to 425 million at a 1:5 dilution. In September 2000, CDC contracted with Acambis to deliver the Acam1000 vaccine. This unique 20-year contract term is designed to avoid supply interruptions and to serve as the backbone of the national smallpox vaccine supply. Only the AvP and Dryvax® vaccines are available today.

All orders include delivery of individually-wrapped bifurcated needles; 15 million for the original Dryvax® stock and 60 million for a 1:5 Dryvax® dilution. Along with an additional 75 million ordered, this will supply a needle for every dose in the National Pharmaceutical Stockpile (NPS). The contract provides for a diluent of 1:5 Dryvax® to be provided under an IND at least to the end of 2003. A contract is now being negotiated for 30,000 doses of vaccine immune globulin (VIG) with an option to increase if needed.

The production passage history was described. Dryvax® is the source for the new plaque-purified Acam1000 and Acam2000 vaccines. The Acam1000 and Acam2000 vaccines share a master seed that makes the products very similar. The Acam2000 product has been grown in bulk and Phase II trials are underway; 150 million doses of vaccine should be ready by October 2002. The Phase I clinical trials for Acam1000 are almost completed; Phase II trials are scheduled for this summer. Production of the Acam1000 will continue into the next calendar year. With these and current stocks, a dose for every citizen is anticipated by the end of this year. The NPS will receive all doses filled and kitted. Sixty million doses of the Acam2000 will be delivered by the fourth quarter of 2002, another 97 million by the first quarter of 2003, and about 50 million doses of the Acam1000 in the second quarter of 2003.

VIG has been collected and one lot bottled to date. It will be in the NPS by the end of October. Over 3000 doses are hoped to be in hand by the end of the calendar year; another 8000-9000 in the first quarter and another 10,000 in the second quarter.

Smallpox vaccine production. Vaccine for "all Americans" is hoped to be in hand by the end of 2002. Wyeth submitted its SBLA to the FDA in September; all other vaccines

are still under IND status. Clinical trials through Phase 2 will be complete by the first quarter of 2003 and licensure of the Acam2000 is expected in early 2004. The production contract includes the supply of bifurcated needles and diluent. The VIG contract has been signed and production is underway. NPS storage sites have been identified for rapid deployment.

Dr. Modlin anticipated the need for ACIP recommendations for use of a licensed vaccine, with discussion focusing on a number of issues relevant to vaccine safety. The current IND informs the process, so some discussion will be possible based on how the vaccine is being given. Even so, that process has not be finalized and some negotiation is still proceeding on that.

Pre-event Vaccination for Designated Smallpox Response Personnel Using 1:5 Diluted Smallpox (Dryvax®) Vaccine.

Overview of Current IND for Pre-exposure Use of Smallpox Vaccine
Ms. Debra Dotson, R.Ph, of the NCID Regulatory Affairs Office, outlined the basic guidelines for the protocol covering pre-exposure use of smallpox vaccine. CDC's protocol, developed in case a licensed vaccine is not available, does not mandate screening for HIV or pregnancy. Pre-vaccination day education addresses that. This protocol will be the standard of care for use of either the IND or the licensed vaccine; in the latter case, it is being rewritten as "guidelines for use".

Pre-vaccination day screening allows the individual to self-defer. Consultation with their health care provider is strongly recommended if any risk factors apply to them or their family. Education is done at the clinic visit, or the information packet can be mailed (less preferable since answering questions is more difficult). The vaccinee receives a non-returnable vaccination checklist with which to do a self-screening at home, an "advice letter, counseling information sheets and a copy of the informed consent document. An information sheet on the medical risks is provided, discussing:

- HIV risk factors and other contraindications to vaccination: pregnancy, skin conditions, and (risks to household members/close contacts, children aged <1 no longer a contraindication, but not vaccinating them is recommended
- Employment and financial risks such as a potentially necessary furlough and issues related to liability and compensation for lost wages. CDC will pay for vaccine and treatment for adverse events if needed, but not yet any other mechanism available for other medical costs and lost wages.

Vaccination day. A participant checking "yes" to any conditions for themselves or their family members would either decline the vaccination or have counseling. If they checked no's, the vaccination process begins:

- They receive a clinic check-in information packet with the counseling information sheets, the informed consent form, and product information sheets written at an 8-9th grade level about the vaccine, VIG, Cidofovir, etc..
- They again receive the screening tool, this time with only yes/no answer options.

- Another education session is done on expected post-vaccination reactions (e.g., to advise that they will feel terrible on days 8-9, but better thereafter), serious adverse events (SAE), local numbers to call in the event of the latter, and vaccination site care. They receive an adverse effect diary sheet, a VAERS form, an interim immunization card (a permanent one is provided later), information on vaccination site care, and an appointment for a "take" ck.
- Logistical issues again involve clinic staffing, scheduling "take" checks, and local phone banks.

Informed consent. The process of informed consent includes explanation of why the program is being conducted; why an investigational vaccine and diluent is used; that participation is voluntary, how this relates to eligibility to be on smallpox teams (not eligible if unvaccinated) and to be vaccinators (currently, eligible if unvaccinated); what is involved and how long the process takes; and the benefits and risks of the vaccine. It explains that no benefit can be guaranteed, since there is no smallpox in the world, and that there are risks to household members and close contacts. It defines who should not be vaccinated and outlines treatments for serious reactions (VIG and Cidofovir), site care, risks related to pregnancy, privacy assurances, how the costs involved are covered, sources of response about vaccine injury for program participants, and vaccine alternatives (i.e., that there are none). Three signatures are requested, one to receive the vaccine, another to allow photos, and one to participate in a 10- and 21-day safety follow-up by telephone.

Monitoring of adverse events will be done by the Data Safety Monitoring Board (DSMB) and by NIP staff (Drs. Casey, Mootrey, and Chen). The latter will work with the Clinical Immunization Safety Assessment (CISA) Network to provide consultation and review for investigators' evaluations of all serious adverse effects, review and facilitate reporting to VAERS of all serious or unexpected reactions, and recommend to CDC for VIG release and/or an indication for Cidofovir or Vistide® in treatment of SAEs. They also will facilitate reporting of all serious and unexpected reactions to FDA, IRB, and the DSMB.

Discussion included:

- *This seems to be a sound plan. Does the scope include vaccinating laboratory researchers?* Other protocols are in place, one for undiluted Dryvax® vaccine use among lab workers who routinely use orthopox vaccine. *That is an important distinction for the local IRBs involved with lab worker issues. They may want to add additional standards.* CDC's IRB is used as the central IRB. If the investigators substantially change the current specific protocol, they are asked to go to their own IRB.
- Counseling information sheets have both pictures and descriptions of adverse events.
- *Will the Dryvax® used be undiluted?* Yes. *Do the vaccinators fall under this protocol?* Yes, but that is now under review by FDA and the IRB and not yet approved. Until then, the state's or institution's IRB would have to approve vaccination of vaccinators.

- Approval was expressed that the packet details what the vaccinee should expect, an important component to ensure no surprises on post-vaccination day.
- The investigators serve as support to the CISA centers. (This was explained in detail later.)
- *The IND defines the presence of a child aged <1 year as a precaution, not a contraindication, and this is an absolute exclusion in most protocols. Will that remain if the protocol uses the IND as a standard?* This was originally a contraindication, since children <1 year old might contact the vaccination site, but this is just a recommendation to caution people about this risk. The Smallpox Workgroup in September discussed that the IND standard is higher and might not apply here. The Neff paper explains why this is a contraindication (fatalities from eczema vaccinatum [EV]), but that recommendation could discourage many health care workers who have children<1 year old at home.
- *Since self-assessment is central to the vaccination decision, does the testing ensure they understand the material and can assess themselves appropriately?* Not at this time. The protocol, currently under review by FDA and IRB, will be shared with the ACIP when approved.
- *What is the intent of the vaccination card?* Part of the post-event protocol, this is to identify those vaccinated to ensure follow-up on days 6 and 8, when the vaccination site is checked.
- *If the second checklist on immunization day is not adequately filled out, is that an exclusion?* A "yes" to any contraindication prompts exclusion. Everything must be completed to be vaccinated.
- *How does the IND address HIV? Are those tests available or are they referred?* Testing is not mandated and the protocol does not provide testing. The pre-vaccination day education details those associated risks. The clinics will be asked to identify area testing clinics for interested individuals. Rapid HIV tests are under review.
- *What is anticipated for relicensure in the near future? Once reconstituted, for how long are the 100 dose vials viable; and how many skin punctures are needed?* FDA is currently considering new needles and diluent. There are no clinical data for this supplement; it just allows the vaccine to be released as originally approved, including punctures. There are 2-3 for the primary vaccination and 15 for revaccination. FDA will review any clinical data submitted by the manufacturer to support a different number of punctures or diluent. The company's evaluation of duration of stability supported its certification of ≤30 days if stored at the proper temperature. They are exploring stability to 90 days. FDA will relay any additional information available. Stability is measured by titering the virus over time *in vitro*.
- If/when the product is licensed, CDC will provide the vaccine at no cost.
- *Training: States:* A training program for the states is in development, with all related information. About 5 from each state health department will attend a one-week very detailed training in the whole program, including screening, contraindications, etc., and vaccination technique. Health care providers will be trained through a satellite broadcast accessible to all, at the beginning of the

program. Materials will be on the Website as well as distributed in print. A *patient education* video will be shown at the pre-vaccination visit. A menu of options for a variety of audiences is designed to ensure that all understand what the vaccine is, the need for the program, etc.

DHHS Update: Current Status of Smallpox Vaccination Program
Dr. D.A. Henderson commented on the difficulty to assess an unquantifiable disease risk against a vaccine risk. While the ACIP recommendation was greatly supported by numerous professional organizations, there are also those not wanting vaccination at all and those wanting to vaccine everyone.

The risk of release is still small, but not zero. A smallpox release could be catastrophic; in the absence of a vaccine, the only response could be to isolate patients. While the nation is much better prepared than it was a year ago, there is much more to do. Dr. Henderson addressed two aspects of dealing with smallpox:

Response in the event of an epidemic. About a year ago, it was reaffirmed that limited supplies of vaccine would be restricted to contacts of cases and their families, and larger scale vaccination would be limited. With sufficient cases, community-wide vaccination may be necessary (e.g., triggered by ~40-100 cases), but the terms and extent for that require discussion. Vaccination of contacts, cases and their families would be pursued regardless of the number of cases.

However, vaccine supply now is ample for wide scale vaccination in an emergency. Emergency response programs are prepared to vaccinate contacts and families widely if needed within 5-10 days. A plan was distributed to help the states organize. Every regional hospital was asked to prepare to accommodate 500 acute patients and all hospitals were asked to set up a negative pressure room to house patients with fever or rash, to avoid transmission in an ED. That is in progress. Restrictions were reduced for an emergency versus a pre-event setting.

DHHS decided to move ahead to provide vaccination to the high risk medical groups for two reasons: 1) if a flat or hemorrhagic case presents, or if a case is missed, exposed people will not be diagnosed for some days; and 2) vaccinating teams should be protected so that if a release or outbreak occurs, they will be more confident monitoring the responders. Finally, documentation of the vaccination process will be very helpful to help physicians less than 60 years old, who have never vaccinated for smallpox.

How best to facilitate the process while assessing risk for complications among patients? Ample stocks of a licensed vaccine are still somewhat uncertain, but a licensed Dryvax® is likely and screening/vaccination should be possible in a single visit. *Furlough* of hospital workers was thought by the Workgroup to impose an impossible burden on hospitals. *The risk of secondary transmission* of vaccinia was addressed in a paper published in the latest *JAMA* (Neff, Fulginiti and Henderson). Its analysis of 1963 and 1968 reports, including unpublished data, indicated surprisingly infrequent

spread by contact and that very close contact was required. Spread was mostly child-child or child to adult; few were adult-adult. However, the 1968 experience cannot be wholly extrapolated to the present. Primary vaccination would now shed much more virus, and the population has significant rates of atopic dermatitis (AD), eczema and immune deficiency. Although there is some comfort that secondary transmission may be less of a problem than thought, further study is required.

Communication is important to broadly inform healthcare providers as well as the public. A pocket guide developed by PHARMA with DHHS was shared on the vaccine and its complications. About 250,000 have been printed and they will be transmitted widely to professional groups, hospitals, nurses, etc. The CDC Website also will post photos (~180) of complications, etc., and will link to other Websites as possible.

An announcement of a policy and its implementation is imminent, as the nation needs to proceed with preparations to respond to an emergency.

Discussion with Dr. Henderson included:

- Dr. Offit noted the June 2002 ACIP decision to not recommend vaccination of the general public without credible evidence of an imminent massive release in small droplet form. However, recent media reports indicate that the vaccine is likely to be offered to the general public. He strongly felt that to be a mistake in the absence of that risk, entailing a shortfall in public health's responsibilities to a public that may not truly understand the risks and benefits. He asked if a reaffirmed ACIP recommendation may help? Dr. Henderson responded that the decision has not been made. DHHS has no intention of doing a mass vaccination without a licensed product, which will not be in hand before the end of 2003 (the Acambis tissue-culture vaccine). The government wants to implement the recommendations made to date: to conduct pre-event vaccination and to prepare for any emergency.
- Dr. Abramson was concerned at continuing hesitation about doing studies among a small number of children to assess the vaccine's side effects. The AAP favored studies only in a limited number of children to have the needed data in emergency event. Some think that this would be unethical, since a benefit cannot be offered; but others favor it to ensure that children respond promptly. The conduct of pediatric studies is still being discussed.
- *What if an "untraditional", modified smallpox agent is used? The vaccine, with all its risks, would then also be only partly efficacious.* A paper by Richard Preston of Princeton University suggested this as well, but DHHS reviews concluded that this is unlikely. Such viral manipulation, testing to ensure it works, and large-scale manufacture is not impossible, but is unlikely to be done undetected. CDC is continuing to work with orthopox viruses generally. Currently, DHHS feels best advised to prepare to handle the standard strain more likely to be released and then the less likely strains.

VACCINATION OF HEALTH CARE WORKERS

HICPAC Vaccination Options of Selected Health Care Workers
Dr. Jane Siegel, of the Healthcare Infection Control Practices Advisory Committee (HICPAC), presented data developed by herself, HICPAC Chair Dr. Robert Weinstein, and Dr. Michele Pearson of CDC. She outlined two basic approaches with which health care workers could be selected for vaccination.

Option A: Two regional approaches. In this approach, a smallpox care team will be vaccinated to care for the first smallpox patients, through: 1) a regional approach (cadre /team/pod approach) in a Type C facility (the ACIP's original approach), or 2), a hospital-based approach with vaccinated teams in each hospital with negative pressure rooms (i.e., acute care hospitals). The numbers were estimated based on a 24/7 capacity to deliver care for the first 4-7 days during which subsequent staff vaccinations 'take'. It considers work schedules, vacations, and the workload anticipated with smallpox patients presenting.

The composition of the care team was proposed to include selected physicians and nurses (including in pediatrics) and representatives from the ED, ICUs; the same for the general medicine units, plus internists and obstetricians in hospitals where family practitioners are the main providers, and selected house staff (medical, pediatric, OB); and infectious disease physicians. Sub-specialists would be in a regional team to consult with the hospitals: physicians experienced with smallpox in the past, dermatologists, ophthalmologists, and a pathologist for post mortem examination. Engineers have been considered as well. Others include selected respiratory therapists, radiology technicians, and security staff.

Discussion is ongoing about offering property service workers (housekeeping) the opportunity of vaccination. Real-time data to guide this will be important. Clinical lab workers also were initially considered at risk, but it was concluded that since their work is with clinical specimens rather than viral isolates, the viral load will be low enough for standard precautions to suffice for protection, at least in the beginning.

Number affected. The Department of Labor (DOL) estimates ~6 million hospital workers in the U.S., another million in non-hospital settings (e.g., community clinics), and another ~1 million of EMS providers. Drs. Rafael Harpaz and Pearson estimated a need for about 100 health care workers per hospital care team to care for the initial 3-4 patients with a presumptive diagnosis of smallpox, assuming 12-hour shifts, backup, etc. Nationwide, that would total about <500,000 health care workers.

The *advantages* of the Option A-1 regional concept (relying on catchment area and team concepts) are that many states have already addressed these issues. It would involve less pre-event disruption, fewer staff on administrative/sick leave, lower vaccine morbidity, less need for VIG, fewer vaccine candidates to be screened for contraindications (i.e., prior vaccinees), and that more voluntary cooperation facilitates a vaccination strategy. The *disadvantages* include hospitals' reluctance to be

designated a Type C facility; greater risk of smallpox transmission among workers responding to the first unidentified cases, and a potential underestimate of the number of workers needed to respond to the first wave.

Option B: Vaccination of all health care workers and first responders. The latter are those most likely to respond first before the case is recognized (e.g., police, firefighters, EMTs, ED staff and ~6 million health care workers nationwide). This would total approximately 10 million Americans. This would be a suitable approach for a Phase 2 of a pre-event vaccination program. The *advantages* include less risk of smallpox transmission, more staff available to care for patients, less need for cross-training, familiarity with the care facility, and fewer healthcare workers to vaccinate in a second-wave post-event vaccination. *Disadvantages* include more pre-event disruption, potentially more vaccination refusals, increased vaccine morbidity and need for VIG, more screening and greater difficulty than the preferred option, vaccination of those previously vaccinated. This also assumes one patient per hospital.

The *Workgroup preference* was for Option A-2 (hospital care team in acute care hospitals). Its composition may vary according to local needs.

Discussion included:

- *State/local health department perspectives* were offered by Drs. Birkhead, Hanson and Thompson. They agreed that Option A-2 is doable and closest to their present orientation, rather than that of a few regional hospital centers. Few hospitals are eager to be designated as the Type C smallpox hospital and, since where patients will present cannot be anticipated, local hospitals need prepared (vaccinated) teams. This approach also best melds with some current emergency response plans. The 500,000 anticipated vaccinees would translate to ~5,000 vaccinees in the state of Mississippi. That state, Georgia and Minnesota have vaccinated more than that in less than a week for other outbreaks.
- Similar agreement to the A-2 approach was reported by Massachusetts and Wisconsin. Not on hospital in Wisconsin agreed to be designated as Type C hospitals, and all agreed that any hospital with a negative pressure room should be prepared. Some are extending this component of disaster planning from smallpox to the similar applicability of an influenza pandemic.
- A rash diversion policy for ambulatory clinics would have such patients taken to a specific place for assessment and treatment, rather than vaccinating ambulatory clinic staff.
- Concern expressed:
  - *EDs are the point of entry and diagnosis, and hospital overcrowding generally requires a wait.* Perhaps the whole ED staff should be vaccinated; but then, why stop there? HICPAC struggled with this Pandora's box as well, but that moves into option B. Dr. Thompson reported Mississippi's conclusion that incidental contact in the ED probably would not involve the highest risk; the physicians and nurses are

likely to be at highest risk. However, it will be hard to identify the staff to vaccinate and to maintain a cohesive team over time.

- Systems in hospitals should be set up to isolate rash patients as early as possible, as with measles, chicken pox, and meningococcus outbreaks. As far as possible, the existing protocols used should be paralleled to smallpox. The problem is that the patient without a rash is not contagious.
- EMTs are a large population (800,000) that could have significant exposure in retrieving acutely ill patients. Perhaps a few EMTs could be identified for transporting patients identified as potentially at high risk.
- *Does choosing A-2 mean there will be no regional response teams?* No. DHHS accepts that regional response teams will be immunized separate from hospital workers.
- Housekeeping and similar staff (e.g., laundry) were excluded from the HICPAC recommendation, which included only those in patient care. Some felt that at least a small number of housekeepers should be vaccinated. One consideration is the perception of discrimination if, as seen in the anthrax events, less educated people feel left out. While in the first few days, perhaps the nurses and physicians most likely to understand the risks of vaccination could do the basic housekeeping chores, Dr. Fulginiti advised that a few housekeepers should be trained on how to handle fomites.
- Others not on the list for vaccination are the vaccinators themselves and those doing invasive procedures such as surgery or even inserting a line or catheter. HICPAC considered that and the topic is still open to discussion. One consideration is how likely it is that such procedures might be necessary. Dr. Fulginiti reported that mistaken diagnosis of early smallpox patients (e.g., for severe abdominal pain) has led to patients being operated on before the rash appeared. Perhaps surgeons could be vaccinated for a regional group rather than in individual hospitals.
- *EMTs may be upset if they wish for but cannot get the vaccine. Are these guidance recommendations applicable even if a licensed vaccine is available?* This is one of the points on the brink of Option 2. But the second stage of vaccinating the 10 million health care workers would open it to any health care worker desiring vaccination. And, patients with rash illnesses generally get to the ED on their own; they are not generally so sick as to require rescue service transport. Only one meningococcal death is known of under such transmission circumstances. One smallpox case in Yugoslavia went in an ambulance from a rural area to Belgrade with an unvaccinated pregnant woman, and there was no spread to the two people in the ambulance.
- *Is there any concern about potential aerosol risk from laboratory procedures such as spinning down urines?* There is that potential. Standard laboratory precautions should address that, but many violations were also seen in the meningococcal experience. The question is whether standard precautions are sufficient, at least in the first stage?

- The only prioritization planned for team members is for those who have previously been vaccinated.

Dr. Modlin summarized the sense of the committee that the Option A2, hospital-based approach, is the choice. However, Dr. Offit reiterated his objection. He pointed out the logarithmic increase from ACIP's reasonable recommendation to vaccinate 10-15,000 people, to ~500,000, for a theoretical disease. No smallpox has been on earth for 25 years. He agreed to the logic of putting the response system in place, but with the vaccine under lock and key, and vaccinating only after the first single documented case. This is a case study in how terrorism works, he said, considering that the vaccine causes serious adverse events and will do some harm. He again asked why the country should not just wait for the first confirmed case?

The response was the opinion of the state and local hospitals that the originally favored regional approach was not likely to work; if smallpox shows up, all hospitals have to deal with that. NACCHO also concluded that the average local public health office, staffed with ~16 people, would be quickly overwhelmed by trying to follow up and trace the contacts of even a few cases, while concurrently trying to conduct a large vaccination program. Pre-vaccination will ensure teams in place to execute an already-functioning system.

Dr. Levin **moved to adopt Option A-2** as the ACIP's recommended approach and was seconded by Dr. Brooks.

Vote:
Conflict: with Wyeth: Dr. Rennels and Belshe.

In Favor: Hanson, Birkhead, Tompkins, Modlin, Word, Zimmerman, Levin and Brooks.
Opposed: Offit
Abstained: Rennels and Belshe.

The motion passed.

Vaccination Site Care

Dr. Rafael Harpaz reported data estimates related to smallpox vaccination of health care workers.

- The Neff et al (*JAMA* 2002) reanalysis of 1960s data and Freis et al's study of primary vaccinees (*J Ped* 1947) indicate a risk of 17-20 EV cases per million primary vaccinees. Risk of inadvertent infection among contacts was 45:1 million. No other forms of vaccinial disease were reported.
- *Vaccinia transmission to contacts* was reported from no revaccinees, but 65:1 million was reported for primary vaccinees. Use of autoinoculation as a marker of transmission risk to contacts occurred in 42 of 1 million revaccinees and 529

of 1 million primary vaccinees. Viral shedding as a surrogate for transmission (Cooney, 1991) showed viral titer of primary vaccinees to be five times higher, and shedding three times greater, than among revaccinees.

Risks of vaccinia transmission in the healthcare setting:

- "Denominator" based data (doses delivered to primary vaccinees and to health care workers who were potentially contagious)"
  - New York City, 1947, 3 million primary vaccinees produced 28 vaccinia cases in close contacts, 3 of those conveyed in the health care setting.
  - Neff et al (*JAMA* 2002) analysis of the 1968 national survey of 5.6 million primary vaccines: 127 cases from close contacts, 1 from the healthcare setting.
  - Sepkowitz (submitted for publication) analysis of 12 anecdotal reports among 87 contacts in the hospital setting, with source cases usually having EV; most secondary cases had underlying skin problems.
- Unclear modes of spread were reported in Glasgow (1935, 100% attack rate in primary ward, and 36% in an adjacent ward with shared healthcare workers), Marseilles (4 cases in cribbed infants exposed for only 2 hours), and California (transmission by patients who just passed in the hall and may not have shared health care workers). The source in all three episodes were eczematous and presumably covered with high concentrations of vaccinia virus.

Conclusion: can historically low risk be extrapolated to current circumstances? While vaccinia transmissions in health care settings are known, those low risks may not be transferrable to current circumstances. Differences include:

- *Past experience:* Most patients were vaccinated and most health care workers were revaccinees who rarely caused transmission; few patients had risk factors; limited invasive procedures were used on wards (e.g., catheters, lines, tubes); there was less attention to infection control and longer health care worker interaction with few patients, and only ~30 large hospitals vaccinated health care workers. The vaccine site was left uncovered or covered only by gauze.
- *Present considerations:* Patients and health care workers are unvaccinated or vaccinated decades ago (or health care worker primary vaccinees); a high rate of patients have risk factors; there is routine placement/use of invasive procedures on wards but also increased attention to infection control; health care workers interact with a high volume of very sick patients for short periods. Vaccination of hundreds of thousands of health care workers is anticipated. There are no standards or recommendations on coverage of the vaccination site as yet.

Laboratory data

Risk of vaccinia transmission:

- Berneson isolated vaccinia from the inoculation site from days 3-14 in 1972.
- Johnson et al (*Western J Med* 1975) studied fomite transmission and found that vaccinia can persist in the environment for 3-4 days.
- Gurvich et al (*J Hyg Epidmiol Microbiol Immunol*, 1974) studied nasopharyngeal

carriage of vaccinia and showed 11% (16/146) children with positive but low-titer specimens of the European vaccine strain isolated 6-12 days post-vaccination. The authors downplayed the epidemiological impact of their findings, and there were questions about the vaccine strain and the studies' low numbers.

- Koplan et al (1965) conducted virologic and immunologic studies of 62 enrolled smallpox vaccinees, mostly revaccinees. Virus was isolated at the vaccination site as early as day 2 in 90% of vaccinees. The duration of isolation was 0-18 days, with a mean of 8 days. Viral shedding sharply decreased shedding with scab separation at ~7-10 days, but viral isolation was still seen in 12%. A subgroup of 4 vaccinees were studied for potential viral isolation from scab surface and/or underlying skin. The results differed, but all had some positive results. No virus was isolated from throat/urine specimens in a subgroup of 8 vaccinees at 2,4,6,7,10 days. The differences from the Gurvich study due to use of a different vaccine or methodologies.
- Cooney et al (*Lancet* 1991) found 11 of 15 revaccinees and two primary vaccinees of recombinant vaccinia vaccine expressing HIV envelope glycoprotein shed virus, at 5.5 days for revaccinees and 16.7 days for primaries. A low-titer virus was isolated from the outer surface of an OpSite semipermeable dressing, but none with two layers of OpSite and gauze under dressing. There was no vaccinia titer boost among household contacts. It was noted that covering the site may extend scabbing time and prolong viral shedding, but no lab data were found to support this.
- Cooney et all follow-up study followed 12 controls who received 1 of 2 doses of vaccinia vaccine. The last day of shedding ranged from 9-21 days, with a median 19 days. Viral isolation occurred in 12 of 66 specimens (18%) when one layer OpSite and no underlying gauze were used; three of 103 (3%) were positive with gauze and two OpSite layers. Dressing effect was not reported.

Impact on health care workers; local reactions and vaccine take.
Local reactions: Routinely, but not consistently, occlusive dressings led to maceration and delayed resolutions, although in a Swedish study, a plastic film sprayed on was well tolerated (Rylander, 1968). An inflammatory reaction was avoided by underlying OpSite with gauze. However, there are no controlled studies on the impact of intermittent occlusive dressings (e.g., while treating patients) nor to resolve speculation that occlusive dressings provoke florid local reactions or satellite lesions.

A tissue culture-based smallpox vaccine trial by USAMRIID (Coster, unpublished) used band-aid dressings; 24/58 developed debilitating erythema and pruritus. 11/24 had no relief from dressing changes or adhesive. A "bandage holiday" to leave the site uncovered provided immediate and impressive resolution.

Site preparation. Also addressed was the impact of site preparation on local reactions, not formally studied to date. Vaccine site bacterial infections have not been historically described and the current recommendations do not call for antisepsis for vaccines or insulin for diabetics. Skin irritation due to antisepsis might predispose to local vaccine

adverse reactions. In fact, alcohol and other agents could inactivate vaccinia virus and reduce take. In an NIH multicenter smallpox vaccine trial, the site using 10% acetone/alcohol as site preparation had 15 no takes while the other two sites had none, but ongoing study showed a small number of subjects who had full responses to smallpox vaccine with that skin preparation.

Vaccine site. The volar forearm, ankle, and other skin sites have been used for vaccination but there are no data on efficacy or immunogenicity according to vaccination site. Factors that could impact take, adverse reactions and spread to others include accessability, ability to scratch, dressing changes, site occlusions and ability to read a take.

The *historic practices* in the U.S. for health care worker vaccination were outlined. Since the mid-1960s, <30 large hospitals did mass vaccinations, sometimes prior to holidays, or reassigned them to lower-risk units. Most health care workers kept the inoculation site uncovered except for clothing above it, and some used gauze under their clothes. There was typically no preparation of the site.

Current ACIP recommendations for non-health care worker vaccinees advise thorough hand hygiene after close contact with the site or material and leaving the site un- or loosely covered by a porous bandage. Any bandage is replaced every 1-2 days. The site is kept dry except for bathing, and separated scabs should be discarded in a plastic bag. *Health care worker vaccinees* should avoid contact with patients with risk factors until the scab falls off. If that is not possible, the site is kept well covered and meticulous hand hygiene is essential. A more occlusive dressing could also be advisable, covering the site with dry gauze followed by the dressing, which is changed once a day.

Current practices. The practices of CDC and DOD responders have similar components to those of the ACIP, except that both recommended keeping the site dry, including in bathing. *CDC responders* are advised to cover the site with a loose bandage or gauze, to protect it from water with a waterproof dressing during showers, to replace dressings with each shower or as the exudate accumulates, and to rotate the tape with each dressing change to reduce irritation and reactions. *DOD* shows a training video to all vaccine recipients and their contacts. It advises leaving the site dressing uncovered or covered with a loose bandage or gauze, but always covering it in public. High risk individuals are to be avoided, or at least the site must be kept covered. Careful hand washing is stressed, but the site must be protected from water during bathing. A separate towel should be used for the site area when drying off, and then laundered. Contact sports should be avoided.

The *Israeli government* has vaccinated ~700 responders (physicians, nurses), soon to be joined by ~15,000 responders, including health care workers. Screening is only for persons with previous smallpox vaccination. Risk factor education and the vaccinee's certification that they have no risk factors are required. Gauze dressing is

recommended; no site preparation is required. All vaccinees are asked for pre-post-vaccination serum and to donate a unit of blood for VIG production. They will be followed carefully, but that data may not be transferrable to the U.S. experience. There have been "a couple of" autoinoculations and one spread to a healthy contact to date, as well as many vigorous local reactions, some treated with antibiotics.

NIH Dryvax dilution trials excluded persons with no prior smallpox vaccination and those who were HIV-positive. They used gauze covered by two layers of OpSite that also covered satellite lesions, and changed the dressing ever 3-5 days until the lesions dried and scab is formed.

Options for health care worker smallpox vaccination

Dressings: Considerations regarding dressings include:

- *During patient care:* Cover with a garment, or loose-fitting gauze, or with loose-fitting gauze covered by semi-permeable dressing. The health care worker or facility has full flexibility.
- *During patient care or around high risk persons:* As above, except the site may be left uncovered. All of these options are at the health care worker's discretion.
- Explore other coverings used historically.

The Workgroup's suggestions were:

- Retain dressing recommendations but be more directive for staff while participating in direct part care. A semi-permeable dressing over absorbent material was advised.
- Site preparation: None, as long as the site is not visibly dirty; if so, clean with soap and water.
- Site selection: No strong basis to consider using a new site than the currently used deltoid region.

Discussion included:

- A recent study of viral shedding by revaccinees produced less dramatic results than the Cooney study of the 1970s. Only a slight difference in clinical response was seen, as opposed to a quite vigorous response in revaccinees. Volunteers liked using the semipermeable membrane over the site; it protects the site from the environment and allows them to bathe. A single layer over gauze is a reasonable protection. Frequency of change depends on the amount of exudate.
- *Is there information on the waterless hand foams being used?* The data indicate them to be effective against vaccinia. Upcoming HICPAC hand hygiene guidelines address this.
- Practically speaking, OpSite dressings are widely used and very effective. And to protect the health care worker's family and patients, there should be a system for identified and trained staff to examine the dressings at the beginning of every shift to examine the dressings and change them if needed. Every rural hospital also has an infection control professional, who is often also the occupational health

control nurse, so there are staff available to do this work.

- *Did the studies showing virus outside of the dressings indicate if it went through or around it?* Nursing staff swabbed the outside of the dressing before changing it. There is confidence that this was not hand contamination of the cultures, but virus penetrating the dressing material. The concentration was probably $<10^1$ outside (it could not be plaqued, but could be grown in roller tubes), so there is a 5-6 log drop in viral content from the lesion itself to that outside. Adding absorbent gauze probably further reduces the penetration.
- *Was pruritus a big problem in the study?* Dr. Belshe reported not much itching. What was reported were more at the edge of the OpSite itself, but that was variable.
- Dr. Sepkowitz stated that the old studies reinforce that hospitalizing the wrong patient on the wrong floor could have catastrophic consequences if proper infection control is not taken. But those contingencies are unlikely, and he supported the workgroup's advice.
- It was suggested that the ACIP explicitly state that previously vaccinated health care workers should be prioritized for revaccination. Dr. Modlin thought that this day's recommendations could be folded into the basis of the June ACIP statement and perhaps published. This day's focus was on gaining agreement on the general principles outlined by the workgroup. But he agreed that the ACIP would encourage revaccinating individuals vaccinated earlier to gain early experience there, and then move on to primary vaccinees.
- *Contact sports were not recommended in post-vaccination activity. Was there any recommendation on sex after vaccination?* Dr. Diniega reported those recommendations as coming from USAMRIID for lab workers. DOD's policy addresses physical activities that might rub/abrade the site.
- *Was there any study of vaccination site relevant to complications? In the past, the deltoid was used in males, but in the gluteus in females.* The NIH studies only vaccinated in deltoid. There is not enough experience or data on efficacy to deviate from that. Vaccination in the buttock risks contamination and bacterial infections, and the most commonly reported site in the old literature of autoinoculation is the vulva. VIG was used in some of those cases, but may not have been warranted.
- *Were there less satellite lesions with OpSite use, and what was the total cost of its use?* Dr. Belshe reported a difference in satellite lesions based on dose (i.e., none in undiluted versus 4% with the 1:5 dilution and 8% in 1:10 dilution). More local inflammatory response was seen with the undiluted vaccine, thought to be from more vigorous CTL induction to control local viral replication in the undiluted versus diluted vaccine. This produced a statistically significant higher rate of satellite lesions, usually within an inch of the vaccination site. The cost of a 2½" square OpSite dressing was 75 cents; the 4" square dressing was $1.64 (T=$2.39) plus about a nickel for a 2" square gauze folded to cover the lesion. But cost was not felt to be a main issue here.
- *Should ACIP expand the recommendation for health care workers to use gauze or a semipermeable membrane beyond direct patient care?* Dr. Modlin thought

that would be good to acknowledge, although no recommendation could be based on data from trials.

- Documentation is needed on everything occurring at these vaccination sites. The anticipated 500,000 vaccinees could serve as a large field trial to expand upon the very limited data from the Israeli experience.

Dr. Modlin checked for, and found, consensus to the workgroup's recommendations, with no changes.

Considerations discussed regarding dressings included: Viral presence on the surface and skin surrounding dressings; the influence of dressings on maceration, irritation and pruritus (e.g., their impact on touching or scratching the site and subsequent spread); the impact on daily activities (e.g., showering, swimming, exercise); the ability to self-apply dressings; the frequency of dressing changes; the ability to monitor take or local reactions; and cost (some options could cost tens of dollars per vaccinee).

The sense of the working group was as follows:

Dressings: Make the current recommendation more directive regarding the dressing while participating in direct patient care. Use of a semi-permeable dressing over absorbent material (gauze) was preferred, although products combining absorbent base with overlying semi-permeable layer can be used. Great emphasis should be placed on meticulous hand hygiene after contact with the site.

Site care: Hospitals should include a site-care component to their smallpox vaccine programs. Staff should be designated to evaluate the vaccinees and the vaccination site, change the dressing, and to reinforce excellent hand hygiene . While not involved in patient care and not among high risk persons, the current recommendations should remain. The site should be left uncovered or covered with porous bandage (e.g., gauze). Any dressings should be changed frequently to prevent maceration.

Site preparation. The recommendations for site preparation should remain. Skin preparation for vaccination is generally unnecessary unless the site is visibly contaminated, when it can be cleaned with soap and water

Site selection. There is no strong basis to consider use a new site.

With no further discussion, Dr. Offit **moved to adopt the workgroup's recommendations** and was seconded by Dr. Tompkins.

Vote:

Conflict: Wyeth: Drs. Rennels and Belshe

In Favor: Offit, Hanson, Brooks, Birkhead, Tompkins, Modlin, DeSeda, Word, Zimmerman, Levin

Opposed: None
Abstained: Rennels, Belshe

The motion passed.

PATIENT CARE

Limitation of Patient Care by Vaccinees

Dr. Siegel discussed the concern that all or some definable subgroups of health care workers should not treat patients after vaccination, and the ensuing options. Considerations include:

- The availability of VIG and the uncertainty of the need for it. That demands good criteria for treatment and efficient and accessible distribution.
- Immunosuppressed populations or those with AD or other skin conditions. In large hospitals, even high risk patients may be housed hospital-wide, increasing the risk of inadvertent spreade.
- The general principle published in 1998 remains, that only immune workers should care for patients with VPDs.
- It is possible that some as yet unidentified health care worker activities could lead to increased shedding and viral transmission.
- There is a need to balance anticipated refusal of health care workers to treat smallpox patients if they are not vaccinated before contact, versus the likely events of refusal of pre-event vaccine and the presence of contraindications.
- Health care workers must adhere to infection control recommendations consistently.
- The current nursing shortage could be exacerbated by increased leave by or reassignment of vaccinees. Staff shortages in the past have led to increased risk and to health outcomes (e.g., shock, cardiac arrest, lengthened hospital stay, nosocomial infections).
- Health care workers must be protected from occupational hazards from either vaccine or disease.

She outlined several options for vaccinated health care workers:

1. *Universal administrative leave* would place all vaccinated health care workers on administrative leave from all patient contact from the first appearance of papules (day 2-5) to the time of the scab's separation (day 14-21).
   A. *Advantages:* Provides maximum protection to patients and other health care workers from inadvertent inoculation with vaccinia virus; allows data collection to more accurately define risk and challenges to operationalizing a modern smallpox vaccination program; minimizes liability; assures the public that patients receive maximum protection from any possible adverse events or "medical errors"; eliminates the need for individual decision-making.
   B. *Disadvantages:* Disruption of the healthcare system; places a severe

burden on an already-stressed system with severe nursing shortages; staggered vaccination within each area is likely to be necessary; active surveillance could be discouraged with the health care workers staying at home; the function of ICUs and EDs will be most challenged with many staff on administrative leave; both human and financial resources will be wasted; and this amplifies the public perception of the risks associated with the vaccine.

2. *Reassign vaccinated health care workers* from high risk patient care areas to those care areas with patients at lower risk of severe disease if inoculated with vaccinia virus, and areas without the prolonged activity and contact duration associated with increased viral shedding (e.g., general medicine ambulatory clinics and general medical inpatient units). Health care workers in low risk areas would have their inoculation site inspected daily by a specifically trained supervisor and patient care assignments would avoid higher risk patients. This option would allow a staggered schedule within an area (e.g. ICU, ED). A protective dressing could be a single semi-permeable layer over gauze, changed every 3-5 days.
   A. *Advantages:* Maintains workforce total numbers without disruption in lower risk areas; minimizes risk of exposure to higher-risk patients during shedding period; makes short-duration patient contact more likely; provides reasonable assurance to the public that efforts are being made to protect the highest risk patients. Re-assignment to lower risk patients within an area is at the discretion of individual facility or supervisor.
   B. *Disadvantages:* Compromises workforce in the areas with the most intense patient care needs; human resource utilization requires re-assignment of health care workers; it places the unknown or as yet unidentified patient at risk for severe adverse events ; it requires a vaccine site monitoring program; public perception that some patients are still at risk; liability for adverse events still exists; and it requires individual decision-making, especially in institutions where higher risk patients may be distributed across the facility.

3. *No health care workers are placed on administrative leave* unless physically unable to work due to systemic signs or reactions to the vaccine. Daily inspection of the inoculation site would be performed by specifically trained personnel, and individual decisions for administrative leave may be made based on condition of the inoculation site and fitness for duty.
   A. *Advantages:* Maintains intact workforce with little disruption of patient care assignments, simulating conditions of a post-event health care worker vaccination program and allows daily monitoring of condition of inoculation site by trained personnel.
   B. *Disadvantages*: Places patients with known high risk conditions at a small but existent risk of acquiring vaccinia virus from a health care worker and developing severe adverse complications; requires more individual

decision-making; maximizes liability and public perception that patients are not being protected.

4. *Phased-in health care worker vaccination* would be done in three phases:
   A. *Phase I*: Administrative leave would apply until the scab separates for all health care workers of a small pilot group (e.g., approximately 10% of target groups), during which time studies are performed to identify potential obstacles, risks, ease of site management, signs/symptoms temporally related to vaccination causing health care workers to use sick leave, etc. to guide next phase (i.e., a smaller pilot). Vaccinators and ED staff are likely to be in the first group.
   B. *Phase II*: Based on the findings of Phase I, the next 30% of health care workers would be vaccinated and re-assigned to low risk patient areas with careful supervision. Health care workers would not work in highest risk patient areas delineated above. Within EDs and clinics, alterations of patient assignments would be required to minimize contact with the highest risk patients.
   C. *Phase III:* The remainder of the target groups would be immunized with alterations in management based on the experiences of Phases I and II.
      i. *Advantages:* Provides opportunity to adjust management based on experience in modern environment and not compromise workforce unnecessarily; minimizes risks to patients; builds health care worker and public confidence in the vaccination program; minimizes liability.
      ii. *Disadvantages:* Delays completion of immunization of designated health care worker groups, which could also increase vaccine wastage; may place some patients with unknown or unidentified high risk conditions at risk; requires ongoing structured evaluation and potential development of revised recommendations; requires individual decision-making.

A chart was provided of qualitative ratings for issues related to health care worker staffing; patient safety, individual decision-making, ability to do active surveillance, public perception, liability, and expediency of achieving vaccination of the target population.

There is a precedent for not selecting worker leave. California's bioterrorism response plan (www.dhs.ca.gov/Inc/btr/btr.pdf) recommendations for vaccinated health care workers allow continued patient contact, including with immunosuppressed patients, if the vaccination site is covered with gauze reinforced by a semipermeable dressing and if meticulous hand washing is done before patient contact and after any contact with fluid or pus under the dressing.

The *sense of the workgroup* was to favor Option 3 due to its lesser disruption to healthcare delivery. The requirements for Option 3 to work are to have an adequate VIG supply with timely distribution, use of the semipermeable dressings and daily monitoring and assessment.

The questions remaining to be answered include:

- Is semi-permeable dressing necessary and feasible? Will it remain intact under working conditions with sweating and motion? What sensitivity relates to the dressing tape? Is it an effective barrier? With what frequency should the dressing be changed? How can cost be minimized?
- How can vaccine acceptance be optimized by health care workers in various healthcare settings? By patients being cared for by health care workers who have received vaccine recently? What is the safety and efficiency of the multidose vials necessary in such big programs? Can health care workers adhere to the recommendations for screening and site care? Is screening effective? What will be the complication rate? What is the risk of vaccinia transmission to other health care workers and patients under modern conditions?

Discussion included:

- *There is an apparent inconsistency between the recommendation of health care workers' patient contact and those with people at high risk at home, since the data indicate that most transmission occurs in the household than at home.* Agreed; the recommendation would have to be very clear about the data to back that up.
- The 3-week staggered schedule is recommended to ensure adequate staffing.
- Option 3 is necessary to keep the health care workers with appropriate skills where they are. Diversions already are common. Rather than being negative, public perception will be that public health is not doing its job if diversions are caused by staff shortages.
- Dr. Neff wondered how many would have to be immunized, and how fast? Ideally, this should be done slowly minimize the risk to patients. The process is beautifully lined up, but it is easy in a busy hospital for protective methods to break down. And any inadvertent smallpox inoculation to someone with immune disease is a tragedy much larger than the risk figures of 1:1 million. This should be done slowly, with great care, and recently vaccinated people should not work in such high risk areas as oncology wards. Dr. Abramson agreed, noting that this recommendation is based on a presumed low risk situation. Option 3 creates a huge human experimentation and the inconsistencies troubled him.
- Dr. Fulginiti suggested using scab formation as the endpoint since it holds little virus and covers the site. Some take a long time to separate (e.g., a week) and there is no need to furlough workers for that long.
- Dr. Rennels suggested an "Option 5", blending Option #3 (no administrative leave or reassignment) with a slow phase-in focused onsite surveillance and monitoring. The site surveillance teams need time to be comfortable with what they will be doing, and the first few patients are the ones for whom mistakes are made. The speed with which that is done should be subsumed to phase in and then, as that experience is gained, to move more quickly. So, as in Option 4, rather than immunizing the whole hospital, a percentage will be vaccinated (e.g., 10%) and then followed.

- There was general agreement to this approach, particularly since the proposed program was vastly expanded from the past June. The risk for side effects is increased, as is the risk that they would not be well managed, and inadvertent transmission is also more likely. An attack situation would require such speed, but if the time is available, a slower pace than Option 3 is suggested. And, since those first vaccinated will likely be revaccinees for whom the observed risk is low, that allows some slowness.
- The problems with this approach pointed out were that "phasing in" has many interpretations. Faster implementation is needed than a year's time. Another was that the vaccine comes in 100-dose vials and must not be wasted.
- The counter argument was that the vials go not to individual hospitals, but to regional health departments. Each hospital in the area could select 10 people from their 100 for vaccination, as long as there is a central site or the single vial could be taken to different sites in a few days. Staging is built into Option 3, and it could also include analysis of progress, outcomes, and of the overall program before proceeding. Finally, it may allow some breathing room, if revaccinees are taken first, since the real risk to primary vaccinees may still be underestimated.
- Dr. Belshe advocated a modest start, then ramping up, leaving it up to the institution how to do that. He also preferred to take the huge leap from a small number of hospitals (e.g., 5-10) to 2,500 in a staged public health campaign. Two scale-ups are needed: one within any given institution and the second nationally.
- If the state local health departments give the vaccine, they could send 20-30 vaccinators to CDC for a week, and then take only 2-3 months to fan out across the state. But, since variability is inevitable between hospitals, regions, and risks, the hospital administrators will need flexibility. That can be provided, but it is important to clearly enunciate the principle about gradual introduction to ensure adverse effect surveillance, training, etc. This approach would parallel a planned multicenter study, examining the data collected over time to do this as safely as possible. Dr. Henderson commented that Option 3 provides that, and the differing experience of the states can be gathered in a national data collection system being contemplated.

Dr. Modlin summarized the committee's strong support for Option 3. It will be fleshed out, incorporating the underscored desirability of a deliberative and careful approach.

Dr. Tompkins **moved that the ACIP recommend Option #3**, and was seconded by Dr. Brooks.

Vote:

In Favor: Offit, Hanson, Brooks, Birkhead, Tompkins, Modlin, DeSeda, Word, Zimmerman, Levine
Opposed: None
Abstained: Rennels, Belshe.
The motion passed.

SCREENING

Contraindications/Screening, Pre-Event Smallpox Vaccine IND

Dr. Joanne Cono of the CDC Bioterrorism Office, outlined the 2001 ACIP recommendations on contraindications to smallpox vaccination (for a small number of laboratory workers), and the proposed approach to screening for contraindications under the IND.

Contraindications listed in the June 2001 ACIP recommendation included: 1) eczema or history of eczema, 2) pregnancy, 3) altered immunocompetence, 3) persons with HIV, 4) those aged <18 years, and 5) those with allergies to vaccine components. For the first four, vaccination is not recommended if a household contact has condition. HIV household contact is implied within #3.

Specifically, vaccine is *not* administered if the individual has eczema of any degree or a history of eczema, or household contacts with those risk factors.

The vaccine *is* administered if:

- The condition is resolved for acute, chronic or other exfoliative conditions such as atopic dermatitis (incorrectly listed, to be corrected at this meeting), burns, impetigo, and zoster.
- The individual is pregnant. However, there was no specific wording about delaying pregnancy for 30 days following vaccination as in the IND protocol and as recommendation for other live-virus vaccines.
- The individual is not immunocompetent due to disease, such as leukemia, lymphoma, Graffherster's disease, generalized malignancy, or treatment for disease, such as solid organ or stem cell transplants, treatment with alkylating agents, antimetabolites, radiation, high-dose steroids, etc.
- The categories of HIV and infants and children, in the July recommendation, does not apply to the IND.

Proposed Approach to Screening for Contraindications

Dr. Cono described the two-step process developed to screen for contraindications under an IND. This uses a pre-vaccination day advice packet (received at the clinic or by mail, supported by counselors and/or a telephone hotline) and vaccination day screening done at a clinic and supported by counselors.

The *Pre-Vaccination Day Advice Packet* is given to all potential response team members (the volunteer) before vaccination day, allowing them time to review the materials, receive private consultation, and obtain lab tests before vaccination day. It also allows the opportunity for private self-exclusion. It contains the advice letter, the medical screening checklist, the contraindications information sheets (AD/eczema, pregnancy, relevant immune system problems, presence of a child aged <1 year), and includes a copy of the informed consent form.

The *advice letter* advises about the medical, financial and employment risks, the availability of counselors to discuss these with, and that the volunteer take the packet to discuss it with their own health care provider. In fact, it urges discussion with the health care provider several times.
It lists:

- *Contraindications* that if present, prevent vaccination or participation on a response team.
- *HIV status* is addressed in several ways: many are unaware of their infection; one can seem well and be infected; it advises the volunteer not knowing their status to get tested, as it is in their best interest; and reassures them that they can decide not to participate on a team and no one will ask why. It lists high HIV-risk activities and again advises testing if any apply or if HIV status is unknown.
- *Pregnancy* advice is similar: the volunteer should get tested if pregnancy status is unknown and practice effective contraception for one month post-vaccination.
- *Skin conditions* advice lists contraindications, focusing on eczema, but also addressing acute conditions (impetigo, varicella, burns) and chronic conditions such as psoriasis or acne. It advises consultation with their health care provider if they are uncertain. Questions asked address itchy rash of >2 weeks duration, itchy rash in skin folds, history of eczema or food allergies or history of asthma or hay fever.
- *Contacts* preventing vaccination include living with anyone with a contraindication (e.g., eczema, skin- or immune-compromising conditions).
- The financial risks are outlined, such as unpaid furlough from work and the absence of any present mechanism to cover the costs of hospitalization or other care if necessary due to vaccine outcomes.

The *pre-vaccination medical screening checklist* is self-administered and not collected. It has yes/no/do not know responses, the latter of which should be taken up with the health care provider. They are also told they will be asked the same questions on vaccination day.

On *vaccination day*, the same screening questions are asked, but with only yes/no answers possible. The volunteer's signature indicates that s/he read and completed the pre-event ck list, received the pre-event information package, had the opportunity to consult health care worker and obtain testing, and answered all questions to best of his/her ability. The form is also reviewed and signed by the medical screener.

In summary, this two-step screening process of the IND protocol allows private consideration of the risks and lab testing; allows private self-exclusion, is done apart from the employment setting and colleagues and ensures that all test results remain confidential, and the data are not collected. This process can be maintained and still offer on-site testing, if available, but all attempts are made to separate the confidential issues from the employment setting.
Discussion included:

- *The first dissuader is the financial risk. Does this mean that people have to call*

their own providers to do something in spirit of public health? Dr. France reminded the committee that the budgets for next year are now being set, so unexpected adverse events requiring hospitalization will not be covered. Great variability of coverage is likely across plans. The vaccine might be considered experimental and liability is also an issue (i.e., the health plan could be involved in an adverse event suit). *One aspect is that medical screeners will sign self-evaluation criteria; what is their liability?* Dr. Cono was not sure, but the screener only attests to witnessing the review of what the vaccinee read on the sheet.

- Coverage under the National Vaccine Injury Compensation Program (NVICP) would help to resolve liability questions, as would a clear indication that Workers Compensation would apply. And, if federal workers are deputized to administer the vaccine, they would also be protected.
- *Under the current IND, how many have been or would be excluded under this?* Dr. Belshe reported that ~20% of healthy young people aged 18-32 were excluded from the study, most for chronic skin conditions. A higher percentage (probably >50%) of older groups were excluded by other screening procedures (e.g., hemoglobin screens).
- *Please clarify the HIV status criterion. Those who do not know their status are advised to be tested. But if this is an exclusion and individuals accepting the vaccine may mistakenly identify as HIV-negative (or, for that matter, not pregnant), why not test everyone? Will the test result be required?* This was to be discussed later in the day. But the issue was noted of the degree to which individuals' own responsibility will be the focus, rather than that of public health or the hospital to address every issue.
- The list of contraindications was found by some to be too inclusive.
  - Dr. Shekler, for example, had safely received three smallpox vaccinations despite having several contraindications.
  - The workgroup had noted that the past practice was to vaccinate those individuals with skin conditions frequently to reduce the risk of any subsequent vaccinia from occurring, but primary vaccinees are a different case.
  - Virtually everyone from age 12-20 has acne; those with red hair have it for a lifetime. Dr. Cono responded that any acute or chronic conditions involving breaks in the skin may be more able to transfer vaccinia. However, acne "under good control" is not a contraindication. The total absolute absence of acne is not necessary. Dr. Fulginiti reported that patients with sebborheic dermatitis and acne were infected and confused their lesions with those conditions.
- Dr. Stephen Allred, of www.getaflushot.com, found it hard to reconcile the seeming contradictions, medically or from a concept of public trust, about not vaccinating the household contacts of anyone at risk, while not restricting health care providers caring for the same people (e.g., those immunosuppressed). Dr. Modlin raised the difference between giving a vaccine under an IND, with greater stringency involved than that for a licensed vaccine. Dr. Lisa Rotz of NCID, added the level of risk in the household setting and that of the healthcare setting. Longer sustained and closer personal contact, and potentially less thought given

to hand washing and other infection control processes than taken in the hospital setting, also apply.

- *What is the relationship between hay fever and asthma and the skin conditions? Are they a marker for skin conditions?* Yes, they are a way to screen out atopy.

After a short break, the attendees' attention was drawn to two reports that were distributed and available at this meeting. Developed by the National Foundation for Infectious Diseases, they address the NIP and immunization disparities in race and ethnicity for both pediatric and adult immunizations. Comments on the reports were welcomed.

Atopic Dermatitis

Dr. Christine Casey, of the NIP's Division of Epidemiology and Surveillance (ESD), reported on the pathogenesis and risk of eczema vaccinatum (EV) as it relates to screening and atopic dermatitis (AD). Input on this was obtained from the American Academy of Dermatology and Dr. Sharon Friedlander, of UC San Diego.

Background. The 1991 ACIP recommendation inappropriately placed AD with acute exfoliative skin disorders rather than with eczema. That led the 2001 ACIP recommendation to list quiescent AD as an acceptable skin condition for vaccination rather than as a contraindication.

Eczema is a complex skin condition, including everything from contact dermatitis to sebborheic dermatitis to acne, and AD is a subset. Since there is no clear definition of eczema, screening for it is a challenge. The U.S. literature shows eczema as a risk factor for EV, and the European literature reference "atopic eczema" and "atopic dermatitis". CDC convened an expert panel to interview the authors, and found that AD was the intended condition to list as a risk factor. EV was found to occur not only in those patients, but also with greater frequency in their close contacts. Clearly, screening is critical.

The Dryvax® vaccine label will state that a vaccine candidate with a personal history or close contact to someone with eczema or AD, regardless of disease activity, will be contraindicated from vaccination. The broad wording from the early1960s to the 1970s was attempted to be better specified in the 1991 recommendation, broadening it to present or past history of eczema. However, it also inappropriately listed AD with burns, impetigo and varicella. The 2001 update included past history and eczema of any degree, and added household contacts with any such history.

AD goes by many names; there are >20 in the literature. One distinguishing mark from eczema is its pruritus, preceding the eruption, as opposed to contact dermatitis that initiates the scratch. Epidemiological studies and clinical trials were needed to clarify that distinction. Hanifin's study criteria was revisited in a U.K. study whose survey tool was later validated with good sensitivity (75%) and specificity (97%). Hanifin in 1991 validated more of the discriminatory criteria and achieved a sensitivity/specificity of 88

and 89%. He cited the constraints of linguistics and culture, and parental attitudes and called for a world-wide clinical picture. Among AD clinicians, more immunologists and allergists focus on the atopy than dermatologists. The latter met in 2001 to craft a consensus statement. The product is useful for clinical discussions, but not for screening.

Most providers do not distinguish between eczema and AD, and the ICD9 codes also lump them. AD's clinical features include variable distribution in the flexor creases, but it also can occur in the extensors or be generalized. Its morphology can be acute, sub-acute, chronic or lichenified. Most cases are first seen in children aged <5 years and thereafter can be episodic with flares and remissions, or chronic.

Prevalence data indicate a rising trend in the past 40 years, although some countries have plateaued. Worldwide prevalence in children ranges from 2-35%. Hanifin's U.S. study estimates prevalence from 7-17% in school children, depending on the criteria used. European data show a one-year prevalence of 1-3% but its episodic course probably makes that an underestimate.

Extrapolating the 1960s data to the present is not possible. Prevalence data of that time are unreliable, and only one study (Hanifin, 1999) has been done among U.S. school children. As a result, the absolute risk for EV in this population with AD is unknown. However, eczema and AD have distinct and unrelated risks of developing EV. The pathogenesis of AD is now known. Animal models demonstrated an anomalous immunoregulation in atopic skin which causes elevated activation of T_H2 cells, which then begins a cascade of replication of the vaccinia virus. However, there have been instances when eczematous patients (including those with AD) had minimal ill effects after vaccinia vaccination. Not all AD patients are prone to that unchecked replication, but uninvolved atopic skin does have that disregulation, which explains the distant metastases.

Data:

- Copeman et al in 1964 published a case-review study of EV and AD which found an AD incidence of 3-4% in infancy or childhood. It had a characteristic morphology and distribution and was genetically linked with asthma and hay fever. They found an incidence of 1/20,000 primary vaccinees and only one case in a revaccinee (consistent with the Lane and Neff data of the 1960s). Quiescent disease occurred in two-thirds of cases with no active skin disruptions. But, since there was no comment given on antecedent disease severity, no linkage can be determined. For 83% of the unintended vaccinees, sources were a family member (primarily a sibling), a vaccinated infant for 4% (in adults); and 6% were untraceable. One nosocomial infection was found. Of the unintended vaccinees, 2/3 of cases were in contacts and 2/3 of those resulted in death. A full 80% had AD or atopic eczema, 60% with inactive disease. Of the underlying dermatological disease, 16% was unclassified; 4% was sebborheic eczema

(dermatitis) and 2% was Darier's Disease.[1]

- A CDC review (Sepkowitz) of 10 iatrogenic-spread episodes reflected 55 spread cases, most with existing skin conditions, and eight deaths. Three sources were themselves infected by contacts (tertiary spread).
- However, the *mode of spread* was not always clear; some occurred within wards or among adjacent wards in Glasgow (1935). When two patients contacted smallpox patients, the entire ward was vaccinated (84) except for two with AD who had "already been vaccinated". Four events ensued, one unrelated and the others mild.
- Kemp et al studied an attenuated vaccinia strain among 3500 patients, including those with eczema and AD of various stages from mild to acute. They estimated that 25-50 patients would have effects, but they had no EV patients. They were then revaccinated with the standard (more virulent) strains, and again had no complications.

Copeman's data and modern technology support that patients with AD are most likely at risk for complications. But there is no marker to predict the severity of adverse events, making screening challenging. The highest risk group may be a subset of AD (e.g., as in the disseminated replication of molluscum or herpes). However, there is also evidence that eczematous and AD patients can be safely vaccinated.

The workgroup offered several options that the ACIP consider for the vaccinia vaccination:

1. No change to ACIP 6/01 recommendations.
2. Group AD with eczema as a contraindication.
3. Try to distinguish eczema from AD as a contraindication.
4. List Darier's Disease's serious adverse effects as a contraindication.

Option 2 was favored by the workgroup. A broader exclusion was balanced against the risk of inappropriate vaccination due to a provider's lack of distinction between conditions. It was recognized that providers will need guidance on the screening approaches

Discussion included:

- No known data support that people with eczema and AD have more severe smallpox.
- Minnesota data tracks ICD9 codes for procedures and diagnoses for active diseases. From 1999-2000, of 62,000 patients in eight family practice clinics, 5.2% had the code for eczematous AD, mostly in older age groups. They do not distinguish.

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[1] Darier's Disease is a slowly progressive autosomal dominant disorder of keratinization characterized by pinkish-to-tan papules that coalesce to form plaques. These lesions become darker over time and commonly fuse, forming papillomatous and warty malodorous growths.

- The protocol allows vaccination if a case of eczema (e.g., poison oak) is resolved and the skin is intact. The distinction between eczema and AD will be addressed in the screening tool. But there is a tension between sensitivity and specificity, between potentially screening out too many people and safety.
- Dr. Neff reported that most of the cases in 1968 which had a history of AD but not active skin disease at vaccination developed mild EV. There were no deaths. Those occurred in the populations at risk who had active disease and contacts at home. The question is whether to exclude a substantial number of people or to accept a few mild EV cases. He advised initial caution about who to exclude.
- Although the Copeland study found two-thirds of deaths in those with only a past history of disease, other details of those children are unknown (e.g., failure to thrive, underlying conditions, etc.). The generalized vaccinia used in the U.S. among individuals with only a past history resulted in only mild forms of EV. But no European study examined the NYCBOH vaccinia strain. European strains have significantly higher EV rates and vaccina viremia was found in the oral pharynx.

Screening for AD

Dr. Casey noted that although AD is the risk factor for EV, there is no consensus on clinical criteria or a diagnostic test to identify those individuals in advance, frustrating extrapolation from 20th century data.

Screening tools have been validated, but differ by geographic location and cultures. There is acceptable sensitivity and specificity, but they are not intended to identify individuals at risk of vaccinia-related adverse events.

Studies. There have been three validated studies which produced criteria.

- The Hanifin-Rajka study which established criteria whose specificity favored cases that may be immunologically predisposed to severe disease.
- Williams (1990) validated and refined these criteria in a cross-sectional study in three London clinics, producing a sensitivity and specificity of 75% and 97%, respectively.
- Particular to the U.S. experience is the Schultz-Larsen and Hanifin study of 1991, which validated the Hanifin-Rajka criteria among Oregon school children. They found a 7-17% prevalence in the age group of 5-9 years of age. One question asked, but not scored, was most revealing: "Did your physician ever say your child has eczema?" This had a very high predictive accuracy (91%) for those who recalled the physician's diagnosis. The question was 88% accurate compared to a dermatologic exam, probably because there are few other eczema types than AD among young children. Study limitations include no specification of diagnostic criteria and no concessions for quiescent disease. This may have led to underestimation.
- The Firooz *et al* (*Arch Dermatol* 1999; 135(5):514-6) study, although with significant limitations, compared these criteria to diagnosis in a double blind, cross-sectional study in an Iranian outpatient dermatology office of 416 patients,

60 of whom had AD. Within the 95% CI, its sensitivity and specificity were 10% and 98%, respectively, with a PPV of 50% and NPV of 87%. Hanifin responded in an article about the importance of considering the culture involved and the need to use screening tools carefully.

- The Israeli Defense Force studies identified AD and Darier's Disease as contraindications which, if properly identified, would have prevented an estimated two-thirds of complications. Their improved screening (not specified as to how improve) dropped the complication rate from 0.15 per 10,000 vaccinees to zero in the third and last year of screening.
- A study of the VSD by the Wisconsin Marshfield Clinic, as yet unpublished, assessed how well patients self-identified as having AD. Their methodology enabled validation of the ICD9 code to the medical records. The VSD data was of patients with known AD diagnosis, defined as notification of the ICD9 code in two or more visits separated by >60 days from 1979-2001. The goal was to determine the prevalence of AD and eczema diagnosis, and to assess the sensitivity of screening questionnaires in patients with confirmed diagnoses. A telephone survey of adult AD patients and their contacts then found an AD prevalence of 1.2% and 4.5% for AD/eczema. The validation of the codes showed 96% sensitivity and 97% specificity. Importantly, 30-40% of those at risk for EV did not correctly self-identify because they were diagnosed as AD. A functional screening tool is clearly needed to identify those at risk in a pre-vaccination setting.

What was learned from these studies was that the validated questionnaires for AD are not designed to identify patients at risk for vaccinia complications or to be used in a large-scale vaccination campaign. Patient recall of a physician diagnosis is very predictive, but a sole reliance on patient recall may miss >30% of at-risk patients. However, effective screening may have prevented two-thirds of complications in Israeli military recruits. A functional tool to identify these patients is clearly needed.

A multidisciplinary ad hoc AD workgroup convened by CDC proposed, as a screening approach for deferral, that 1) the vaccinees be asked about a history for themselves or a close contact, of ANY of three features (pruritus, red scaly lesions [perhaps oozing/crusting] and chronic or chronically relapsing course), AND 2) they respond yes to two of the six questions asked:

- Diagnosis of AD ever provided by a physician.
- Presence of an itchy rash lasting >2 weeks.
- Itchy rash in folds of arms or legs (debate over cheeks of infants, but not validated so dropped).
- Eczema with food allergies in infancy or childhood.
- Physician diagnosed asthma or hay fever.
- Physician diagnosed asthma or hay fever in a first degree relative.

A full 38% who had a diagnosis of these atopic conditions recalled them, indicating a good starting point.

Options developed for the ACIP were to: 1) take no position on the endorsement of screening, or 2) recommend use of this proposed but untested questionnaire, with further revisions as more is learned to improve the specificity over sensitivity. The workgroup favored Option 2, to give guidance to physicians facing this clinical dilemma, and to provide the military with a higher-level screening tool. They may wish to improve on this themselves. Collaboration to refine these tools was hoped for by the workgroup.

Discussion included:

- *Is there any update on whether the Israelis have data to validate their screening tool, or work to validate the short form used by Marshfield?* Israel has not released any details due to national security issues. This tool will be piloted for refinement, first in the military and then perhaps at the Marshfield clinic.
- Option 2 provides the needed guidance to avoid confusion about what is AD and what is/is not a skin condition contraindication.
- *If we are ever to vaccinate large numbers of people, can we modify the distinction between the patient's and contact's active disease and quiescent disease, since the latter is still a contraindication?* Dr. Fulginiti reported that most patients with history of disease and present quiescent disease had after effects of at least mild disease and some had severe disease. He thought that quiescent disease could not be excluded as a contraindication.
- *Can the contraindications be weighted? For example, someone with psoriasis will develop hay fever, so excluding 2 of the 6 items listed does not allow specificity.* The question on physician diagnosis has the best specificity and was validated in children, but that will not be true in adults. The military's study of some form of screening tool will provide more information on this tool's value.
- A hospital or state epidemiologist will want a tool that does not require them to decide about screening out the possible/probable categories. It should also have pictures as well as words and it should be validated. However, others felt that the guidance was sufficiently clear about having all of the three features (itch, erythema, and chronic or chronically relapsing course), and two of the six others questioned.
- The ad hoc group did not include a primary care physician. Qualitative information should be obtained from focus groups of family doctors, internists, and patients. Concern was expressed again at the guidance that a physician can take care of patients with all these contraindicated diseases, but could not go home to a person with risk factors. The risk at home should not differ from that in a hospital if they wear an occlusive dressing. The suggestions were appreciated. This ad hoc group was formed quickly to set a foundation from which to proceed. Specialists can now be consulted.
- *Do not wait until question #2 to deal with eczema. The real point is not a known history of eczema, but those with undiagnosed skin rashes or rashes of unknown character. It is simple to begin by asking and screening out presence of or history of eczema rather than trying to determine if that was AD. That would help address rashes of unknown cause.* Yes. This level of screening is not the first

pass; it is only for those who are uncertain about themselves, their family history, or on the provider's part.

- *How complex is the Shultz-Larson Questionnaire (SLQ) used in Oregon? If it is difficult, the time should be taken do a more detailed screening tool.* The workgroup found the SLQ to be very tedious, and it is validated only for children, so it has limited utility in the adult population.
- Dr. Grabenstein, of the Army Surgeon General's office, feared that the data resulting from this tool would be hard to use. The outcome of EV would be a rare event. With the proposed questions, the validation is to confirm a diagnosis, but the military is not going to test this tool to see if rates of adverse effects could be lowered. That would require a test of several screening methods and hundreds of thousands of persons.
- *This tool needs real testing, and that is possible in the current pre-event period. With the shortage of nurses, there may not be enough people to vaccinate. One 12-bed Pediatric Intensive Care unit reported only 8 of 12 beds occupied, solely due to the nursing shortage.* Dr. Modlin thought that this tool would probably be concurrently field tested and implemented.
- The vaccine administration by the limited state/local health department staff could be the pilot. But this tool is too complicated to be feasible and few want to use an untested questionnaire. This has to be simple. Dr. Henderson thought that asking about physician diagnosis of eczema would be sufficient. The rest begins a research process, especially when even dermatologists debate the definition of "dermatitis". A history of eczema or AD in the vaccinee or a family member could be used as a screen, and then test the others in another setting. NIP's estimated number of erroneous vaccination is very small. Those with active disease are of the most concern and most of this discussion was about those with quiescent disease. Question #1 should be used as the screening tool for people who remember a rash but do not know what it is.
- *The ability to cure EV affects whether to select the sensitive or specific route.* Dr. Fulginiti reported a 7% mortality rate among patients given VIG after developing vaccinia vaccinatum. But some where misdiagnosed and treated late. Prompt and early treatment is critical. He suggested just asking about the presence of redness or itching in the individual or the family. However, the workgroup had found this too be too broad an exclusion criterion, risking the unnecessary screening out of too many individuals.
- *Why are the two specific questions about eczema needed if it was already determined?* That will be reviewed by the workgroup; these were extracted from the Hanifin validated data. *What do these six questions add?* Information of duration and location, to avoid a physician's diagnosis of, for example, poison ivy as eczema.
- *How many people who had eczema and got vaccinia developed EV?* There is no way to know from the 1960s how many children with atopic disease were vaccinated. That can only be based on the population as a whole. Even though the screening of the time asked about a personal or family history, people were missed. This provides a codified way of asking those questions, as a ck box, to

get some degree of consistency and to uncover more information. In a hurried situation, it will help remind the screener to ask about household contacts.

- *Dr. Dorothy Scott, of the FDA, found this questionnaire to be no more complicated than that used for blood donors. She asked what the workgroup considered on the use of VIG to prevent EV in an AD group, and if the role of VIG was considered at all in terms of the AD problem?* This workgroup did not address that, but this discussion is only on the pre-immunization of health care workers believed to be at low risk A post-event situation would be very different.
- The workgroup was asked to simplify this process to two stages rather than three. Drs. Levin, Birkhead and Casey agreed to meeting with Dr. Friedlander to suggest some recommendations on the following morning for the options and the questionnaire. Dr. Word asked them to consider, in the question about lesions with redness and scale, that people's pigmentation may not always be red.

Screening for HIV Infections

Dr. Ida Onarato, of the NCID Division of HIV/AIDS Prevention, reported on the considerations of smallpox vaccination among those who are HIV-positive. The ACIP voted to not recommend the use of live virus or live bacterial vaccines in persons with HIV. However, measles-containing vaccines may be given to those persons without evidence of severe immunosuppression. The ACIP did not recommend HIV testing before vaccination.

Data. Live virus vaccines have been associated with severe adverse effects in HIV-infected persons. Two cases of vaccine-associated poliomyelitis were reported and one case of vaccine-associated measles pneumonitis from an MMR shot required for college entry. The patient developed measles giant-cell pneumonia a year later and died, with vaccine virus in his lung tissue.

The only American data are from 732 army recruits vaccinated during basic training from 1981 to 1985. Screening implemented in 1985-88 indicated that probably ~50% of the recruits were vaccinated while they were HIV-positive, based on the CD4 counts at the time of the test. One serious adverse effect of disseminated vaccinia resulted (rate of 0.137 with in 95% CI of .084%-.22%) in a recruit who developed cryptococcus meningitis 2½ weeks later and disseminated vaccinia 4 weeks later. He responded to treatment with VIG but died about 18 months later of progressive neurologic syndrome. No autopsy was done.

Relevant Data Analysis

- A survey indicates that ~75% if the ~850-900,000 persons live with HIV/AIDS in the U.S. (0.3%). The balance of 25% are undiagnosed.
- ~7-8 million American health care workers x 0.3% = 21-24,000 potentially HIV-infected.
- 5% of the HIV-infected (as of June 30,2001) were health care workers = 43-48,000, or 05.-0.7% prevalence, or 1500 to 3500 infected health care workers.
- Rate range of adverse effects is a minimum/maximum if 0.1-0.4%.

- Vaccinating only undiagnosed workers (25%) = 375-875 infected health care workers; minimum/maximum estimated adverse events = 0.1% (0.3 adverse events) and 3.5% (3.5 adverse events) respectively.
- 25 states with stable (≥10 years) HIV reporting indicate 40% with CD4 counts <200, 35% at 200-500; and counts in the 25% more recently infected at >500.
- Since 1985, blood banks screen for HIV, but a high number of donors do not report the status correctly.

Conclusion: Severe adverse events may occur if smallpox vaccine is given to HIV-infected persons, particularly those with immunosuppression. Significant numbers of health care workers in the U.S. may be infected with HIV. Excluding them from vaccination will markedly reduce the number of serious adverse events.

Behavioral screening strategies to exclude those HIV-infected include self-deferral, screening for behavioral risks since 1977, and HIV testing. Since 1985, all U.S. blood donations have been screened for antibodies to HIV. Current lab screening tests are extremely effective, but a small risk remains, so the blood banks use a pre-donation questionnaire and HIV testing. The combination of behavioral risk assessments and HIV testing is the most effective method for identifying HIV-infected persons. However, since it is well known that the banks do HIV testing, those who are positive will not present, and that number of self-deferral is unknown.

Data: a blood donor study of 28.3 million blood donors found 3672 to be HIV-positive (12/100,000). In follow-up interviews of the 2224 who could be found, 44% of males and 65% of females still did not report any HIV-related risk. Many females cannot report any risk factor, since that is their male partner, who may not disclose his own risks. One risk assessment used in an STD clinic demonstrated a sensitivity of 57%.

However, there are several caveats in considering screening for behavioral risk: misinterpretation of questions depending on cultural or social context; that many HIV-infected persons doe not understand or know their risk (particularly women, as noted before); the reluctance to admit to specific behaviors; and finally, confidentiality concerns.

NCHSTP offers HIV testing at clinics and could do so for this program. The principles of HIV counseling, testing and referral (CTR) are confidentiality; voluntary, non-coercive testing; informed consent; an option of anonymity; adherence to the laws, regulations and policies (including HIV reporting); accessible testing sites; and low- or no cost.

FDA is reviewing the requirements for approval of rapid HIV tests of fingertip blood specimens, enabling report in 20 minutes. These will soon allow point-of-care testing at low cost ($0.45-$7.50), have minimum equipment requirements, can be interpreted visually, provide timely, same-day results, and are suitable for low-volume testing programs (<100 tests/day). The negative result is so accurate that it can be told immediately, but a positive result still requires a Western Blot confirmatory test, the

result of which the individual returns to learn.

Considerations of HIV testing in this program include that it sets a precedent for vaccination policy, since current recommendations do not call for testing. C&T will be required. Other considerations include perception that a test is not needed, its availability or costs, legal and ethical considerations, the need for safeguards to prevent disclosure and stigma, and requirements for HIV reporting.

Discussion included:

- Blood donor forms ask about male partners and have been refined over years to the best they can be. But even when exploring lifetime risk of any behaviors, women do not report that risk.
- *Can the rapid diagnostics distinguish between those who may receive an AIDS vaccine and a real positive?* A paper has been submitted for journal publication on false-positivity in HIV vaccinees. The rapid ELISA test could not distinguish, and as more and more antigens are added to the vaccines, it will be more of a problem, even using the Western blot.

Options for HIV Screening

Dr. Ben Schwartz outlined four options considered by the workgroup:

1. No specific recommendation for testing; HIV is just listed as a contraindication, education would be provided, and the vaccinee would choose testing and vaccination.
2. Do risk screening for those with identified risk factors or those just concerned.
3. Test all vaccinees to avoid the insensitivity of risk factor screening and to eliminate the stigma of those who are tested.
4. Mandatory testing for all vaccinees.

Other issues considered by the workgroup included that education/information should be provided to vaccinees, the availability and confidentiality of testing, and the use of rapid tests. Since the latter are not yet licensed, they were not recommended for the Phase 1 vaccination program. No workgroup members supported mandatory testing (Option 4). The most support was for risk factor screening with testing recommended for both those with a risk factor or just wanting the test (Option 2). The barriers of test cost, timeliness, and confidentiality were also discussed.

The workgroup's proposed recommendation was as follows:

- HIV infection is contraindication to vaccination.
- HIV testing should be readily available.
- Testing is recommended for those with risk factor and unsure of their status.
- Anyone else concerned should also be tested.
- Available testing should be confidential or anonymous, and the results should be communicated before vaccination.
- HIV-positive persons should not present for vaccination.

The proposed wording was as follows:

"Persons with HIV infection or AIDS are at increased risk of progressive vaccinia (vaccinia necrosum) following vaccinia vaccination. Therefore, vaccinia vaccine should not be administered to persons with HIV infection or AIDS. Before vaccination, potential vaccinees should be educated about the risk of severe vaccinial complications among persons with HIV infection or other immunosuppressive conditions; persons who think they may have one of these conditions should not be vaccinated.

"HIV testing should be readily available to all persons considering smallpox vaccination. HIV testing is recommended for persons who have any history of a risk factor for HIV infection and who are not sure of their HIV infection status. Because known risk factors cannot be identified for some persons with HIV infection, anyone who is concerned that they could have HIV infection also should be tested. HIV testing should be available in a confidential or, where permitted by law, anonymous setting with results communicated to the potential vaccinee before the planned date of vaccination. Persons with a positive test result should be told not to present to the vaccination site for immunization. Information about local testing options should be provided to all potential vaccinees, including sites where testing is performed at no cost."

Discussion included:

- This language was agreed upon as a compromise, to let the candidates know that risk factor screening may not rule out the potential of error, but also to avoid recommending testing for everyone. The testing should be readily available beyond a simple referral to their personal physician (which may take weeks). Since state and local health departments administer this program, that should be relatively easy to accomplish. However, people may still be missed, and there is a potential for serious adverse events.
- *Was a CD4 count discussed as a cutoff?* Yes, but only briefly; that was not deemed suitable at least in an initial pre-event program.
- The data presented suggest that women will not be concerned, and they do present to blood banks. There is no question that this is a weak point. However, the C&T of pregnant women is one model that could be a paradigm of whether women will accept, and their rate of acceptance (e.g., they generally decline based on the risk to the fetus). Another option is to narrow down the risk by being specific; asking women about sexual encounters without using a condom. Many women may be in a relationship with HIV-positive bisexual men, for example, should be referred for testing.
- Dr. Martin Myers could not see how this would identify the person unaware that they should be concerned. Another option would be to recommend testing, make it available and let them opt out. Dr. Schwarz reported consideration of testing all persons in this program but that was felt to be excessive by many workgroup members.
- *What is the downside of recommending testing?* It was concern that mounting an

unnecessary barrier requiring another stop between the initial encounter and vaccination could eliminate too many people, and pediatric ICUs have too small a personnel pool to begin with. A balanced, reasonable approach is critical. The intent was also to emphasize that adequate information is provided. The pictures are expected to eliminate more people than anything else.

- *Was there any assessment in the blood donor study of how many people were correctly identified, to indicate the sensitivity of the questions used?* Yes, but those data were not on hand (Dr. Scott offered to provide them). However, HIV transmission declined by ~90% upon the initialization of testing.
- The testing might be a marker of people with risk factors, constituting a stigma. It might be a good idea to encourage testing for everyone. The onus of being tested for HIV might be the greater deterrent, and the more it can be avoided, the better.
- Data indicate the increasingly routine nature of HIV testing in the U.S. population (e.g., for insurance, during physicals, etc.). Testing rates for pregnant women are 60%-90% depending on state policy regarding the mandatory testing of newborns. This provides some reassurance that women in the age group of interest may have been tested.

Dr. Birkhead **moved to accept the workgroup's recommendation** and Dr. Offit seconded the motion.

Vote:

In favor:	Offit, Hanson, Brooks, Birkhead, Modlin, Word, Zimmerman, Levin
Opposed:	None
Abstained:	DeSeda, Rennels, Belshe abstained.

The motion passed.

Screening of Pregnant Women

Dr. Ben Schwartz, of the NIP, then outlined the considerations of vaccination relevant to pregnancy. Pregnancy is a relative contraindication to live virus vaccines (LVV), which pose theoretical risks to pregnant women and their fetuses. The risks associated with attenuated viral vaccines are less well described, including those for smallpox, and native smallpox disease increases the risk of adverse pregnancy outcomes. Fetal/infant anomalies could be inappropriately attributed to a vaccine and threaten pubic confidence in the vaccine program. The ACIP recommended not vaccinating pregnant women with live viral vaccines (LVV) and advising the candidate to not become pregnant within a month of receiving one. Pregnancy testing was not recommended before vaccination in any regular CDC programs.

1. Adverse outcomes. The risk of administering an LVV to a fetus is primarily related to fetal infection with the vaccine virus. The risk of morbidity pertains to prematurity and congenital defects. The mortality risks are from miscarriage or spontaneous abortion, fetal death or still birth, and neonatal death. Case reports were provided:

- Levine (*Lancet,* 1974) summarized 21 published cases involving 20 pregnancies from 1932-1972 that demonstrated that the vaccinia virus can cross the placenta with fatal consequences. The pregnancies ended after a mean delay of 8 weeks, one was full term, 19 were premature; 11 were abortions or stillbirths; 10 were live births; and 3 survived.
- A fetal vaccinia cohort study in Stockholm, 1963, examined 170 pregnant women vaccinated (158 previously vaccinated). Many of them were nurses with increased risk of occupational contact. Thirty-three were hospitalized for complications of pregnancy and there were 11 cases of fetal or early neonatal death. The vaccine could not be eliminated as the cause for four of them. Stillbirths and perinatal mortality of the cohort exceeded those of the general Stockholm population.
    - Caveats of the cohort studies that preclude quantifying rates include: incomplete detection of fetal loss; the inability to definitively associate vaccinia with adverse outcomes; vaccinated women may be at increased risk of complications; the high rate of prior vaccination in these cohorts, and the different vaccinia strain used in Europe. The NYCBOH strain may less often become viremic and therefore pose less risk (Lane et al).

Literature indicate that fetal vaccinia is a severe infection that culminates most often in fetal or neonatal death; the risk to the fetus is hard to quantify but must be small, and there has been no evidence of increased risk of adverse events from smallpox vaccination in the pregnant women themselves, although the disease may be more severe.

Characterizing the number who may be exposed is necessary to quantify the risk. A cross-sectional prevalence of occult pregnancy was calculated (those not knowing they are pregnant upon vaccination) and the incidence of subsequent pregnancy within one month. Assuming that the risk of occult pregnancy is a 4-week period, cross sectional prevalence and incidence of subsequent pregnancy would be equal.

Assumptions were that women are aged 20-44 years; time to knowledge of status is 4 weeks; and there are similar fertility and contraception rates among health care workers and the general population. This resulted in an estimate of 664 per 100,000 women aged 20-44 years who are vaccinated. Census data indicate, of physicians and nurses who are women, that 44% are <45 year old. Thus, per 100,000 women vaccinated, 664 x 70% x 44% = 205 pregnant women unaware that they are vaccinated (or 1000 per 500,000 women).

Strategies to reduce inadvertent exposure of pregnant women to vaccine include self deferral, improved contraception to decrease the risk of pregnancy, and improved identification of pregnancy through testing. The strategy selected varies according to risk. For example, self-deferral is recommended for rubella vaccination, but the protocol for Accutane's greater risk (25-30% with serious birth defects and additional risk for spontaneous abortion) uses negative clinic-based pregnancy testing, monthly pregnancy

tests, and documentation of agreement to use several different contraception methods or to be abstinent.

The considerations of strategies to reduce the inadvertent exposure of pregnant women to smallpox vaccine include practicality and reasonable cost, minimizing unintended consequences such as unwanted disclosure of pregnancy or pregnancy intention, avoiding fear that could cause women to self-exclude from vaccination or cause undue concern, decreasing vaccination uptake if a smallpox exposure occurs, and the ethical need to protect volunteers from risks.

Potential strategies discussed were: education about vaccination risks, attention to timing of menses at prescreening, improved contraception or abstinence, and appropriate use of pregnancy testing. Serum and urine tests cost $8-12, are available over the counter, and are generally very sensitive 4-6 weeks post-conception when done after the first morning void.

The proposed wording details what should happen at the time of vaccination and at pre-screening, and the risks of inadvertent vaccination during or within one month of pregnancy. The sense of the workgroup of the four options (self deferral, voluntary testing, mandatory testing, and vaccination only during menses) was that education (information) should be provided. Mandatory testing was not supported. Pregnancy testing should be available for women who wish to be tested pre-vaccination. There was some disagreement as to what "available" means, whether on site or purchased at any local pharmacy.

Discussion included congratulations to the workgroup on this language, and:

- *Was assessment of women not knowing they are pregnant considered to gather more data on that? That would not be gathered by a registry in the absence of such a study.* That type of a study would generate data and require informing the subject, meaning that vaccination could not be done. Doing that study is unlikely. But a registry could record potential congenital anomalies.
- Other considerations are the need for clear language about contacting, and the availability of VIG to treat, women who discover their pregnancy after vaccination, and instances such as when a male discovers his sexual partner was pregnant when he was vaccinated. For example, the latter should be advised to minimize contact and VIG should be given to the woman.
- *A statement about such tests should be made available at prescreening and vaccination sites to help overcome the barriers to potential testing. Was this discussed in workgroup?* Yes.
- *Did the workgroup considered the technique, to reduce unintentional vaccination of pregnant women, vaccinating only within the ovulatory of the last menstrual period and then refraining from sex until the scab fell off?* That was one option considered, but it would require doing this for all women of childbearing age, not a feasible proposition for any vaccination program.

Dr. Offit **moved to accept the language proposed by the workgroup,** and was seconded by Dr. Tompkins.

Vote:

In favor:	DeSeda, Offit, Hanson, Brooks, Birkhead, Modlin, Word, Zimmerman, Levin
Opposed,	None
Abstained:	Rennels and Belshe.

The motion passed

With no further comment, the meeting adjourned at 6:13 p.m. and reconvened the next morning at 8:00 a.m.

OCTOBER 17, 2002

INFLUENZA VACCINE RECOMMENDATIONS FOR 2003

Dr. Bonnie Word, Chair of the Influenza Workgroup, reported that the workgroup had held four meetings since the last ACIP meeting. She also noted that this was the first time that influenza recommendations were discussed in October rather than February, which is very helpful to CDC's preparation. Whether to continue the tiered distribution and utilization of vaccine will be discussed in February, when a clearer assessment of the season's progress will be possible. She introduced the topics to be covered.

Vaccine Supply Update

Mr. Dennis O'Mara, Associate Director of Immunization of the NIP, reported that the vaccine supply to date had exceeded that of the last three years and that the vaccine companies' production projections are on target. This could be a record year for influenza vaccine production in the U.S. in terms of timing and volume.

Influenza vaccine is currently available in the millions of doses, since many purchasers placed multiple orders and accepted the earliest offer. In addition, some providers who complained of being "shut out" of the market early thought they would be unable to get their vaccine and sent their patients elsewhere, thinking its was now too late to purchase. As a result, there is still some maldistribution.

The vaccine ranges from $6.40 to $7.50/dose. There is little price speculation and production and distribution is timely. Medicare payment rates are $8.02 per vaccine and an average of $4 for administration (in a range of $2.68 to $5).

Data of the National Immunization Survey (NIS) indicate the 2002 vaccine coverage (actual coverage in 2001) of 66.4% for those aged ≥65; 36.3% for those aged 50-64; and 16.4% for those aged 18-49. This is an upturn since the 2001 report (actual year 2000), but is not equal to the coverage before the shortages.

Inactivated Influenza Vaccine and VFC Program Update
Dr. Lance Rodewald reported for the ill Dr. Jean Santoli. The challenges to deciding how much vaccine to order include the reimbursement issues (by private insurers and Medicaid, especially for the administration), liability concerns, and coverage under the NVICP.

The time line for determining how much vaccine to order for the VFC program's use is tight. From September through November, CDC works with its grantees to gather estimates of their need for VFC eligible children for the 2003-4 influenza season. In December, the states will need to finalize their need, and in January 2003, CDC begins contract negotiations for the VFC providers for the 2003-4 season.

Grantee level estimates of need: In June, the ACIP heard national estimates of the VFC vaccine needed for three age groups. These were based on population data, proportion of children eligible for VFC coverage, and modest estimates of uptake.

To improve uptake, a study is being done to collect information from health care providers regarding their implementation of expanded influenza vaccination. Six states and urban areas were sampled, according to the volume of the recent state vaccine order. They were asked about their plans for implementation, the perceived barriers, and their estimate of the proportion of children in their practice to be vaccinated. They will compare this to the national sample of providers done by Dr. Gary Freed at the University of Michigan.

Reimbursement issues: Coverage by private insurers and health plans remains uncertain with the ACIP's current "encouragement" rather than full recommendation for vaccination. How Medicaid will handle administration fees is also uncertain, although CDC thinks that they will cover that. Since this is a state Medicaid decision, they will survey states in early 2003 to see if they will cover the cost for children other than those at high risk.

Liability concerns: Currently, influenza vaccine is not covered by the NVICP until it is recommended for routine use in children. This will be considered by HRSA and their Advisory Committee on Childhood Vaccination (ACCV).

Discussion included question of what the ACIP should say to the pediatrician waiting to vaccinate for influenza but concerned it is not covered by VICP. Dr. Evans advised them to say that it is likely to be recommended for routine use in children in the next two years, and that the compensation program's coverage is retroactive by 8 years. Any shots given today will be covered. If parents think that a child has a reaction, they can sue in the tort system. If the VICP covers it eventually, the claim can be filed and the suit dropped. Some states are not covering 6-22 month-old children because they think they are not at high risk, despite ACIP's statement. Dr. Graydon reported feedback indicating that most states probably will cover it, but until a universal recommendation is in effect, some will not.

Parent/Physician Focus Groups on Vaccination of 6-23 Month-olds
Ms. Jeri Pickett, of the NIP, reported on formative research done to assess physicians' knowledge, attitudes, beliefs (KAB) and practices about immunizing healthy children aged 6-23 months against influenza and their awareness of the ACIP recommendations and their implications. Parallel groups were conducted to assess parental knowledge, attitudes and beliefs, and to gather information to support the development of education programs for parents and providers. Focus groups and in-depth interviews of providers and parents were conducted in the Washington D.C. area. The parent focus groups were divided by ethnicity (African American, Hispanic, and general audience). All participants had at least one child aged 6-23 months.

***Providers** knowledge*. The providers were aware and/or understood the ACIP recommendation, but did not think it a mandate for action; further guidance is needed. Those employed by a hospital or an HMO had little knowledge or concern about reimbursement, vaccine purchase, supply, capacity to deliver services and the costs associated with parent education activities and reminder/recall systems. But those in private practice knew these issues and identified them as significant barriers to universal implementation.

Practice. All thought that the influenza shot was important and advocated annual shots for their high risk patients aged ≥6 months. HMOs and hospital-based physicians used sophisticated reminder recall systems and databases to track immunization, but private practitioners used more informal methods, usually chart reviews.

Attitudes/beliefs. More than 50% had reservations about immunizing healthy children in this age group. Nearly all thought the data to be insufficient to support a universal recommendation, and many cited rotavirus as the basis for their skepticism. Many were also concerned about thimerosal. Several thought thimerosal content to be higher in influenza vaccine than other routinely recommended childhood vaccines. Many also felt that influenza is not a problem for healthy children compared to other VPDs and would be hard to justify to a parent.

Barriers cited included reimbursement and lack of daycare/school entry requirements to foster parental compliance, parents' concern over the number of routine immunizations a child receives at this age, and lack of safety/efficacy studies. The vaccination is not yet endorsed by the AAP and AAFP, and logistical difficulties are associated with seasonal healthcare needs and lack of alternative resources to handle increased patient volume. Many felt that public health should handle this burden, not the private provider.

Education/Outreach: Pediatricians and family practitioners reading *Infectious Disease* and the *MMWR.* They want CDC fact sheets and newsletters to be sent directly to them, rather than through their provider organizations. More than half do not use the Web routinely as an information source. Pediatricians, more than family practitioners, relied heavily on the AAP endorsements and communications. Almost all felt that large

public health information campaigns are effective in disseminating important messages.

***Parents** KABs* reflected no differences by ethnicity in recognizing the symptoms of influenza. Overall, parents wanted more information about the need for an influenza shot. Latino parents were more willing to give their child an influenza shot if recommended by their physician, but African Americans and Caucasians were more likely to want more information before they decided on immunizing their child. All groups were interested the cost and reimbursement issues. Most were unfamiliar with their insurance plan's benefits.

Discussion included:

- The disconnect was noted that most physicians believe in giving an influenza shot for high risk children, but only 10% do it.
- The data were broken down by income levels, not by Medicaid or private coverage.
- *Were they asked if influenza vaccine was effective, and if so, for what?* The providers agreed that the shot is a good prevention. They recommend it to parents and adults who ask about the vaccine, but only 10% had patients asking for it. While they regarded it as positive, they were not ready to take action on it from the parental perspective.
- *Were they told that the risk of hospitalization for those aged 6-20 months is approximately the same as those aged ≥65 years?* Yes, but their comments were given beforehand. After the sessions, it was explained that the client was CDC, why the groups were held, and what was published about risk factors, etc. They were not aware of that.
- *What follow-up is planned to assess the evolution of the vaccine's use over the next few months?* Messages will be tracked through the media to gauge the message content, and uptake will be assessed from other sources. This study was to establish the baseline for providers/parents KABs and then to follow up in next 2-3 years through education programs, as the studies are completed or the recommendation is issued. *Explore also any geographic differences; for example, Rhode Island provides the vaccine to everyone and has a public health campaign.* That will be done.
- *Was the similarity to rotavirus in the context of the need to give it, or of safety?* Safety. Physicians were very jaded by the rotavirus experience. Pediatricians in the focus groups wanted to wait and see about this recommendation and were not excited about pursuing this without more data to encourage it.
- *Can you explain why pediatricians felt that it was highly effective while still citing a lack of studies? And, were all the barriers equally important, or were any more weighted?* Pediatricians and family practitioners feel the shot is positive for high risk patients (as opposed to complications from getting influenza), but while not they are not negative, they are hesitant about giving it to healthy children.
- *How many parents were in a group?* Six to eight in each of the three groups. *So all these conclusion are based on 18 physicians, one nurse practitioner, and 18 parents.* Yes, but given the limitations, this is a baseline study. It gives a feeling

of what providers think on a regional level. More in-depth study is needed, but it is important for ACIP to know that providers have some hesitancy about these issues, and significant barriers are probable to effecting a universal recommendation.

- *Was there any discussion of new ways to administer influenza vaccine, particularly related to concern about "shots"?* There was low awareness of the research being done, although there was some discussion of a rapid test for influenza, internasal administration, etc. There was more apprehension than enthusiasm in the providers groups. They are waiting for information.

Clinical Trial Data

Dr. Kathleen Neuzil reported on the data of the influenza vaccine clinical trials. Influenza attack rates and morbidity are high in 6-23 month-old children, who are also at high risk for influenza complications. The vaccine is effective and efficacious as a biologic product across a broad range of age groups. What is not known is if expanding the vaccination program will help young children; in other words, how much prevention is enough?

The workgroup reviewed these issues, focusing on studies of healthy children aged <3 years given a split-virus trivalent inactivated vaccine (TIV) with the current antigen content. Since foreign TIV is often not directly comparable to that used in the U.N., foreign studies were not used.

Historical perspective. The Red Book recommended vaccination of high-risk children without evidence of efficacy, based on serious morbidity. A series of studies were done to study age, size and multiplicity of dose in the various influenza vaccines on the market in 1976. Multicenter randomized trials (Wright et al, *JID*, 1977) included 2326 healthy children and 1200 high risk children, 81 of them aged 6-36 month old. The vaccine was a two-dose regimen of monovalent split virus vaccines. There were no systemic reactions or excess fever in this age group compared to placebo, and there was mild erythema in the vaccine group. These studies led to the ACIP's recommended two-dose vaccine regimen in young children. In 1977, another set of studies (Wright et al, *Rev ID*, 1983) looked at 358 children and adolescents, 39 at high risk aged 6 months to 6 years, who received monovalent and trivalent combinations.

Current vaccine. Data on the current vaccine come from small studies of safety and immunogenicity and trials on children in day care, randomized control studies comparing TIV to the live attenuated influenza vaccine (LAIV), and one large unpublished safety study.

Safety studies offer variable data on safety and reactions.

- Piedra et al (*Vaccine* 1993; 11:718-724) followed ten children who received two doses of standard TIV vaccine, and noted no local reactions.
- Gonzales et al (*Arch Dis Child* 2000) followed 67 healthy children aged 6 months

to 3 years who were given two doses of the current vaccine and closely monitored. There were no control groups. They reported immediate reactions in 9 of 57 (16%) children after injection and in two, small local "allergic type" reactions. Other local reactions of tenderness/erythema occurred in 6-7%. There were no serious adverse events. Systemic events reported included rhinitis, cough, and fever.

Daycare safety/efficacy-effectiveness studies

- Heikkinen et al (*AJDC* 1991:187) studied children aged 1-3 years given two doses of TIV; 187 remained unvaccinated. No safety data were reported, but 83% efficacy was reported, including an 83% reduction in acute otitis media associated with influenza and a 32% overall OM reduction.
- Clements et al *(Arch Ped Adoles Med*, 1995) studied 186 day care attendees aged 6-30 months. This randomized controlled clinical trial did not report safety data. Blinded weekly otoscopy was done. The vaccine was protective against acute OM during influenza season and efficacy was 69%.
- Hurwitz et al (*J Inf Dis* 2000; *JAMA* 2000) studied 60 children in day care in the vaccine group and 67 in the control hepatitis A vaccine group. Both were well tolerated. Efficacy for prevention of infection demonstrated a 31% efficacy for H3N2, 45% for influenza B, and 45% overall. There were no significant differences between the two vaccine groups for respiratory illness, otitis, physician visits, antibiotic use, days absent from school, etc. But interestingly, unvaccinated household contacts of the vaccinated children had 42% less febrile illness than the unvaccinated children, suggesting lower transmission from the vaccinees.

Randomized, controlled trials of the current inactivated vaccine (TIV) and a different cold-adapted vaccine (CAV) in children were outlined. Only one included children aged <3 years.

- Edwards et al; Neuzil et al. The Edwards study was published in 1994; those data were reanalyzed for a subset of children and published in 2001. The study followed 5210 healthy subjects (half aged <2 years) in a randomized control trial comparing TIV, LAIV, and placebo over 5 years. All children aged ≤2 years old received one dose of vaccine. For two years, the H3N2, one drift strain circulated, and H1N1/one drift strain did so for one year. The safety assessment recorded mild to moderate reactions of fever, local reactions and systemic reactions. Local reactions in the vaccine group of children were redness (in 3%) and induration (in 6%). Attack rates were measured by seroconversion by age group. The placebo group was higher than the TIV group for both H1N1 (44% in the youngest age group) and H3N2 (49% in the youngest age group). Culture positive illness was assessed by patients presenting to clinic. Small numbers prevented an age group breakdown, but overall efficacy was 91% for H1N1 and 77% for H3N2.
- The Baylor Family Studies of 1995-1998 (Gruber et al, Clover et al, Piedra et al) showed a pattern similar to the Edwards study. These demonstrated attack rates

of 30-40% in the unvaccinated group, much lower in the TIV vaccinees, and a statistically significant trend of increased efficacy with older age. Overall efficacy in the 3-6 year-old group was 50%, and as high as 80-85% in the older groups. Hoberman et al (University of Pittsburgh, unpublished data reported in abstract form) studied healthy infants aged 6-24 months who received 525 doses TIV and 261 doses placebo. Half were given in the 6-12 month age group. No serious adverse effects were related to vaccine or placebo and immunogenicity was high. Attack rates for culture positive illness were ~16% compared to the placebo group and the vaccine group had a statistically significant reduction for a high overall efficacy of 66% in year one. Year two was one of the mildest influenza seasons of the last decade, and the study showed no difference between the groups, as seen often in studies of adults. This showed the importance of doing studies over more than one influenza season.

Experience in high risk populations includes studies in children with underlying conditions (which were listed). They showed comparable safety and immunogenicity profiles as seen in healthy children. However, the efficacy studies were small and covered a wide range of ages (e.g.,1-14 years old) and were underpowered to break down result. However, Groothius et al (*Pediatrics*, 1991) followed 113 children (62 were aged 3-5 months) with bronchopulmonary dysplasia defects and congenital heart disease. Multiple vaccines were examined, but the seroconversion rates for H3N2 were higher than for influenza B and H1N1. An important aspect of the study is that influenza vaccine was well tolerated even in very young children, with low rates of adverse reactions such as irritability and fever.

Studies outside the U.S. have been done (e.g., in Japan, Russia, France) among varying numbers of children in randomized and nonrandomized trials. In general, the safety/immunogenicity profiles appear to be comparable.

The limitations of the current studies are that they were done after the vaccines were licensed, with variations in age groups, study design, safety assessment, and reporting of results. The Edwards study gave only one dose of vaccine, which may affect efficacy.

In VAERS data from 1991-2001, there were 89 reports on influenza vaccine used in children aged 6-23 months (no known denominator). Effects were not serious, such as fever, rashes, etc.

In summary, the analysis of TIV safety studies in children assessing safety encompasses ~1000 doses administered to healthy children aged 6-23 months. The vaccine was well tolerated, but there was insufficient power to assess adverse events. Efficacy varies by year and age group, ranging from 0-83% (0 being the first year of the Hurwitz study). But again, most studies were underpowered for an efficacy endpoint.

Discussion included:

- *Was there any difference in efficacy between one versus two doses?* There was no difference for safety in the 1977 studies. Reactogenicity was lower overall for either one or two doses (<5%). The same was true for efficacy, but no study compared one versus two doses. Immunogenicity was clearly better.
- *Has anyone tried to correlate efficacy with immunogenicity? And are the antibodies comparable after two doses in younger children versus one dose in adults?* In some ways, immunogenicity is a larger and more difficult topic. On the correlation of efficacy and immunogenicity, Hurwitz found that a higher antibody titer before vaccination led to more efficacy when done in adults, but not in the 120 children studied. The Edwards study could have reviewed this, but did not. Immunogenicity in adults was higher than in children even after two doses. Response rates in these children could reach 80%, but vary greatly depending on antigen. The Baylor studies did correlate immunogenicity with efficacy in older children. Dr. Modlin added that the swine influenza trial studies in Boston, among high risk and healthy children, found that even after two doses, the GMTs were slightly lower in younger than in older children, who in turn were slightly lower than in adults after two doses.
- *Are there any studies of attenuation as opposed to prevention of disease?* The 3-5 year-old group in the Baylor study had reduced febrile illness. The day care studies use clinical endpoints (e.g., less OM in 2 of the 3 studies).
- Dr. Chen reported that the Brighton Collaboration is standardizing how adverse events are measured in different vaccine trials, even things as simple as fever (oral, rectal, at 24 or 48 hours). Hopefully, this will facilitate future interpretation of data across studies.
- *How were efficacy and immunogenicity defined?* Immunogenicity is immune/antibody response to the vaccine measured by antibody titers. Efficacy is the outcome, different in each trial, but usually involving a lab-confirmed influenza outcome of some kind (e.g., influenza or OM).

VSD Safety Study of Pediatric TIV Vaccine

Dr. Jason Glanz, of Kaiser Permanente/Colorado, reported on a study of the Vaccine Safety Datalink (VSD) data on the safety of the pediatric TIV vaccine. Large post-marketing trials of new vaccines are often required of new vaccines, but no large studies had been done of the relationship between the current TIV and adverse events in children. This VSD study was done to address that gap in the current research. It involves a cohort of 3.5 million children aged <18 years from five managed care organizations in the U.S. Kaiser Permanente (KP) groups in Northern and Southern California, KP Northwest and KP Colorado, and the Group Health Cooperative (GHC) in Seattle. They screened data to find 251,000 children who received 430,000 TIV vaccinations from 1993-1999, for evidence of medically attended events (MAE) after vaccination.

The study design used a self-controlled method to compare the odds of an MAE in a 14-day risk window after vaccination to the odds of MAEs in two control periods outside

the risk period. The Day Zero (vaccination day) was excluded from the analysis because it was more likely that children may then be diagnosed with illnesses for which they would not normally seek attention.

The control periods were days 15-28 post-vaccination and the 14 days that ended on day 14 pre-vaccination. Since the latter group was likely to be healthy (physicians vaccinate healthy children), their incidence of MAEs could cause underestimation of the true baseline of illness, so they also were dropped from the analysis.

The self-control method allowed the study to control for confounding factors such as preexisting disorders (e.g, asthma, diabetes) and other factors such as ethnicity and SES. The estimates derived from this method differ from that of the traditional epidemiologic method when diseased/nondiseased, exposed/nonexposed populations are compared. The odds ratios from the self-controlled method can be interpreted by asking, given that a person experienced an MAE, what are the odds that they would experience that in the postvaccination period outside the risk period?

The final data set held outpatient visits from 1995-99 and inpatient visits from 1993-99. Children who received at least one TIV shot were analyzed, and the first shot was analyzed if the child received two in a season. The diagnosis codes combined similar codes into broader (roll-up) variables (e.g., for OM, UR/colds, etc. and for allergic reactions such as unspecified allergy, anaphylactic shock, etc.)

To minimize the possibility of finding a significant association by chance alone, they split the 221,484 shots into two groups. Sample 1's odds of MAEs were compared to both control periods. Those showing a significant association in Sample 1 were then analyzed with Sample 2. Those with significant associations to both samples were considered to have a possible significant association with vaccine adverse events.

For odds ratios that were >1.0 and p values <.05 in both samples, medical chart reviews were done to confirm case status. They will next reanalyze the data with the confirmed incident cases.

Several analyses were done, of outpatients, inpatients and ED visits, and three different risk windows to 14 days (0, 3, 14) for the 6-24 age month group. Sixty-eight cases were needed to detect an OR = 2 with 0.8 power and an alpha of 0.05. Dr. Glanz outlined the case numbers for common symptoms reported after vaccination to VAERS post-vaccination, which demonstrated sufficient power to detect outcomes.

The results showed no overtly worrisome associations with ORs > 1.0, and those <1.0 were for minor illnesses. One association, with diabetes, was explored, but most (>80%) visits were found to be related to follow-up or well child visits unrelated to diabetes. All other associations were negative, suggesting they were more likely in the control period than in the risk period.

A few explanations for the inverse relationships and negative ORs were developed:

- The "healthy vaccinee effect", in which the periods both before and after vaccination are expected to be healthy. The OR of nearly 1.0 suggested that illness rates were equivalent; children who were healthy when vaccinated, stayed that way.
- The "expected symptom effect", in which the child develops an expected symptom after vaccination. This is diagnosed over the telephone and the patient does not return to the clinic.
- The "sick of the clinic effect", in which returning for medical care is deferred for illnesses that arise immediately after the vaccination visit, to see if they resolve unaided.
- The "vaccinated when sick" effect. in which the parent brings the child in for a common illness and while there is vaccinated for influenza. The child is therefore less likely to return within the 14 day period thereafter.

The analysis of 16-24 month-olds used 8476 shots, analyzing the odds of MAEs against the two control periods of the total sample. The only positive association shown was with atopic dermatitis, for no known reason. But the chart reviews demonstrated that >60% of visits were for follow-up among children with ongoing AD. There was no way to determine if the remaining visits were for onset of AD or exacerbation of AD. Remaining associations were negative. Impetigo was the only positive association to arise in the 3-day window. The case review revealed that the eight cases were all incident cases, which occurred at different body sites, but none near the vaccination site.

The last analysis liberalized the significance to ensure that no potentially large associations were missed due to a lack of statistical power. They divided the 1-14 day outpatient group into two groups by OR s ≥2.5 and p values ≤0.2. The MAEs meeting these criteria were analyzed with sample 2; then, the cases meeting those criteria were analyzed with the total population to see if the results were significant. An association with renal disorder was checked in the outpatient setting in the 14 day risk window (OR of ~4.0). However, the diagnosis category was very broad and later chart reviews revealed a wide variety of unrelated diagnoses, so they were not combined.

Conclusions. No signals of any serious events were noted. There was a possible but unlikely association with impetigo. The results were limited by electronic data (e.g., the "healthy vaccinee" effect). This confirms that a signal was not missed by VAERS.

Discussion included:

- *Was there any Guillian Barre Syndrome association seen?* That is too rare to detect and requires a large cohort to explore it. GBS peaked between 2-4 weeks during the swine influenza epidemic, different than the period explored in this analysis. But the problem is that the rare background rate (1:100,000) is not detectable among 250,000 children. However, one comforting factor is that the

association seemed to be only among adults.

- *Of the 8,476 doses, how many were the first dose to the child?* All were first doses; that number is the total of children, all of whom were in the 6-23 month age group. The risk after second dose was not analyzed.
- *If only 25% of the children were at high risk, who were the other children?* That could not be characterized; only the ICD9 code was searched.

Sense of the Workgroup. Dr. Word summarized the workgroup's finding that the studies reflected no concerns with safety data, but there was concern about the limited data on efficacy and effectiveness. Although the numbers were small, they were consistent. But now, going into the 2002 season, larger numbers are desired to support a broader recommendation. Therefore, the current recommendation of the workgroup is to continue to "encourage" vaccination, with strong consensus that studies of effectiveness should be conducted during this time period.

Discussion included:

- *How many years would it take to compile efficacy data?* Demonstrating a reduction in hospitalization could be done with the power of the present epidemiologic data. But for efficacy, at least a two-year study would probably be needed due to the tremendous variability in influenza morbidity year to year. The recommendation for high risk children and older adults was based on morbidity without efficacy data. That came after the strong ACIP recommendations and was then demonstrated by Kristen Nichol.
- Dr. Belshe was reassured by Kaiser's safety data from such large numbers. He wished for more details on the risk of renal disease and would like to examine dose 2's association with more local inflammatory response. The latter is to be expected, but would be good to quantify. The review of efficacy was good, despite little data; more is needed. To design a clinical trial of children 6-23 months, a stepwise approach first could explore efficacy relative to culture-confirmed disease in ~2,000 children. In two years, there would probably be significant lower respiratory disease in the placebo group that would allow an efficacy measure. Most would not be hospitalized, but extrapolation could be done to hospitalizations prevented.
- Dr. Abramson expressed his own frustration that continuing the "encouragement" is inconsistent with the recommendation for pregnant women, which was based on no efficacy data, only some safety data. The recommendation for other high risk groups (e.g., diabetes) was also based on as little efficacy data as there are for this 6-23 month old group. AAP asked CDC to do this study 2-3 years ago, but was turned down due to lack of funding. The efficacy study would have to show decreased culture-positive disease to presume prevented hospitalization. But the ACIP would have to agree to that up front, and with membership turnover, that agreement may change. And regarding thimerosal, some reduced thimerosal-reduced vaccine is likely to be produced this year. The remaining issues to be overcome relate to logistics, since the problems of liability and

reimbursement will be solved by a universal recommendation. That was the only reason he agreed to refrain from a universal recommendation for one more year.

- Dr. Orenstein's concerns were not so much related to efficacy, but to safety, the area about which he expected the most questions to be raised. The issue is whether there is enough experience with children to be sure that there is no significant adverse event such as intussusception that would be detected later. He asked if the VSD would have enough data to determine that, with an ACIP "encouragement", and whether the cohort would be 8,000 children or 4,000 with two doses.
- Dr. Snider asked if the studies of inactivated and live attenuated vaccines were discussed by the workgroup, since a study of the former would be irrelevant if the latter was preferred in use. Dr. Word answered that this was not discussed specifically, but the population for the LAIV would not include children <12 months old; and, based on the presentations, it remains unclear if they would even seek an indication for children <2 years old.
- Dr. France reported that the VSD participant HMOs are variable in encouraging the 6-24 month vaccination, but there will be more vaccinated this season than in the past. In the study presented, 8500 individual children received at least one dose, which is expected to be doubled next season. A study of the utilization of out- and inpatient use of the ED by infants of vaccinated mothers is also beginning, and there will be some discussions at the October national VSD meeting about examining utilization of health services among 6-23 month-olds over the next 2 years to assess the impact of vaccination. However, one problem is the confounding bias of self-selection by those vaccinated versus non-vaccinated.
- Dr. Chen warned of two factors that will alter how the VSD data can be used. One is new HIPPA limits on how data can be shared among sites, making initial data sharing agreements important; and the other relates to concern about CDC's ability to protect data. Managed care organizations (MCO) now are reluctant to send their data tapes to CDC for analysis such as Dr. Glanz's pooled data of the five MCOs. A method needs to be determined on how to analyze that data separately at each site and then compiled. This is a new era of research that probably will require more time before data can be presented.
- *More information on feasibility is needed. A recommendation that practitioners cannot follow puts them in a medical and legal bind. No demonstration or feasibility studies in different types of office settings have yet been mentioned.* Dr. Abramson reported a report on such work to be given at the November conference on infectious disease, as well as consideration of models in the private and public sectors. That study is needed now to do the logistics. Dr. Zimmerman reported that such a study was just begun in inner city Pittsburgh. The feasibility results should be reportable in June 2003.
- Dr. Fukuda asked the ACIP to state whether sufficient efficacy and safety data are needed prior to a full recommendation. NCID and NIP had met to discuss what would be required to develop those data, and the funding will have to be

considerable. He doubted that a single study would suffice. While a prospective study is reasonable to assess efficacy, the varying rates of hospitalization in any high risk group would require another study design (e.g., case-control) done over 2-3 years. Since 2003 is the earliest that could begin, 3-4 years will be needed to gather those data. So, while the "encouragement" approach may lead to a recommendation in ~2 years, studies may take two more. A combined study of feasibility with efficacy outcomes would probably not work, and a case-control study in a large database could be challenged by the few numbers receiving influenza vaccination.

Dr. Modlin asked the committee's opinion of what would be needed; well-controlled safety/efficacy data or just feasibility data. Most members requested safety data, particularly in light of recent vaccine-related problems. Dr. Offit wished for larger numbers of children to be studied to determine the vaccine's efficacy, especially since discussions will begin soon on the use of the LAIV.

Dr. Zimmerman pointed out that the current ACIP recommendations on influenza vaccination of the elderly are based on ~40% efficacy against illness, better for hospitalization, and ~80% against death. They also have more conditions of higher risk and decreased immune competence. A child <5 years old does not have the same immune competence as older children or healthy adults, so the same expectation of 80-90% efficacy is unrealistic. For that reason, he was not troubled by the efficacy already documented, although he would like to see the data gathered. He expected it to be in line with older adults.

Dr. Word personally agreed with Dr. Abramson, and reported the workgroup's consensus that there is no indication of a safety question. She was not even as concerned about feasibility, since once the AAP endorses it, most physicians will incorporate it into their practice. The reason that practitioners are only beginning to think about this is that they have only had an e-mail from the AAP. It will not be published until December.

There was general agreement that the Kaiser study, although excellent, had insufficient data on which to base a recommendation. Dr. Offit responded that the better response of ≥5-10 year-olds is probably because they are being boosted from a previous mucosal prime. The 6-23 month-old is probably having their prime, and it is hard to prime the mucosal immune system parentally. This will be one advantage of using the LAIV, in very young children.

Dr. Midthun expressed FDA's comfort with the historical data and experience of this vaccine, as well as the thimerosal-reduced vaccine approved this fall. While there is no large controlled safety and efficacy study, the accrued information over time is impressive. FDA welcomes the opportunity to work with any other agency to supplement that knowledge.

lasts more than 2 weeks and often comes and goes. If you or member of your household have **ever** had a rash like this, you should NOT receive the vaccinia vaccine at this time unless you and a healthcare provider are sure that this rash is not atopic dermatitis or eczema.

- In cases where the dermatological risk factor or diagnosis is uncertain, some organizations, such as the military or CDC may elect to develop more precise screening tools. These secondary screening tools should weigh the individual's risk of developing an adverse event with the requirement of occupational readiness through safe smallpox vaccination to ensure national security.

Discussion began with Dr. Modlin's expressed opinion that this is a reasonable approach that errs, if anything, on the safe side. Suggested edits offered by the committee were:

1. Cite "increased risk of autoinoculation" rather than risk of EV; the risk is actually superinfection of broken skin.
2. Be consistent in calling this "smallpox" vaccine rather than vaccinia vaccine.
3. Reinsert "severe or uncontrolled acne" as a contraindication.
4. Remove "unfortunately".
5. Clarify that the household contact contraindication based on viral shedding is for a short period (2.5 weeks) after vaccination.
6. Use the term "inadvertent" inoculation, not "autoinoculation" since the latter infers self-inoculation rather than by another person.
7. Add that those with active ongoing AD and not vaccinated in 30 years should not be vaccinated unless absolutely necessary, nor those with chronic or acute exfoliating conditions or with a household contacts with those conditions (e.g., burn).

Further *discussion* included:

- *What is the expected percentage of people who will accurately identify a history of eczema and exclude themselves?* Dr. Belshe reported an exclusion rate of ~20% among >600 vaccinees in their IND studies, based on their recall of any history of a rash themselves or among their household contacts. Dr. Casey reported an informal estimate of 15-30% of the U.S. population.
- This document is to prepare for vaccine use on a non-emergency basis; different language will be needed in an even wider immunization.
- Screening specifics for those not recalling or not knowing about eczema still require attention (e.g., who will decide the vaccination; what documentation is needed, etc.), and other specific diagnoses could be added over time.
- These restrictions apply to both primary vaccinees and revaccinees.
- Further study needs to be planned of how to better focus on risk and to gather vaccination results (i.e., the number screened out, returning for follow-up, etc.)
- *Why are these rules so draconian? Their conditions would exclude persons from inoculation for the response team, but there are no data to suggest that successfully vaccinated people who had childhood eczema have had any*

The issues to be decided on this day related to unknown pregnancy, HIV, AD. It was agreed that the adverse event rate for ~1000 health care workers in stage one was fairly negligible; for unknown HIV infection, military data indicate a 0.1-0.4% rate. But AD has a (probably underestimated) ~2-5% prevalence. The rate of adverse events in this group is unknown, but significantly higher than the first two.

The ad hoc group agreed to favor Option 2 in view of providers' lack of distinction in diagnosis. She noted that the screening response rate of actual diagnosis/ICD9 code rises, with prodding, from 20% to 70%, but that is still a poor number. She offered the language for consideration, which also endorses the development of precise eczema screening tools as a priority research agenda item.

> "Atopic dermatitis, irrespective of disease severity or activity is a risk factor for developing eczema vaccinatum following vaccinia vaccination in either vaccinees or in their close contacts.
>
> "Unfortunately, the majority of providers do not routinely make the distinction between eczema and atopic dermatitis, particularly when describing chronic exfoliative skin conditions in infants and young children.
>
> "Therefore, due to the increased risk for eczema vaccinatum, vaccinia vaccine should not be administered to persons with a history of eczema **or** atopic dermatitis irrespective of disease severity or activity. Additionally, persons with household contacts that have a history of eczema or atopic dermatitis, irrespective of disease severity or activity are not eligible for vaccinia vaccination because of the increased risk that their household contacts may develop eczema vaccinatum.
>
> "Persons with other acute, chronic or exfoliative skin conditions (e.g., burns, impetigo, varicella zoster, herpes, or psoriasis) might also be at higher risk for eczema vaccinatum and should not be vaccinated until the condition resolves. The literature reports that persons with Darier's disease can develop eczema vaccinatum and therefore should not be vaccinated.
>
> "To assist providers in identifying persons that should defer vaccinia vaccination, the ACIP offers the following screening questions:
> - Screening those that know: 1) have you, or a member of your household ever been diagnosed with eczema or atopic dermatitis? If you answered yes, you may NOT receive the vaccinia vaccine due to the risk that you or your household contact might develop a severe and potentially life-threatening illness called eczema vaccinatum.
> - Screening: those who don't recall or don't know (from the VSD-Marshfield study): Eczema/atopic dermatitis usually is an itchy red, scaly rash that

Dr. Modlin expressed his personal surprise that the committee was "getting cold feet" at this point. The safety database is substantial and the vaccine has a long track record in all age groups without no substantial safety concerns. Even if it is not 70-80% effective, he believes it to be at least 50% effective, and preventing hospitalization in even half these children for about $5/dose he felt to be a good investment. He was also less concerned with feasibility based on the field's past implementation of recommendations.

However, he summarized the sense that a slight majority of the committee wishes for more safety data, although a substantial minority is comfortable with the safety database. If case-control studies can be done in the next 2-3 years of children being immunized, that would add to the comfort level; large scale randomized controlled efficacy trials are not necessary.

There was general agreement to this assessment. Drs. Tompkins and Hanson emphasized that the safety data desired would be all that could be collected as quickly as possible; that is, in the next year. There was no discomfort with the data collected or with its safety, but the focus groups' link of the vaccine to the rotavirus experience begs more information. A full recommendation was hoped to be implemented in the fall of 2004. The committee asked to be informed about what is needed to be done to effect that.

After a short break, Dr. Snider announced that CDC had established a task order with the IOM to monitor any smallpox vaccination program to be instituted. Dr. Kathleen Stratton of the IOM and Dr. Ray Strikas of the CDC will coordinate the meetings. The IOM also had issued a report on October 15 about CDC's anthrax research program, which included a recommendation for an external advisory committee to oversee that research program. Since CDC cannot establish another advisory committee, CDC will ask that ACIP do this under its aegis and provide a venue to which this group can report. He asked that one or two members interested in participating so inform Dr. Modlin.

ACIP RECOMMENDATIONS

AD and Eczema

Dr. Modlin summarized the discussion of persons with skin conditions, specifically eczema and AD, as a contraindication to smallpox immunization. A past ACIP statement required correction, and there was question about appropriate screening methods for potential contraindications. A small group had discussed this the previous evening, which Dr. Casey summarized.

The workgroup had favored Option #2, recognizing that this encompassed the broad exclusion of people who may in fact not have a contraindication, since providers do not distinguish between eczema and AD. For that reason, an untested screening tool of potential use was presented.

problem. Historical data also indicate a 10% incidence of EV in revaccinees compared to primary vaccinees. Was that mild, and was there any predictability? Option #5 could resolve that in its citation of the need for occupational readiness to support vaccination. And, those few in the population who know they were vaccinated could cite that on the form as informing their choice. But most do not know their status, and vaccine effects to them remain unknown. Dr. Neff thought that revaccinees would probably be safe, but a small number of individuals who were distant vaccinees are known to have developed EV from contacts.

Dr. Hanson **moved to accept workgroup recommendations as modified**, and Dr. Brooks seconded the motion.

Vote:
In favor: Offit, Hanson, Brooks, Tompkins, Birkhead, Belshe, Levin, Zimmerman, Word, DeSeda, Modlin
Opposed: None
Abstained: Rennels, Belshe

The motion passed.

Simultaneous Administration, Vaccines with Smallpox Vaccine
Dr. Ray Strikas noted that the June 2001 vaccinia recommendation did not address simultaneous vaccination. The General Recommendations of February 2002 also noted noninterference of inactivated vaccines to live virus vaccines, but also noted that the immune response to one live virus vaccine may be impaired if administered within 30 days of another live virus vaccine. It also stated that parenterally administered live vaccines not given on the same day should be administered four weeks apart if at all possible.

The literature (Henderson and Moss, *Vaccines*, 3rd edition) cites the ability to administer smallpox vaccine with other antigens, usually at a different site, with comparable safety and efficacy to those vaccines provided separately. The vaccines cited were OPV, BCG, measles, yellow fever, and DTP.

Dr. Strikas reported a workgroup's consideration of three questions:
1. Does ACIP recommend that smallpox vaccine, when necessary, can be administered simultaneously with other vaccines?
2. Is simultaneous administration with influenza vaccine and smallpox vaccine permissible?
3. Is simultaneous administration with varicella vaccine permissible?

Influenza vaccine. Influenza vaccine's common systemic adverse effects are seen in <1% of vaccinees 1-2 days post-vaccination. These should not be confused with smallpox adverse effects emerging 7-14 days post-vaccination.

But *varicella* is a little different; a site rash may appear in ≤3% and 1% of vaccinated persons aged ≥13 years after the first and second doses, respectively, and a rash away from the injection site in 5.5% and 0.9%, respectively, within 23 days of vaccination, in the same age group. There is a possibility that varicella vaccine lesions could be confused with smallpox lesions if the vaccines were co-administered. There are no studies of that concurrent administration.

The ACIP options discussed were: 1) no change; refer to the General Recommendations if asked; 2) issue an explicit statement regarding simultaneous vaccination acceptability as per the General Recommendations; or 3) issue an explicit statement that simultaneous vaccination is acceptable, except for varicella and smallpox vaccination. The latter should be separated by 28 days/≥4 weeks to avoid confusion over the lesions. There was strong consensus among the workgroup to this latter approach. The draft recommendation was:

> "Vaccinia vaccine may be administered simultaneously with any inactivated vaccine, such as influenza vaccine, to encourage appropriate receipt of all indicated vaccines, e.g., in populations such as health care workers. With the exception of varicella vaccine, vaccinia vaccine may be administered simultaneously with other live virus vaccines. To avoid confusion in ascertaining which vaccine may have caused post-vaccination skin lesions or other adverse events, and facilitate managing such events, varicella vaccine and vaccinia vaccine should only be administered ≥4 weeks apart."

Discussion included:

- Dr. Shekler objected that it is a serious mistake, when administering vaccinia for the first time to a naive host, to assume it can safely be given with influenza vaccine. Maximizing vaccination opportunities is good, but this is a unique pre-event experience in health care workers who can get influenza shots at a different time. As much as possible information on side effects needs to be collected, and the waters should not be muddied. Dr. Siegel agreed to the wisdom of avoiding yet another variable.
- However, since the smallpox vaccine will be administered through state and local health departments, and influenza vaccination is typically provided in different settings, there was general agreement that it would be safe to recommend this as stated.

Dr. Tompkins **moved to accept the recommendation** and Dr. Zimmerman seconded her motion.

Vote:

In favor: Offit, Hanson, Brooks, Birkhead, Modlin, Zimmerman, DeSeda, Tompkins, Levin

Opposed: None

Abstained: Rennels, Belshe

The motion passed.

Vaccinating the Vaccinators
Dr. Melinda Wharton reported on the background developed on this topic. Historically, vaccinators were immunized and revaccinated frequently. There are no specific data on the risk to susceptible vaccinators, but it must be assumed that they would be at risk for inadvertent inoculation.

Recommendations and Risk. CDC and DOD do not require vaccination for smallpox vaccinators of laboratory workers, although Israel does. However, the ACIP did recommend that lab workers handling smallpox be vaccinated. Data on the risk of inadvertent inoculation among adults shows it to be decreased among revaccinees (606/1 million) as opposed to primary vaccinees (25/1 million), and revaccinees have substantially less shedding in quantity and duration. The U.K. does not have a recommendation on workers handling the virus, but a paper written 10 years ago is nuanced. They point out the degrees to which these infections can occur in previously vaccinated persons, and that protection does not appear to be absolute.

Advantages of vaccinated vaccinators are that this: 1) provides protection from occupational exposure to vaccinia; 2) contributes to preparedness for post-event vaccination; 3) assures education and screening before deployment as vaccinators; and 4) contributes to their comfort level with both the vaccine and the vaccination process. And, if done before the larger effort began, it may allow for pilot testing of education and screening procedures, safety surveillance procedures, information systems, etc.

Disadvantages include: 1) a potential violation of privacy if vaccinator candidates are not themselves vaccinated; 2) if working under IND, protocol approval by the DSMB would be required before vaccination, which could involve delays; and 3) and if all vaccinators are immunized at the same time, there would be trouble delivering vaccination on days 7-9.

The options considered for the ACIP were:
1. Recommend that the administering person be vaccinated.
2. Recommend that only vaccinated persons or candidates for vaccination serve as vaccinators.
3. Limit any recommendation to persons administering high-volume vaccinations. This would not involve, for example, the occupational health nurse vaccinating the occasional lab worker.
4. Recommend as per the 2001 statement.

The workgroup recommended that the administrator in a pre-event vaccination program be vaccinated..

Dr. Wharton offered the suggested language:

"In order to minimize the clinical impact of inadvertent inoculation, should it occur, ACIP recommends that persons administering smallpox vaccine in the proposed pre-event smallpox vaccination program be vaccinated.

"Vaccination of this group will also contribute to preparedness for smallpox response, should a smallpox release occur, with development of a cadre of vaccinated, experienced vaccinators who could be immediately deployed for outbreak response."

Discussion included:

- Add to the list of those needing vaccination anyone changing the bandages, which presents greater risk than the vaccine itself. Another addition is the person who reconstitutes the vaccines, but those are presumed initially to be also administering.
- *How can a vaccinator be vaccinated without a licensed vaccine? The IND does not cover that, and it needs to be done at least a month in advance of the vaccination program.* Dr. Strikas explained CDC's anticipation, although it is not certain, that a licensed vaccine will be available in the next month or so, which would make this moot. If not licensed, the vaccinators will be vaccinated several weeks before the larger program begins, in a phased-in fashion that includes training. Dr. Snider added that CDC could ask FDA, for example, to modify the IND protocol for the 1:1 dilution for the laboratorians, in order to begin vaccinator immunization. There have been several requests to begin the smallpox vaccine trials, but there is no currently legal way to do it.
- *They are protected from day one from vaccinia, as from smallpox; is the delay necessary?* No, but it is desirable to ensure adequate staffing from days 7-9. They will be vaccinated with undiluted Dryvax®, but FDA will quickly consider the company's request for a 1:5 dilution.
- *What is the status of the 1:5 dilution and the number of skin punctures? The undiluted vaccine used to be given in 2-3 punctures for primary vaccinees and 1:5 for revaccinees.* Dr. Heilman reported that DHHS asked NIH to move toward a licensure protocol for the 1:5 dilute with 15 injections for both primary vaccinees and revaccinees.

Dr. Birkhead **moved to accept the workgroup's proposed recommendation** and Dr. Zimmerman seconded the motion.

Vote:

In favor:	Offit, Hanson, Brooks, Birkhead, Modlin, Zimmerman, DeSeda, Tompkins, Levin
Opposed:	None
Abstained:	Rennels, Belshe

The motion passed.

Proposed Smallpox Immunization Safety System
Dr. Gina Mootrey outlined the proposed Smallpox Immunization Safety System (SISS), emphasizing its initial character, and requested any comments. It will be part of the final immunization plan.

The SISS is needed due to: 1) the limited modern knowledge of smallpox vaccine safety issues; 2) the high reactogenenicity of smallpox vaccine shown in the (36.4% absent from school, work, recreation or who had trouble sleeping (Frey et al, 2002); 3) the limitations of screening; 4) the size of the population potentially at greater risk of adverse events; and 5) the need to maintain the credibility of and public confidence in the program. She suggested that the committee keep in mind the experience of the swine influenza program as the smallpox vaccination program is developed.

The tasks of the SISS involve a wide range: training, data management, identification of adverse events, evaluation, treatment, reporting, analysis, and assessment.

Structure of the SISS. The structure of the SISS for referrals is in "pyramid" fashion. Assuming that the program begins with 500,000 vaccinees, the process involves:

1. Assigning each vaccinee a number to link their data through the process.
2. Establishing a national immunization safety hotline (to handle, at 35%, an estimated 175,000 calls) with nurses to advise physicians about adverse effects and to update the states.
3. Identification by the states of geographically assigned physicians (specialists in infectious disease, dermatology, allergy and immunology). The hotline will refer vaccinees to them or to their primary care physicians (~10% of referrals equals 17,000 patoent visits for evaluation),
4. The CISA center referral/consultation hotline may be accessed (at ~30%, 5250 consults) as needed by their geographically assigned or primary physicians. The CISA network has four academic centers and seven sites that do research in the pathophysiology of adverse effects, serving as the clinical arm of the vaccine safety infrastructure.
5. The CISAs and CDC doing the medical monitoring (a CISA investigator and several CDC staff) are consulted about the use of VIG or Cidofovir (at ~2%, administered to an estimated 100 individuals). Data also will be gathered from VAERS reports and from 10- and 21-day telephone follow-ups to ~15-20,000 vaccinees who consented to that upon vaccination. Detailed data will be collected on reactions at two time points. This is hoped to detect inadvertent inoculations and perhaps generalized vaccinia.

Unresolved issues that could impact viabilty of this program include liability and vaccine injury compensation; whether to have a national or state hotline; whether the protocol will be for an IND or a licensed vaccine; recruitment of subspecialty clinicians for

consultation; reimbursement for medical care; data management and the extent of data collection (this requires standardization, part of the reason a national system is being considered); training for varied audiences; ensuring surge capacity if >500,000 are vaccinated; and the guidance of the DSMB. Dr. Mootrey asked the committee for additional sources of information (e.g., hospital infection control or occupational health programs) that may not have been considered to date.

Training/education: includes plans for target audiences and content areas. Safety training begins in December.

Data management considerations include rapidity of report, volume and complexity of data; multiple stakeholders; ensuring a coordinated effort between CDC/IRMO, CISA, the Hotline, VAERS, and the states; scrutiny by the public and political entities; and arranging for a unified spokesperson. She described the pre-event smallpox system (PVS) envisioned, in which all vaccinees are entered into a database upon vaccination and assigned a patient vaccination number (PVN). This tracks the vaccinee at all steps in the system and includes information on demographics, vaccination, occupation, referral source, prior vaccination history, a "take" check, and vaccine adverse events.

Vaccine Adverse Events (VAE) identification will be done through a 24/7 national hotline, health care providers, and vaccination clinics. The Hotline will have one telephone number, standardized documentation of adverse effect inquiries, standardized procedures for evaluation and triage, and a standardized report. VAEs will be explored and documented on the history form by a "take" check at 6-8 post-vaccination; by active surveillance done at days 10 and 21 post-vaccination; by phone surveys of 15-20,000 vaccinees by the CISA Network; through requests for VIG and Cidofovir (IND); and by review of the 28-day Vaccine Adverse Event Diary (if the vaccine is used under an IND protocol.

VAE Evaluation, of the 10-35% anticipated, will be done at the vaccination clinic. The national hotline will also evaluate and triage these, determine if no medical visit is required (e.g., a low grade fever, vaccine site pain), or refer the patient to geographically assigned physicians who can consult with CISA 24/7, or their primary care physicians.

CISA consultations will be done remotely unless the person happens to live near the CISA site, using standard diagnostic methodology. CISA consultations will be done upon: serious or unexpected adverse events, breach of vaccination protocol (e.g., misadministration), if a front line provider is uncomfortable about assessing or managing the patient; if the vaccinee is hospitalized or his/her clinical course deteriorates or exceeds the clinical capability of the treating provider/facility; and if VIG and/or Cidofovir are considered.

Treatment will mostly be provided at the local level by the primary care physicians, but states may also identify providers/facilities for medical care of vaccinees, who will also

be seen at CISA centers when feasible. Standardized practices will be encouraged.

Release of VIG/Cidofovir To access these for treatment of certain adverse effects, the attending physician consults with the CISA via the hotline, and CISA would contact the medical monitors. The latter would inform CDC drug services, which would release these two treatments under an IND protocol to the attending physicians.

Reporting to VAERS should be done for all serious vaccine adverse effects: death, life threatening event, hospitalization, prolonged hospital stay, or permanent disability. The reporting requirements for an IND are more specific and involved that those for a licensed vaccine.

Analysis: Interim and cumulative analyses will be done for the 10 and 21-day follow up survey. It will be nationally representative, stratified at least by gender and age, and able to detect adverse events occurring down to a rate of 1:4-5000. Daily review of VAERS reports will be done, as well as of visits and calls to CISA and requests for VIG/Cidofovir. If the program is done under an IND protocol, at least a weekly review will be done of the 28-day diary card submitted. The analyses will be compiled in regular reports in various reporting formats .

Assessment: A DSMB will be constituted (e.g,. by the IOM) to review intermediate and cumulative safety data for its quality, timeliness, adverse events, and (if applicable) adherence to the IND protocol. There will be periodic meetings that will be publicly reported. CDC's IRB will be informed of any serious or unexpected events, and reports will be provided to the FDA under regulatory requirements. Medical monitoring will be ongoing from onset of vaccination.

Vaccine safety research needs include: risk factors for adverse effects, long term follow up of serious/unexpected VAES, risk of chronic disease (cause or aggravation of underlying illness) following smallpox vaccine. Dr. Mootrey asked for other suggestions as they emerge in the statement development.

Discussion included:

- Without delay, begin to get significant input from CDC's state and local partners. Hospitals' full involvement will be needed for VAE reporting. The health department will have a difficult time identifying geographic physicians, since that essentially endorses their medical practice, and they are also responsible for physician disciplining. Perhaps adverse event reporting can be funneled the physicians who are trained. Dr. Mootrey reported a series of calls soon to begin with ASTHO to discuss such issues.
- *Reorganize the CISAs for better dispersion than three on the east coat and one in Colorado.* There is only funding for these sites, but this infrastructure is hoped to be expanded upon recognition of a broader need to gather knowledge to treat these patients, and to have accessible consultation by subspecialists. The

advocacy of such entities as the ACIP would help that. In the interim, CDC has asked those doing the NIH trials, who are geographically well dispersed, if they would serve as "backup experts". CDC also is exploring the interest of smallpox veterans to volunteer and is exploring treatment algorithms.

- Evaluation data will be collected. The vaccination clinic will keep records on how many people are screened out due to medical reasons, and how many self-screen out on the prescreening day.
- Dr. John Riggs, of the Surgeon General's Office, complimented the system, but noted the need for comparison groups. Research should be done to answer the concerns sure to arise (as in the swine flu experience). The normal ambulatory and hospitalization rates for health care workers over a 30-90 day window should be known, for example, to be able to compare those who are vaccinated to an unvaccinated cohort. He was also concerned that the HIPPA VSD process is slowing, when smallpox interim answers will be needed rapidly.
- Dr. Barbara Styrt, of the FDA, commented on two layers of data collection; that for the vaccine's safety profile, and that on the unknowns in treating smallpox complications in the 21st century. All should be aware that Cidofovir is not FDA-approved for treatment of vaccinia complications, and there will be other treatments similarly unevaluated systematically. She urged the inclusion of treatment evaluation into this system.
- The first 500,000 vaccinees are unique in all being health care workers, making the inclusion of hospital and the infection control field more important.
- There was support for the idea of having hospital staff reporting the adverse events. Perhaps CDC should require that the hospital physicians be trained in their basic evaluation of adverse reactions. That might reduce or eliminate the need for regional evaluators and could add another layer of primary care physicians to detect adverse reactions, and who could be a resource in subsequent program phases.
- Although this is a good system, it offers another reason to start slowly; if anything goes wrong, the SISS will fail rapidly.
- Dr. Michelle Pearson of CDC saw an opportunity, given the benefit to the hospital to monitor and report adverse events among their staff (e.g., beginning with the vaccination site care team), to link public health more strongly to the healthcare setting for data collection. Dr. Tompkins agreed and envisioned a team representing infectious disease, infection control and employee health clinicians. They should be responsible to assess any adverse effects in their facility's population, not the county or state health department, and they should be linked to the CDC network immediately.
- Be clear that the primary care physicians monitoring the adverse events need to be vaccinated, something not yet stated, and that not everyone's primary physician will do that evaluation.
- An overarching policy is needed to address the obligation of vaccinees who are not furloughed. That is, should they, or the hospital, advise the patient coming in of a small but present risk from inoculation? This should not be addressed

hospital by hospital.

- *What are DHHS' plans for vaccine injury compensation?* This was discussed in the workgroup, but CDC asked the ACIP to proceed in the context of formulating a program; this is not primary issue for the ACIP. Dr. Snider reported continuous CDC prompting on this issue to ensure that those at the higher levels understand the importance of addressing liability issues. DHHS has reassured CDC that they are aware of it and are developing options to deal with it. But no specifics have been shared in great detail or vetted publicly.
- Dr. Dan Bradshaw, of the DOD, suggested adding ophthalmologists to the list of specialties, and specifically involving the VSD to facilitate comparative studies.
- Since there may never be an end to the threat, stop criteria for this program also need to be considered.

2003 Harmonized Childhood/Adolescent Schedule

Dr. Greg Wallace, of the NIP, reported the changes made to the 2003 harmonized childhood and adolescent immunization schedule. The changes are underlined:

1. The hepatitis A footnote to state that "four doses of vaccine may be administered when a birth dose is given. The second dose should be given at least 4 weeks after the first dose, except for combination vaccines which cannot be administered before age 6 weeks." It calls for maternal blood to be drawn as soon as possible to determine the mother's status, and it recommends the second dose to be given at age 1-2 months. The last dose in the vaccination series should not be administered before age 6 months.
2. The hepatitis A footnote was changed to clarify that the schedule for unimmunized children can begin at any visit; added "children and adolescents", consult local public health authorities for specific recommendations;" administering the two doses in the series at least 6 months apart; and added "can"
3. The reference in the influenza footnote was updated, and the recommendation was modified to encourage vaccination in 6-23 month-olds since they are at substantially increased risk for influenza-related hospitalizations.
4. Additional information was inserted at the end on the Website and phone numbers for information, adding vaccine precautions and shortages specifically.

Discussion included Dr. Rennels' report that the AAP approved this schedule. It was noted that the language encouraging influenza vaccination in the homes of people at high risk from flu was gone, due to lack of space. It will be reinserted if possible.

The ***catch-up schedule*** format was agreed upon by the workgroup and was forwarded to the AAP and AAFP. It was hoped to be published simultaneously with the harmonized schedule and in the Red Book. It was reviewed at the June meeting and there were no further comments at this meeting.

Dr .Word **moved to accept the harmonized schedule as presented,** and Dr.

Zimmerman seconded the motion.

Vote:
In favor: Offit, Hanson, Rennels, Brooks, Birkhead, Tompkins, Modlin, DeSeda, Word, Zimmerman, Levin, Belshe.
Opposed: None
Abstained: None

The motion passed.

Focus Groups: Revised Childhood Immunization Schedule
Dr. Wallace reported on a focus group study by Drs. Sarah Clark and Gary Freed of the University of Michigan, to assess provider opinion on the harmonized and catch-up schedules. Four options of the latter were presented to them and questions were asked based on vaccination scenarios. Group discussion was based on the questions. Twelve focus groups at seven rural and urban sites were held, fairly equally divided between physicians and other health providers.

Findings: The colored schedule will survive multiple copying; the emphasis of a birth dose for hep B was clear; and the providers rely heavily on footnotes for providing and seeking advice. The harmonized schedule format was preferred for both schedules.

Other issues raised by the focus groups were the varying practices of provider vaccination; all stakeholders in vaccine administration (not just physicians) should be targeted when promoting vaccine schedules; that correlation of catch-up schedules with school requirements may vary by state (e.g., that for Hib and PCV). How this schedule is used perhaps should be reconsidered, and more formalized surveys done of its acceptability; and the prioritization of vaccines was raised when many shots are required. It is not certain that CDC wants to address this.

Combination Vaccines
The workgroup requested discussion of the options for presenting issues relevant to combination vaccines. This arises with every new harmonized schedule and will be increasingly beyond the address of footnotes. Options include an updated Website, as used during the vaccine shortage; an *MMWR* article or Notice to Readers. This relates mostly to the hep B doses in the first six months of life, and catch-up schedules (particularly when single-antigen vaccines are less used).

Some vehicle beyond the language in the General Recommendations is needed. For example, one member questioned the CDC's advice that "When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components; the minimum interval between doses is equal to the greatest interval of any of the individual vaccines." That is, if one vaccine has a minimum age of 6 months and another's is four months, then the minimum age of their combination

would be six months. Dr. Atkinson reported that this is a daily questions by phone. That sentence was inserted to prevent the administration of Comvax® at birth. To prevent such frequent questions and the necessity for separate ACIP recommendations, a clear communication to the field is needed. Dr. Modlin asked the harmonized schedule workgroup to review this question and that it be on the February meeting agenda for discussion.

Vaccine Shortage

Recommendations for Storage of Vaccines: Cold Chain Management
Dr. Wallace discussed the problem of immunization of children with vaccines stored outside the recommended storage temperature. This generally applies to frozen vaccines stored at insufficiently low temperatures.

Background. The success of the immunization program depends in part on cold chain maintenance, an integral part of preserving the integrity of vaccine products. Storage below the recommended range is an increasingly recognized problem, as well as above the range.

Issues. Public and private providers are seeking standardized education as the key to maintenance of the cold chain. Key topics for provider education include description and proper use of thermometers (failures or storage elsewhere than vaccine storage areas), standardized guidelines for temperature monitoring, and refrigerator/freezer recommendations. For example, sometimes the refrigerator is turned down to adhere to varicella vaccine requirements, but is too cold for other vaccines. Evidence suggests that vaccine storage below the recommended 2°-8° C range adversely affects vaccine potency, but there is limited literature on the impact on vaccines. Potency or physical chemical testing is limited and costly, and some tests require advanced laboratory methods.

Current guidance for the administration of mishandled vaccines calls for reimmunization of children unless serologic testing indicates a vaccine response. Vaccine providers want more specific guidance on response options including data on the risks/benefits of revaccination; the number of doses required for revaccination; guidelines for serologic testing, and guidelines for the temperature cutoff for "mishandled" vaccines.

ACIP guidance was requested in three areas:
1. Should resources be identified and prioritized to develop standard education on proper maintenance of cold chain vaccine storage? CDC, states, and manufacturers are all doing their own programs. This should be unified and standardized with partnerships to enhance this education.
2. Should resources be identified and prioritized to study the impact of freezing temperatures on vaccine potency, given the limitations of the antigens that can be tested, the utility of this information, and the cost?

3. Should guidelines for response to the administration of mishandled vaccines be expanded? Perhaps the current policy of encouraging revaccination over serologic studies is not always the best policy; incorporating data on efficacy and serologic responses to give providers a decision tree for this, and continued emphasis of state clinic on-site visits, would be helpful.

Discussion included:

- *Is there any evidence that any child has been harmed due to lack of vaccine efficacy?* There is none of any attributable increase in VPDs.
- *Is there any preclinical testing to identify an antigen's response to freezing (e.g., animal testing)?* The package inserts have detailed information on how to store. Vaccine stability is judged on the potency testing done, but the amount of data they might generate on deviations from the recommendations is very limited. That also would not address such problems as potency decrease due to power failures.
- *Has serologic testing to consider revaccination shown decreased titers?* That is not often done, but, although limited, there are a few such tests (e.g., a hep B test is easily available). The data on correlates of protection is based on titers measured 30 days after the primary series, and mishandling episodes are often heard about 6 months to years later. CDC does not now how to recommend doing that testing, or how to interpret the result if done, in view of such different time frames.
- One option might be to give a booster and test them 30 days later. In some episodes, providers and health departments have been reluctant to do that testing, thinking it a research project requiring an IRB. Testing for one vaccine also does not inform about other vaccines given. And in many cases, by the time the mishandling is discovered, a child would have aged out of the vaccination period.
- Pertussis or perhaps pneumococcal disease may be the only markers for this, being VPDs that would circulate even among children who have aged out of the vaccination recommendation. However, pertussis is also the hardest to test for potency.
- Another complication is that vaccines may be stored in different environments. Normally, CDC recommends evaluating each child individually, but there are no formal guidelines.
- *Can FDA request such data for new vaccines?* Dr. Midthun said that it is reasonable to require information supporting the conditions the manufacturer suggests for storage, but not to require more than that.
- It seems there is no way to know for sure if the vaccine is efficacious, so Option #1 seems the only solution, strengthening the ability of the provider to understand the need for storage under proper conditions. However, there may still be hundreds of children affected, requiring a substantial outlay of resources to revaccinate them. According to the present recommendations, that should be done even if the vaccine is found to be stored at 31°-32°, just above freezing.

- The workgroup's public health participants cited a huge number of calls from private providers. Revaccination is one option, but public trust issues also enter into the management of the cold chain. Doing the serologic testing after such mishandling and learning from it reinforces that trust and may inform future events. And, in view of the impending use of a new vaccine for health care workers and others, education needs to be emphasized on how to handle it. Finally, since standardization advances best practices, this will identify and promote existing best practices across the country.

Dr. Modlin summarized the committee's reluctance to deviate from the current recommendation. Onsite visits should be continued and perhaps increased. Providers should be advised to recall children to revaccinate them with all doses in question, according to age-appropriate doses, using the catch up schedule for most children. In the meantime, CDC should explore any opportunities of an Epi-Aid or other investigation of serologic responses as possible, although not systematic studies. Although the latter could identify if individual children are protected, they still could not be generalized to infer anything about the same vaccine frozen for a longer period of time.

Some programmatic flexibility is desirable; for example, a large practice may want to do a sub-sample testing (e.g. for pertussis or diphtheria as surrogate measures). Blanket revaccination will be a problem, and there is no wish to tie the hands of local/state health departments to do mass revaccination if 20-30 of those children are shown to have good antibody levels.

Experience and comments were provided:

- The Minnesota health department has had reports practices with histories of ~5 years of improper storage. This occurs on a fairly regular basis and more guidance is needed to more clearly define what constitutes mishandled vaccine: is it varying from the manufacturers' recommendation, or when it is frozen, or stored at an improper temperature, etc.? Clinics are looking for other options, and without good data, a strong position to support revaccination is weakened.
- One manufacturer had to recall a third of their varicella vaccine from providers in Philadelphia due to mishandling.
- Another factor is storage at higher than recommended temperatures for live replicating vaccines such as measles, mumps, rubella and varicella, perhaps CAV and perhaps vaccinia. Dr. Katz also recently dealt with a health department where several hundred children received hep B from a 5/8" needle instead of the one recommended, and a CDC staffer advised revaccinating with all three doses. That was unnecessary; one blood sample to test for hep B antibodies would have sufficed.
- Dr. Midthun reported that FDA often has data on storage at higher temperatures as part of an accelerated stability program, but that is suported by data on the intended storage temperatures. While potency test are good, they are not perfect instruments. They are generally used to characterize vaccine stored under

intended storage and administration conditions. It is not certain, especially for some products, if that would predict a vaccine's clinical performance.

- There are several issues to sort through. The issue with live vaccines is only its viability, which is easier to answer (e.g, smallpox vaccines can be heated to 100°C or frozen and still be stable). But the result of changes from freezing to liquid in subunit vaccines and proteins is more of a question. For example, IPV loses potency fairly rapidly. This needs to be understood, and supports a request that the manufacturers to do some research on this.
- Aside from costs and administrative problems, another issue is adverse events associated with potentially unnecessary revaccination. This is not a concern for many, but for example, revaccination with DTaP perhaps should not be done without additional information. And parents have asked if vaccine is still safe when frozen, and the data may not support a definitive answer.
- Dr. Phil Hosbach, of Aventis, noted that potency tests have changed over the years, moving from monkey potency model to an antigen model in chickens. Their correlation is not definitive, but they indicate if the vaccine has remained in the range in which the vaccines were tested. He asked what additional points for testing would be desired, noting that there are many; how long afterwards should the vaccine's stability be tested, and is it really relevant regarding potency of response? That is potentially costly research which would have to be passed along to the market. Aventis would recommend education first . Manufacturers are being aggressive in educating private physicians and health departments to use their best practice, such as Aventis' "vaccine inventory management solution program" protocol. They are also working with CDC on issues of storage and handling.
- One issue regarding damage from freezing is in the aluminum absorbed in vaccines. When frozen, the aluminum becomes unabsorbed and precipitates, degrading further with freeze cycles, but that is not apparent. And how CDC responds has effects. Although some practices decided not to do anything regardless of CDC advice; others revaccinated everyone, thousand of children. One health department that spent years reaching a hard-to-reach population to increase their coverage, then had this happen, and lost a lot of work done.
- A workgroup to consider where serology might be useful was suggested, since the guidelines say to revaccinate "unless serology is appropriate". At least an attempt should be made to develop a clinical tree for deviations (e.g., to indicate where serology may be useful after "x" number of doses, such as a mishandled fourth dose).
- New technologies that could be discussed include those pertinent to refrigeration and freezers (e.g,. continuous reading/recording of temperature), but those are not common. GSK reported shipping vaccine to distributors with an external device to indicate if the cold chain was breached (e.g., frozen) and allows returns/reshipment without question. That method could be used for the individual provider as well.
- The requirement to revaccinate for long retroactive periods could be a

disincentive to practices. An investment through the program is needed to help some practices acquire the new technology, or the problem will worsen. Private providers who just improved their refrigerator for varicella vaccine might be reluctant to do more unless supported by resources.

Agency Updates were provided:

Department of Defense (DOD). Dr. Diniega reported DOD's immunization program as underway. Vaccine deliveries are ahead of schedule. In addition to the ACIP's recommended categories, influenza vaccination is required for all active duty personnel. DOD also began hep B vaccination of all recruits in all services. Some preliminary data on anti-HBS collected by the Air Force indicate that about a third of recruits have anti-HBS, a sign of the success of state catch-up programs. Options for smallpox vaccination is still being discussed at the highest levels.

Food and Drug Administration (FDA). Dr. Midthun reported FDA's approval the previous month of a supplement for Aventis Pasteur's Fluzone.® It is available in single-dose presentations, not having a preservative. AvP also manufactures multidose vials with preservative for age 6 months and older. This month, FDA approved Prevnar® for immunization of infants/toddlers against otitis media, based on efficacy data for invasive disease. The protection is expected to be substantially lower against invasive disease by other serotypes and low for OM in general. FDA's Vaccine and Related Biological Products Advisory Committee (VRBPAC) expressed concerns about over- expectations of this vaccine and worded the indications accordingly.

Discussion included confirmation that AvP had recalled single-dose vials of Metamune® since some lots failed stability tests for the serogroup A that is endemic in some African and Eastern Mediterreanean areas. They will recommend revaccination for those traveling to those areas and are informing all the customers who have purchased it. This does not constitute a supply issue since it only applies to single-dose vials; multidose vials are still available.

National Institutes of Health (NIH). Dr. Bruce Gellin reported for Dr. Heilman that the 20th edition of the Jordan report would be released on the following week and is on the Web. An HSV glyocprotein vaccine was to be released on the following week as well. It poses implications for how the ACIP reviews vaccines, which he offered to discuss off-line.

National Vaccine Program Office (NVPO). Dr. Gellin will begin his appointment as the NVPO director on October 28. For *NVAC* , he reported the pandemic preparedness plan as in review by DHHS. It will be integrated with overlaps in bioterrorism preparedness. In anticipation of the need for pandemic influenza surge capacity, alternative approaches are being considered to influenza vaccine manufacturing (e.g., to evaluate cell-culture vaccines). He will meet with the vaccine manufacturers when he is

installed to explore those alternatives. Regarding vaccine supply issues, the GAO has issued a report and NVAC is finalizing its report, including stockpile issues. The CDC strategic plan includes the latter, and they asked NVAC to create a workgroup to advise on that. The Unmet Needs cycle has begun again, and the polio laboratory certification surveillance activity is ongoing.

National Vaccine Injury Compensation Program (NVICP). Dr. Geoff Evans reported and provided the VICP's monthly statistics. This year, a record of claims were received (956), many focused on thimerosal injury. Claims on a small number of "new" vaccines have been received, such as those alleging intussusception from rotavirus vaccine, as well as 87 claims on DTaP. There are six pre-1988 claims remaining. The average time for adjudication of new vaccines is about 3 years, except for hep B. That is judged on a causation basis and relevant research has only recently been done. A total of $1.4 billion has been paid to date and $1.8 billion remains in the Trust fund. This (August 26) summer the final rule was published to add intussusception as a second category under rotavirus vaccine, with a time interval of 30 days from vaccination for onset. Pneumococcal vaccines were also added as a separate category on the vaccine injury table. They have been covered since 1999.

Thimerosal litigation includes 134 individual class action suits against manufacturers of vaccines containing thimerosal were filed in 20 states, in some cases suing both the administration and the distributor. They are seeking lifetime medical monitoring for currently uninjured children to detect any effects in the future. Some of the suits are not only on the child's behalf, but also the parents, for loss of companionship, consortium, etc., factors not covered by the law.

The National Childhood Vaccine Injury Act of 1986 (NCVIC) Act requires petitions to be filed first with the VICP. These thimerosal suits try to get around that by filing claims for <$1000 and by claiming that these are not "vaccine-related" injuries, since the Act excludes coverage for any vaccine containing an "adulterant" or a "contaminant". Both DHHS and the DOJ have asserted that the claims should go first to the VICP, but the decisions on the preliminary motions have been mixed. Some found the Act to completely bar thimerosal claims while others gave the benefit of the doubt; and since the derivative claims by the parents are not covered by the Act, the are proceeding. AvP called these suits the "greatest threat to the future vaccine supply."

A dramatic increase in FY2002 claims were filed, 75% of them alleging thimerosal injury and nearly all providing little or no medical record information. Many allege injury from vaccines given outside the three-year statute of limitations. Those will be dismissed and enter the tort system. The vaccine court issued an autism order in July 2002 with a schedule for discovery/hearings. Many of the claimants, after the 240-day deadline, may opt out of the program and pursue litigation, having fulfilled the requirement to first file with the VICP.

Legislation: The "National Vaccine Injury Compensation Program Improvement Act of 2002" (HR 3741) is a bipartisan bill by Congressmen Burton and Waxman. This proposed bill is controversial. It proposes a 2-year window to allow claims on vaccines administered since 1988 by petitioners unaware of the program or whose claims were dismissed due to late filing. The 14-year retroactive period for claims is not favored by the administration. A similar bill by Frist/Greenwood of the House has no retroactivity and only covers costs (not the attorney fees include in the Burton/Waxman bill), and begins to address some of the loopholes in the law with clearer definitions. No action is probable this year, but is something is hoped for next year. A fourth Burton panel on how to improve VICP process was held.

A very instructive VICP strategic planning retreat was held in October in Bethesda with over 50 stakeholders (industry, plaintiffs, parents, consumers, nongovernmental organizations, and medical organizations, etc.). They reacted to a draft strategic plan formulated by a workgroup. They frankly discussed the issues and challenges facing the VICP and held a forum for processing potential solutions. This will be presented to the ACCV in December and described to the ACIP in February.

National Center for Infectious Diseases (NCID). Dr. Alison Mawle requested agenda time at the next ACIP meeting for a presentation by Dr. Cindy Whitney on meningitis among people with cochlear implants. These were potentially linked in a report to CDC in July. Over 90 cases are known worldwide including 53 in the U.S., including five deaths. Three companies producing cochlear implants are involved. The age range of the cases is from 18 months to 84 years, but most are <7 years old. Etiology is known for 23 cases, and was streptococcus or e-coli; there was no meningococcus. The cases did not occur right after the implant, but as long as six years later. The National Center for Birth Defects and Developmental Disabilities has taken the lead on this investigation. A multistate EpiAid study of case finding is investigating incidence rates by device type and is doing a case-control study for risk factors. Interim recommendations have been issued defining children with these implants as a group to be vaccinated as at high risk. A longer term plan will assess meningitis risk among deaf persons without implants. A wealth of related information is spotlighted on the CDC Website.

Dr. Whitney has also presented data to the ICAC on invasive pneumococcal disease rates gathered from CDC's Active Bacterial Core (ABC) surveillance sites. The average 2001 rates compared to the 1998-99 rates, reflect a nice drop (~60%) in children <5 years, as well in the 22-39 year old adult group (32%) and in those aged 65 and older (18%). This is presumed to be attributable to herd immunity.
Discussion included:

- *Has there been any Type B haemophilus influenza meningitis among children with cochlear implants?* One case occurred in a child not immunized with Hib, and one pneumococcal case, but most of these children are older than the recommended age for pneumococcal vaccination. One case was a possible vaccine failure. Dr. Modlin thought it likely that this group will have to be added

as at high risk.

- *What is the pathophysiology in the cochlear implants?* Dr. Modlin understood that the process involves a likelihood of increased communication between the inner ear and the subretinoid space. Children with basal skull fractures, and children receiving CFS shots have an increased risk of meningococcus, probably from the same organisms. One question is whether congenital birth defects (e.g., deafness) may lead to high risk. Dr. Modlin requested that some language be crafted supplementing the meningococcal statement, to add children in this high risk group.

National Immunization Program (NIP). Dr. Orenstein welcomed Dr. Natalie Smith, a former ACIP member, as Deputy Director of the NIP. In July, the NIP announced the Racial and Ethnic Adult Disparities Immunization Initiative (READII). This is an effort to successfully reduce substantial gaps in pneumococcal and influenza vaccination coverage among African American and Hispanic populations. This program focuses on those aged ≥65 years. There is a state/local planning effort as well as an implementation effort with careful evaluation. This and the next season are key intervention seasons.

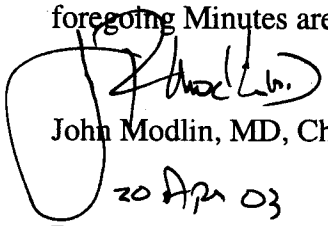
The third Immunization Registry Conference will be held in Philadelphia between October 28-30. In the next few months, a contract will be signed to develop a strategic plan for the vaccine stockpile. Completion of the conference report is hoped in late winter or spring and will include, with substantial manufacturer input, a time table for purchase, the quantity and form, delivery and location of storage, and procedures for implementation and communication, as well as how to better measure state inventories.

The vaccine supply is normal except for pneumococcal conjugate vaccine, where shortages are expected to continue at least through this calendar year. Part of the supply issues relate to vaccine development financing for the public and private sectors. The related IOM study committee report should be issued in 2003.

Finally, he reported NIP work with the NCHS to provide more access by researchers to the VSD data. This will include confidentiality protections.

Public comment was solicited. William Philips and Steven Allred had registered to speak but had departed. Therefore, with no further comment and thanks to the staff and committee, Dr. Modlin adjourned the meeting at 3:15 p.m.

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



John Modlin, MD, Chair

20 Apr 03

Date