DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 24-26, 2009
Atlanta, Georgia

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Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
AGS	American Geriatrics Society
ATP	According to Protocol
BLA	Biologics License Application
BOI	Burden of Illness
CAIS	Childhood / Adolescent Immunization Schedule
CAIV-T	Cold-Adapted Influenza Vaccine
CCID	Coordinating Center for Infectious Diseases
CDC	Centers for Disease Control and Prevention
CID	Committee on Infectious Diseases (CID) of the American Academy of Pediatrics (AAP)
CIN	Cervical Intraepithelial Neoplasia
CMS	Centers for Medicare and Medicaid Services
DBD	Division of Bacterial Diseases (of NCIRD)
DHQP	Division of Healthcare Quality Promotion
DoD	Department of Defense
DSMBs	Data Safety Monitoring Boards
DSTDP	Division of Sexually Transmitted Diseases Prevention [of NCHHSTP]
DVA	Department of Veterans Affairs
DVBID	Division of Vector-Borne Infectious Diseases
DVD	Division of Viral Diseases (of NCIRD)
DVH	Division of Viral Hepatitis (of NCIRD)
DVRD	Division of Viral and Rickettsial Diseases
EIS	Epidemic Intelligence Service
EMR	Electronic Medical Records
FDA	Food and Drug Administration
GBS	Guillain Barré Syndrome
GID	Global Immunization Division
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GSK	GlaxoSmithKline
HICPAC	Healthcare Infection Control Practices Advisory Committee
HepA	Hepatitis A
HepB	Hepatitis B
HHS	Department of Health and Human Services
Hib	*Haemophilus influenzae B*
HMO	Health Maintenance Organization
HPV	Human Papillomavirus
HRIG	Human Rabies Immune Globulin
HRSA	Health Resources and Services Administration
ID	Influenza Division (of NCIRD)
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	Indian Health Services
ILI	Influenza-Like Illness
IND	Investigational New Drug

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IOM	Institute of Medicine
ISD	Immunization Services Division (of NCIRD)
ISO	Immunization Safety Office (of CDC/OD/Office of the Chief Science Officer)
ITT	Intent to Treat
MCO	Managed Care Organization
MenACYW-CRM	Meningococcal Conjugate Vaccine
MCV4	Meningococcal Conjugate Vaccine
MMRV	Measles, Mumps, Rubella, Varicella
MMWR	*Morbidity and Mortality Weekly Report*
mOPV1	Monovalent Polio Vaccine Type 1
NACCHO	National Association of County and City Health Officials
NACI	Canadian National Advisory Committee on Immunizations
NCHHSTP	National Center for HIV, Hepatitis, STD, and TB Prevention (of CDC/CCID)
NCHS	National Center for Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NCPDCID	National Center for Preparedness, Detection, and Control of Infectious Diseases
NCZVED	National Center for Zoonotic, Vector-Borne, and Enteric Diseases (of CDC/CCID)
NIH	National Institutes of Health
NIS	National Immunization Survey
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OCSO	Office of the Chief Science Officer
OD	Office of the Director (of CDC)
P&I	Pneumonia and Influenza
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PhRMA	Pharmaceutical Research Manufacturers of America
RCA	Rapid Cycle Analysis
SAGE	Strategic Advisory Group of Experts
sBLA	Supplemental Biologics License Application
SHEA	Society for Healthcare Epidemiology of America
SIVAC	Supporting Immunization and Vaccine Advisory Committee
SMEs	Subject Matter Experts
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VSD	Vaccine Safety Datalink
VZV	Varicella-Zoster Virus
WG	Work Group
WHO	World Health Organization

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MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia
June 24-26, 2009

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, June 24, 2009			
8:00	**Welcome & Introductions**		
	▪ Opening remarks		Dr. Thomas R. Frieden (Director, CDC and Administrator, ATSDR)
	▪ Introductions and administrative announcements		Dr. Dale Morse (Chair, ACIP) Dr. Larry Pickering (Executive Secretary, ACIP; CDC)
8:30	**General Recommendations**		
	▪ Introduction	Information	Dr. Ciro Sumaya (ACIP, WG Chair)
	▪ Combination vaccines	Vote	Dr. Andrew Kroger (CDC/CCID/NCIRD/ISD)
	▪ Special situations — information & discussion	Vote	
	▪ Vaccination records	Vote	
9:40	**Rabies Vaccine**		
	▪ Introduction	Information	Dr. Paul Cieslak (ACIP, WG Chair)
	▪ Reduced rabies vaccine schedule (post-exposure prophylaxis)	Discussion Vote	Dr. Charles Rupprecht (CDC/CCID/NCZVED/DVRD)
10:55	*Break*		
11:25	**Poliovirus Vaccine**		
	▪ Introduction		Dr. Lance Chilton (ACIP, WG Chair)
	▪ Updated recommendations for routine poliovirus immunization	Information Discussion Vote	Dr. Gregory Wallace (CDC/CCID/NCIRD/DVD)
	▪ Update VFC vote	VFC Vote	Dr. Jeanne Santoli (CDC/CCID/NCIRD/ISD)
11:55	**Measles, Mumps and Rubella Vaccine**		
	▪ Introduction		Ms. Kris Ehresmann (ACIP, WG Chair)
	▪ Proposed changes to current evidence of immunity requirements for MMR vaccination for healthcare personnel	Information Discussion Vote	Dr. Kathleen Gallagher (CDC/CCID/NCIRD/DVD)
12:30	*Lunch*		

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1:30	**Human Papillomavirus (HPV) Vaccines**		
	▪ Introduction		Dr. Janet Englund (ACIP, WG Chair)
	▪ Bivalent HPV vaccine	Information	Dr. Gary Dubin (GSK)
	▪ Quadrivalent HPV vaccine		Dr. Rick Haupt (Merck)
	▪ Cost-effectiveness of male vaccination	and	Dr. Jane Kim (Harvard University)
	▪ Overview of cost-effectiveness models of male vaccination	Discussion	Dr. Harrell Chesson (CDC/CCID/NCHHSTP/DSTDP)
	▪ Issues and potential recommendation options: vaccination of males		Dr. Lauri Markowitz (CDC/CCID/NCHHSTP/DSTDP)
3:00	**Meningococcal Conjugate Vaccine (MCV4)**		
	▪ Overview of Work Group activities	Information	Dr. Carol Baker (ACIP, WG Chair)
	▪ Update: new meningococcal conjugate vaccine (MenACYW-CRM)	Information	Dr. Peter Dull (Novartis Vaccines)
	▪ Estimate of Effectiveness of Meningococcal Conjugate Vaccine (MCV4)	Information Discussion	Ms. Jessica MacNeil (CDC/CCID/NCIRD/DBD)
	▪ Recommendations for MCV4 revaccination for persons at prolonged increased risk for meningococcal Disease	Information Discussion Vote	Dr. Amanda Cohn (CDC/CCID/NCIRD/DBD)
	▪ Update: VFC vote	VFC Vote	Dr. Jeanne Santoli (CDC/CCID/NCIRD/ISD)

Wednesday June 24, 2009 – continued

4:00	*break*		
4:15	**Japanese Encephalitis (JE) Vaccine**		
	▪ Introduction		Dr. Paul Cieslak (ACIP, WG Chair)
	▪ Revised JE vaccine recommendations	Information Discussion Vote	Dr. Marc Fischer (CDC/CCID/NCZVED/DVBID)
5:00	**Hepatitis Vaccines**		
	▪ Introduction		Dr. Mark Sawyer (ACIP, WG Chair)
	▪ Hepatitis B in long-term care residents and the role of vaccination	Information Discussion	Dr. Nicola Thompson (CDC/CCID/NCHHSTP/DVH)
5:30	**Yellow Fever (YF) Vaccine**		
	▪ Introduction: Yellow Fever Vaccine Work Group		Dr. Carol Baker (ACIP, WG Chair)
	▪ Proposed updates to the ACIP YF vaccine recommendations	Information Discussion	Dr. Erin Staples (CDC/CCID/NCZVED/DVBID)
5:45	**Public Comment**		
6:00	**Adjourn**		

Thursday, June 25, 2009

8:00	**Unfinished Business**		Dr. Dale Morse (Chair, ACIP)
8:30	**Agency Updates (CDC, CMS, DOD, DVA, FDA, HRSA, IHS, NIH, NVAC, NVPO)**	Information	ACIP *Ex Officio* Members

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8:45	***Haemophilus influenzae b* (Hib) Vaccine**		
	▪ Introduction: overview of session	Information	Dr. Abigail Shefer (CDC/CCID/NCIRD/ISD)
	▪ GSK monovalent Hib vaccine	Information	Dr. Remon Abu-Elazeed (GSK)
	▪ Hib surveillance	Information	Dr. Michael Jackson (CDC/CCID/NCIRD/DBD)
	▪ Vaccine supply	Information	Dr. Jeanne Santoli (CDC/CCID/NCIRD/ISD)
	▪ Hib vaccine implementation plan	Information Discussion	Dr. Abigail Shefer (CDC/CCID/NCIRD/ISD)
9:45	**Vaccine Supply**	Information Discussion	Dr. Jeanne Santoli (CDC/CCID/NCIRD/ISD)
10:00	*Break*		
10:30	**Measles-Mumps-Rubella-Varicella Vaccine Safety**		
	▪ Introduction	Information Discussion	Dr. Jonathan Temte (ACIP, WG Chair)
	▪ Parental perceptions of MMRV vaccine	Information Discussion	Mr. Alan Janssen (CDC/CCID/NCIRD/ISD)
	▪ Evaluation of MMRV and Febrile seizures: VSD expanded chart review study	Information Discussion	Dr. Nicola Klein, Northern California Kaiser Permanente
	▪ Synthesis of safety evidence for MMRV vaccine and febrile seizure risk	Information Discussion	Dr. Karen Broder (CDC/CCID/NCPDCID/DHQP/ISO)
	▪ Synthesis of analytic framework for MMRV vaccine policy options; options for recommendations	Information Discussion Vote	Dr. Mona Marin (CDC/CCID/NCIRD/DVD)
	▪ Update VFC resolution	VFC Vote	Dr. Jeanne Santoli (CDC/CCID/NCIRD/ISD)
12:30	*Lunch*		

Thursday June 25, 2009 - continued

1:45	**Role of Pharmacists in Vaccine Administration**	Information Discussion	Dr. Stephan Foster (ACIP Liaison American Pharmacists Association)
2 :00	**Influenza**		
	▪ Session introduction	Information	Dr. Kathy Neuzil (ACIP, WG Chair)
	▪ Session overview	Information	Dr. Anthony Fiore (CDC/CCID/NCIRD/ID)
	▪ 2008-09 influenza epidemiology: seasonal and novel influenza A (H1N1)	Information Discussion	Dr. Lyn Finelli (CDC/CCID/NCIRD/ID)
3:15	*break*		
3:30	**Influenza**		
	▪ Influenza antiviral medications	Information Discussion Vote	Dr. Anthony Fiore (CDC/CCID/NCIRD/ID)
	▪ Novel influenza A (H1N1) vaccine development and progress	Information Discussion	Dr. Robin Robinson (BARDA) Dr. Norman Baylor (FDA) Dr. Linda Lambert (NIH) Dr. Bruce Gellin (NVPO)
	▪ Review of existing vaccine prioritization guidance	Information	Dr. Tom Shimabukuro (CDC/CCID/NCIRD/ISD)

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5:30 **Public Comment**

5:45 **Adjourn**

Friday, June 26, 2009

8:00 **Novel Influenza A (H1N1)**

▪ Virology and immunology		Dr. Nancy Cox (CDC/CCID/NCIRD/ID)
▪ Vaccine program implementation plans	Information	Dr. Pascale Wortley (CDC/CCID/NCIRD/ISD)
▪ Review of planned vaccine effectiveness studies	and	Dr. David Shay (CDC/CCID/NCIRD/ID)
	Discussion	Dr. Jose Sanchez (DOD)
▪ Review of influenza vaccine safety monitoring plans		Dr. Cindy Weinbaum (CDC/CCID/NCPDCID/DHQP/ISO)
▪ Summary of issues		Dr. Anthony Fiore (CDC/CCID/NCIRD/ID)
		Dr. Kathy Neuzil (ACIP, WG Chair)

10:00 *Break*

10:30 **Pneumococcal Vaccines**

▪ Overview of session	Information	Dr. Michael Marcy (ACIP, WG Chair)
▪ Planning for use of PPSV23 to prevent novel influenza A (H1N1) - associated pneumococcal disease	Discussion	Dr. Matthew Moore (CDC/CCID/NCIRD/DBD)
▪ Invasive pneumococcal disease burden caused by PCV13 serotypes	Information and	Dr. Pekka Nuorti (CDC/CCID/NCIRD/DBD)
▪ Options for PCV13 catch-up immunization strategies	Discussion	"
▪ Update on investigational 13- valent pneumococcal vaccine (PCV13)	Information	Dr. Peter Paradiso (Wyeth)
▪ Public health and economic impact of PCV13	Information	Dr. David Strutton (Wyeth)

12:30 **Public Comment**

12:45 **Adjourn**

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June 24, 2009

Welcome & Introductions

Dr. Tom Frieden
Director, Centers for Disease Control and Prevention
Administrator, Agency for Toxic Substances and Disease Registry

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Dale Morse
Chair, ACIP

Dr. Pickering called the meeting to order, introducing with great pleasure Dr. Tom Frieden, the newly appointed Director of the United States (US) Centers for Disease Control and Prevention (CDC) and Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR). Prior to having assumed his post at CDC just 16 days before this meeting, Dr. Frieden served as Commissioner of the New York City Department of Health and Mental Hygiene, a position he held for 8 ½ years. During his tenure, important advances in New York City were made in reduction in cigarette smoking; chronic disease control, including diabetes mellitus and obesity; and enhancement of the largest community health records project in the country. Dr. Frieden is a physician with training in internal medicine, infectious diseases, public health, and epidemiology, and is specifically known for his expertise in tuberculosis control. Dr. Frieden began his career at CDC as an Epidemic Intelligence Service (EIS) Officer stationed at the New York City Health Department. Dr. Frieden went on to serve as director of the Bureau of Tuberculosis Control and Assistant Commissioner for the New York City Health Department. In that role, he led a program that rapidly reduced tuberculosis, including a reduction in cases of multi-drug resistant tuberculosis by about 80%. Dr. Frieden then worked for 5 years on assignment to the World Health Organization (WHO) in India where he assisted with national tuberculosis control efforts. The program in India has now treated more than 10 million patients and saved more than 1 million lives. Dr. Pickering stressed that the ACIP members, the 26 liaison organizations, the 8 *ex officio* members, and members of the audience (including international delegates from Japan and the Agency of Preventive Medicine in Paris, France) were thrilled to welcome Dr. Frieden to the June 2009 meeting of the ACIP.

Dr. Frieden expressed his gratitude, pointing out that it had thus far been a great 2 ½ weeks and that he wished he could stay for the ACIP meeting all day. The first thing he learned about being the CDC Director was that it would have been very helpful if he could have cloned himself first, because he was supposed to be in three places at once most of the time. He said he was delighted to join the meeting for at least a short time to recognize the terrific and incredibly important work that ACIP does. Sometimes, when close to a process, it is possible to lose sight of the big picture in terms of the importance of ACIP's work, particularly as the country moves forward with health reform under the current administration. The evidence base and effectiveness of vaccination is prominent in the understanding and rigor of groups such as ACIP. In fact, ACIP is a model for evidence-based decision making—a model that is well worth understanding and emulating elsewhere in the health system. In addition, Dr. Frieden recognized ACIP for 45 years of outstanding leadership in immunization policy. In many ways,

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vaccines are not only one of the great success stories of public health, but also hold the potential to have the ultimate in sustainability, which is what eradication represents (e.g., smallpox, and hopefully soon polio). ACIP is the prototype for immunization committees in other countries, and it is hoped that evidence-based vaccine immunization policy will become the norm in the US and globally.

There is much in the news in terms of vaccination and influenza. Novel H1N1 presents major challenges in spite of enormous thinking and preparation for pandemic influenza. During this meeting, ACIP was to hear information presented on H1N1, and very important immunization decisions would need to be made in near real-time over the coming days, weeks, and months as they began to learn more about the pattern of infection, disease, and severity of illness; transmission / rapidity of transmission; and availability of vaccines. In addition, it would be essential to continue with the shared responsibility and understanding that the government, health providers, individual patients, and others play key roles in the H1N1 effort.

Not only do vaccines effectively prevent disease and save money, but also they are very effective at reducing racial and ethnic disparities. Vaccines are available to all, they prevent illness in all, and they have a great ability to make a considerable difference in health status. At the same time, a number of issues remain to be understood and studied Also known is that the Vaccines for Children Program (VFC) relies heavily upon ACIP, is part of the ACIP meetings, is a critically important component of the US healthcare landscape, and offers important lessons learned as efforts are made to improve vaccinations for children, adolescents, and adults.

Dr. Frieden concluded that he primarily wished to thank ACIP for what they do; the attention they give to challenging issues, many of which involve complex reviews of data; their valuable questions and input, and their suggestions / recommendations. It is imperative to focus on two issues: 1) building the data: rigorously assessing what the data show and where that leads them in terms of recommendations, taking into consideration the costs and benefits; and 2) transparency: all deliberations and other information about vaccine policy must be completely open and completely transparent. CDC and ACIP have a bond of trust with the American public, and it is their shared responsibility to respect the intelligence, integrity, and caring of parents, healthcare workers, and others to develop health-based recommendations. People must clearly understand how decisions are reached. That is the most prudent way to make the best possible decisions. In closing, Dr. Frieden thanked the ACIP membership and saluted them for their excellent work in achieving evidence-based public health policy.

Dr. Morse thanked Dr. Frieden for addressing ACIP, stressing that it meant a great deal to have the support of the CDC Director and for him to take time to deliver the keynote address. As a fellow New Yorker who was glad to see Dr. Frieden in attendance, Dr. Morse said it was New York's loss and CDC's and the nation's gain.

Dr. Pickering recognized several people throughout the room who were to be in attendance throughout the duration of the ACIP meeting to assist with various meeting functions: Antonette Hill, Committee Management Specialist for ACIP, Natalie Greene, Tamara Miller, Tanya Lennon, Suzette Law, and Cindy Fowler. He also indicated that boxed lunches were to be provided for each of the three days of the meeting in the hallway outside of the auditorium for a cost of $10. Coffee and tea were also to be available for the duration of the meeting.

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Handouts of all presentations were distributed to the ACIP members and were made available for members of the public each day on the tables outside of the auditorium. Slides presented for this meeting will be posted on the ACIP website, generally within a week of the end of the meeting, while the minutes of the meeting will be posted within 90 days of the termination of the meeting.

Members of the press interested in conducting interviews with ACIP members were instructed to contact Tom Skinner for his assistance in arranging interviews, and the press table located in the auditorium was pointed.

Recognizing the extent of the interest in this particular meeting, two additional rooms were reserved (247 / 248) as overflow space for additional seating. These rooms are located across the hall from the auditorium where the meeting could be viewed in real-time via audio visual all three days.

Dr. Pickering recognized and welcomed the following international visitors: Dr. Kamel Senouci, Director of the Supporting Immunization and Vaccine Advisory Committee (SIVAC) Initiative of the Agence de Médicine Préventive, Institut Pasteur, Paris France. This program aims at contributing to the development of national immunization technical advisory groups in six resource-poor countries in Africa and six in Asia. These committees will help national health authorities to establish vaccination advisory groups adapted to their needs and to introduce new vaccines in these areas. This project was funded by a $10 million grant from the Bill & Melinda Gates Foundation, and will be conducted in partnership with the International Vaccine Institute in Seoul, Korea and in cooperation with the World Health Organization (WHO) and its regional and national offices. Dr. Pickering also extended gratitude to three visitors from Japan led by Dr. Nobuhiko Okabe, the Director of the Infectious Disease Surveillance Center at the National Institute of Infectious Diseases in Tokyo, Japan. They came to participate in the meeting of ACIP to observe the US process of immunization policy development, which reflects international reach.

Also in attendance was new liaison representative Dr. Alexis Elward from Washington University School of Medicine in St. Louis, who was selected to represent the Healthcare Infection Control Practices Advisory Committee (HICPAC) as its liaison representative to ACIP.
All ACIP members were present with the exception of Dr. Susan Lett who had a previous commitment on Wednesday and Thursday, but attended Friday and was connected by telephone for certain sessions. Ms. Amy Groom attended on behalf of Dr. James Cheek from the Indian Health Services (IHS) who was unable to attend. Dr. Sandy Fryhofer attended on behalf of Dr. Greg Poland from the American College of Physicians (ACP) who was unable to attend. Dr. Mark Notalski attended on behalf of Dr. Tamara Lewis from American's Health Insurance Plan (AHIP) who was unable to attend. Dr. David Salisbury from the Department of Health United Kingdom was unable to attend.

To avoid interruptions during the meeting, those present were instructed to conduct all business not directly related to discussions of ACIP in the hallways to avoid disruptions to people in the audience. Attendees were also instructed to turn off all cell phones or place them in the vibrate mode to avoid disruption.

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The ACIP home page was shown on the screen. The url is: **www.cdc.gov/vaccines/recs/acip/** This website is updated at frequent intervals with current versions of the meeting agenda, minutes, presentations, and other information. Other useful and interesting and useful were also shown, which included the following:

Vaccine Safety: www.cdc.gov/vaccinesafety/
Vaccine Abbreviations: http://www.cdc.gov/vaccines/recs/acip/vac-abbrev.htm
Vaccine Scheduler: http://www.cdc.gov/vaccines/recs/scheduler/catchup.htm

Given that the meeting could not begin unless a quorum of members was present, all appointed members were asked to return from breaks and lunch in a timely manner to participate in the meeting. Dr. Pickering stressed the importance of this due to the record number of votes scheduled during this meeting (n=8).

The ACIP charter gives the Executive Secretary, or his or her designee, the authority to temporarily designate *ex-officio* members as voting members. This occurs only when there are fewer than 8 appointed members available or qualified to vote due to potential conflicts of interest (COIs). *Ex-officio* members are requested formally to vote when necessary and to disclose any potential conflicts of interest if, indeed, they were going to vote.

Topics presented at the ACIP meeting include open discussion with time reserved for public comment. In certain circumstances, a formal comment period may be scheduled during the deliberations of a specific agenda item rather than at the end of the day. Comments from the public may be received during open discussions depending upon time constraints. Those who planned to make public comments were instructed to visit the registration table at the rear of the auditorium to have Antonette Hill record their name and provide information on the process. Those who registered to make public comments prior to the meeting were instructed to with Ms. Hill to verify that their names were listed and to receive any additional information.

Microphones were placed at each end of the committee tables for the members of the audience to use when they addressed the committee. Those planning to make comments were instructed to identify themselves and their organization before making their comments.

As had occurred in previous ACIP meetings, the committee discussed topics related to vaccine safety and engaged in a discussion about of the supply and availability of recently licensed and approved vaccines.

With regard to disclosure, the goal in appointing members to the ACIP is to achieve the greatest level of expertise while minimizing the potential for actual or perceived conflicts of interest. To summarize conflict of interest provisions applicable to the ACIP, as noted in the ACIP policies and procedures manual, members of the ACIP agree to forego participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance the members' expertise while serving on the committee, CDC has issued limited conflict of interest waivers. Members who conduct vaccine clinical trials or who serve on data safety monitoring boards may serve as consultants to present to the committee on matters related to those specific vaccines; however, they are prohibited from participating in deliberations or committee votes on issues related to those specific vaccines. Regarding other vaccines of the affected company, a member may participate in a discussion with a proviso that he or she abstains on all votes related to that vaccine company.

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The ACIP Secretariat solicits applications throughout the year for candidates to serve on ACIP. Detailed instructions for submissions of name of potential candidates may be found on the ACIP website. Applications may be submitted at any time of the year. Materials in support of the next cycle of applications for ACIP membership (beginning July 2010) are due no later than November 15, 2009. ACIP meeting registration dates are established for security reasons. The CDC complex is a secured environment and pre-registration for meetings is posted on the ACIP website. This pre-registration is time-sensitive for international visitors since the Office of Security and Emergency Preparedness is required to pre-approve access for all non-US citizens visiting CDC facilities. The next ACIP meeting is October 21-22, 2009.

Dr. Morse expressed CDC and ACIP's appreciation to Dr. Robert Beck who was cycling off the ACIP committee following four years of dedicated service as a consumer representative. Mr. Beck's previous top leadership positions with autism groups, and in the creation of a new national early childhood development screening intervention program that was adopted by the CDC and the Department of Education has proven to be of tremendous benefit to ACIP for four years. While serving on the ACIP panel, Mr. Beck chaired the Evidence-Based Recommendation Work Group and participated in the Anthrax, HPV, Japanese Encephalitis (JE) and other vaccine work groups. More important have been his major contributions to ACIP's deliberations where he has provided a unique perspective, asked probing questions, provided keen insights, and kept everyone well-rooted in the real world. With gratitude from CDC and ACIP, Mr. Beck was presented with a certificate and an award made of glass to represent what he had added to the transparency and clarity of ACIP's work.

Mr. Beck said he was absolutely overwhelmed by the ACIP experience over the past four years, and by having the opportunity and privilege to work with some of the most wonderful people he had ever met. He stressed how talented each member of the committee is, and acknowledged the incredible amount of time and effort each of them contributes. Even after 20 plus years of being in and out of government, until joining ACIP, he had no idea how much work they do and how important the individuals are who make up the committee. Their work benefits the public health of the entire nation. He concluded that it had truly been his privilege to be a member, and that he had been deeply touched by each member in the nicest way. He wished them all the very best of continued success.

The following conflicts of interest were declared:

Dr. Janet Englund: sanofi pasteur; MedImmune; Novartis Pharmaceuticals, ADMA Biologics, Inc.

Dr. Cody Meissner: Payments are made to Tufts Medical Center from Wyeth and MedImmune

The remainder of the members declared no conflicts.

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General Recommendations

Overview

Ciro Sumaya, MD, MPH
ACIP Chair

Dr. Sumaya pointed out that the general recommendations are published in the *Morbidity and Mortality Weekly Report (MMWR)* at approximately three- to five-year intervals. General recommendations addresses immunization issues relevant to all vaccines, and topics ad hoc that cannot be attributed to a single vaccine. General recommendations are directed to providers who are administering many different vaccines every day, and who come from variable backgrounds (e.g., physicians, nurse-practitioners, nurses, pharmacists, medical assistants). Thus, the recommendations are made as user-friendly as possible.

During this session, information was presented on combination vaccines, special situations, and vaccination records. There are complex issues that must be addressed with respect to combination vaccinations. Working from the last iteration of the general recommendations, the General Recommendations Work Group refined, reviewed, and made some changes. Special situations were reviewed from an updating / editing standpoint, with few changes. The vaccine records section, a very important and fast moving field, was edited and updated.

For the next session of ACIP in October 2009, the final recommendations on altered immune-competence will be reviewed. There remain some outstanding issues in this area, particularly with respect to transplant patients. In addition, the vaccination programs will be reviewed for infants and children, adolescents, and adults. A final vote on the entire document is anticipated during the October 2009 meeting. The document will then proceed to the CDC clearance, with an expected publication date of April 2010.

Andrew Kroger, MD, MPH
CDC / NCIRD / ISD / EIPB

Turning first to combination vaccines, Dr. Kroger indicated that the general recommendations language is derived from a 1999 specific *Morbidity and Mortality Weekly Report (MMWR)* on combination vaccines for childhood immunization that describes what combination vaccines are, states a preference for the use of combination vaccines, and offers supplementary guidance on issues like the interchangeability of products and extra vaccination doses. It has been 10 years since that specific statement was published, since which the environment has changed. There are many new vaccines, and many new combination vaccines. It will be important to define what a combination vaccine is definitively. New reactogenicity data with one combination vaccine (e.g., MMRV) suggest a higher risk of febrile seizures with the combination product compared to single component administration.

Originally a work group dedicated solely to combination vaccines was constituted to address the fact that the 10-year old recommendations must be updated. This workgroup initially focused on specific products such as Pentacel® and KINRIX™. It was clear from the outset that a more general perspective was necessary, not only because of the issues with the MMRV vaccine

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specifically, but also because any discussion of combination vaccines brings in general immunization topics like simultaneous vaccination, vaccine administration, and other types of programmatic issues. It was deemed necessary to deal with these issues, which is when the task fell to the General Recommendations Work Group. A manuscript was drafted and reviewed by four members of the original Combination Vaccines Work Group prior to being discussed by the General Recommendations Work Group, a draft of which was provided to the ACIP members in their briefing documents. On page 2, line 6, a combination vaccination is defined as "a product whose components can be equally divided into independently available routine vaccines."

The draft also contains Table 5 which is located at the end of the Combination Vaccine section. This table lists the combination vaccines, which include: COMVAX™, TriHIBit ®, Twinrix®, PEDIARIX™, ProQuad ®, KINRIX™ and Pentacel®. The definition would exclude a laundry list of other vaccines (e.g., HepB, RV, TT, DT, DTaP, Hib, IPV, PCV7, MMR, Var, HepA, TIV, LAIV, MCV4, Tdap, Td, HPV, PSV4, PPSV23, ZOS, Ty21A, YF, JE, Typhim VI, Rabies, BCG, Anthrax, and Smallpox. Vaccines such as inactivated polio virus vaccine, IPV, pneumococcal conjugate vaccine, PCV7, MMR, Td, and TDaP are excluded from the definition even though they do consist of multiple antigens for different strains of the various microbes or the antigens. For these, separate components are not routinely available. The Tdap vaccine is not considered to be a combination vaccine by the strict definition because it really cannot be equally divided into separate vaccines; that is, Td is an available vaccine, but a single antigen acellular pertussis component does not exist.

In addition, Dr. Kroger pointed out that the general preference statement needed to be revisited. As listed in the 2006 general recommendations, the current stated preference for combination vaccines is, "Use of licensed combination vaccines is preferred to separate injection of their equivalent component vaccines to reduce the number of injections and missed opportunities to protect through vaccination."

Based on the history, the work group met by teleconference to discuss the advantages and disadvantages of combination vaccines. Before offering options for revisions to this statement, Dr. Kroger reviewed these advantages and disadvantages with the larger membership. Vaccines have site-specific requirements. As many as nine vaccines could be recommended at a single visit. If the wrong site is used, vaccine could be less effective (HepB, Rabies) or more reactogenic (most adjuvant-containing vaccines injected subcutaneously). A challenge of vaccine administration and particular guidance needed for specific vaccines include: the need to re-administer vaccine doses if the wrong site is used for Hepatitis B or Rabies vaccine; and issues of reactogenicity when vaccines that contain aluminum adjuvants are injected subcutaneously. Another topic that has been discussed is the issue of patient preference for a reduced number of injections. The existing literature on this topic does not narrowly address a combination vaccine. A paper published in 2001 by Maureen Kolasa [Kolasa MS, et. Al. Impact of Multiple Injections on Immunization Rates Among Vulnerable Children. Am J Prev Med. 2001; 21(4), p. 261-266] suggests that providers and patients seemed comfortable with increasing the number of injections per visit from 3 to 4, but this was in a historical context of the switch from the oral polio vaccine to the inactivated polio vaccine. There have been other discussions and focus groups about this topic, but there is limited published literature.

There is evidence in the literature that combination vaccines improve vaccination coverage. In a retrospective analysis of over 18,000 Georgia infants, Marshall and colleagues demonstrated that the use of COMVAX™ and PEDIARIX™ improved the coverage of the DTaP, IPV, 4:3:1, 4:3:1:3, and 3:3:3 (by 3 to 6 percentage points) [Marshall GS, Happe LE, Lunacsek OE et. Al.

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Pediatr Infect Dis J 2007. 26:496-500, 2007]. These are good data and this is an important question. More data are need with respect to exactly why the coverage has improved in terms of whether it is due to reduced injections, reduced requirements for visits, or both. While this is really unknown, it is probably a combination of both.

There is also improvement of vaccination timeliness. There are several studies on this. In 2700 children in Germany, it was documented that vaccine doses were given earlier if combination products were used. The difference was not huge (less than a month) [Kalies H, Grote V, Verstraeten T, et al. The use of combination vaccines has improved timeliness of vaccination in children. Pediatr Infect Dis J. 2006;25:507–512]. A study of 5,000 children in Georgia documented a timeliness rate of 66% versus 61% for the DTaP, IPV, Hib, and HepB components if the DTaP-HepB-IPV vaccine was used [Happe LE, Lunacsek OE, Kruzikas DT, et al. Impact of a pentavalent combination vaccine on immunization timeliness in a state Medicaid population. Pediatr Infect Dis J. 2009; 28:98-101].

Reduced shipping and storage costs are also advantageous. With regard to the outright cost of vaccines, the cost of shipping can be presumed to be less if shipping fewer products. Older combination vaccines are, on average, cheaper than the sum of the components. However, for newer vaccines, the combinations are more expensive. The issue of storage is complicated and relates to how providers respond to any type of preference recommendation in the first place. If preference is given, they may purchase both combination and single component vaccines. It is likely that they will not purchase as much of the single component product, which probably would have an effect of reducing the amount of storage space required. Vaccines are stored in refrigerator and freezers. If more storage space is required, there will be a cost for an additional unit. Providers who purchase single components MMR and Var vaccines, and combination MMRV vaccine, store them all in the freezer, although MMR does not need to be stored there. There were discussions in the work group pertaining to how complicated it is for providers to use a single component MMR vaccine with the single component varicella vaccine, given that one must be frozen and one can either be frozen or refrigerated. Providers probably preferentially place the MMR in the freezer, which may have a storage effect due to the need for freezer space in the first place or the lack of enough freezer space. With MMRV vaccine alone, one could argue that a simple freezer message could be endorsed.

Another advantage is the reduced cost of extra health care visits. It is not crystal clear why combination vaccines improve rates, but perhaps it is related to reduced healthcare visits. Data from the 1999 National Immunization Survey indicate that 71% of children receive no more than four immunizations per visit. What is not definitive in that data is whether more than four doses were acceptable and if not, how that would affect extra vaccination coverage. Data on missed opportunities to vaccinate discuss the fact that not all of the doses may have been given at a visit that were recommended for that visit, but it is not entirely clear how the combination versus single component factors into this or how much weight can be given to this difference. CDC recommends vaccination not only at well visits, but also at any kind of visit as long as the child is not ill. Thus, there are many reasons for missed opportunities that are beyond the scope of combination vaccines. Combination vaccines also facilitate the addition of new vaccines into immunization programs, and present opportunities to educate and re-educate providers about the diseases prevented by various components. This is another opportunity to bring training messages forward.

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There are disadvantages of combination vaccine as well. The first regards increased risk of adverse reactions. There is known to be approximately a two-fold higher risk of febrile seizures in children 12 to 23 months old vaccinated with MMRV instead of MMR + V. Additionally, an observational study of 3938 6- to 10-week old infants showed an infant receiving Pediarix® to be 6.8 times more likely to receive a fever work-up than infants who received the single component vaccines [MMWR March 14,2008 57; Thompson LA, Irigoyen M Matiz LA, et al. The impact of DTaP-IPV-HB vaccine on use of health services for young infants. Pediatr Infect Dis J. 2006;25:826-831]. This was already expected from the pre-licensure trials and this particular issue is currently undergoing follow-up studies to clarify exactly what this increased risk is about.

Confusion and uncertainty also represent a disadvantage. CDC recommendations are very complicated, so confusion and uncertainty make constant education necessary. In the case of a combination vaccine preference, we have witnessed extra doses of an antigen being administered. Patients are seen by different providers, they have different contracts for different types of vaccines, and data from the National Center for Health Statistics (NCHS) suggests that 95% of children do have a usual place of health-care. Thus, 5.5% of children see more than one provider. With the complexity of health care delivery as it is, multiple venues for vaccine administration are expected. A single provider may be limited with a particular choice of a formulation for a set of antigens. He/she may only provide one particular combination product and since every single possible combination is not available for every provider, a patient who sees multiple providers may be in the environment where they have to be administered an extra antigen or perhaps even skip an essential antigen if a provider decides not to administer the combination product.

There is evidence that vaccine components are not as effective when given in combination (e.g., reduced immunogenicity). This reduced immunogenicity typically occurs when a particular combination vaccine is given off-label or against ACIP recommendations. An example is TriHIBit ® which is licensed for the fourth or last dose of the Hib series. If it is given as one of the first 3 doses, pre-licensure trials suggest reduced immunogenicity of the Hib components in this instance. ACIP recommends repeating the Hib component. This would not be a problem if vaccines were administered correctly all of the time; however, this does not happen and mistakes do occur.

Extra doses of antigen in the fixed product represent another disadvantage. This can be an issue even when a patient stays with the same provider. Sometimes an extra dose of antigen is necessary when using combination vaccines. Because CDC universally recommends a birth dose of Hepatitis B vaccine, if the provider chooses to use 3 doses of PEDIARIX™ as per the product insert recommendations, they will administer 4 doses of the Hepatitis B component overall because PEDIARIX™ cannot be used for the birth dose of Hepatitis B vaccine. Similarly, if Pentacel® is administered per product insert, 5 doses of IPV total would be administered in 41% of states per an informal survey of state health departments in 2008.

Another disadvantage pertains to differences in shelf life. Combination products can have a shorter shelf life. PEDIARIX™ is an example of this. The shelf life of PEDIARIX™ is 24 months and the shelf life of the single component INFANRIX ® is 36 months. The actual number may vary from what is listed in the product insert because obviously things can change depending upon supply issues. However, many providers are going to use the information that is presented to them in the product insert.

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Based on the aforementioned advantages and disadvantages, the work group crafted three potential options for revision to the general preference statement for combination vaccines and discussed the pros and cons of each.

Option 1 is to make no changes to the 2006 statement, leaving it as, "the use of licensed combination vaccines is preferred over separate injections of their equivalent component vaccines if licensed and indicated for the patient's age." This option was not favored by any members of the work group. The pros are that this option requires no revised communications messages, it is the status quo, and it is simple to implement. The cons are that providers are currently faced with a lack of flexibility regarding choice of antigens due to restrictions that may exist for their formularies, increased costs of vaccinations, increased activities like screening and counseling that may need to occur with the use of a combination product, et cetera. Just because there are fewer injections does not necessarily mean that there is any less labor involved, and that comes with a cost and should be appropriately reimbursed. Another con to leaving the recommendation as is regards the history of ACIP having removed a preference for the particular specific combination vaccine, MMRV, over MMR + V so it seems like some change in this language should naturally follow.

Option 2 involves adding language to the existing preference for combination vaccines to state, "The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines if licensed and indicated for the patient's age, but depends on the vaccination status of the patient, provider preference, patient preference, the potential for adverse events, and vaccine availability." The pros for this statement are that it is still a general recommendation for combination vaccine with caveats. There will be a potential for less missed opportunities, it recognizes programmatic issues and vaccine availability as important considerations, and it is permissive and allows a choice for the provider and patient. The major con is that the language is somewhat wordy and complex and it may take some time for people to remember the criteria.

Option 3 is to state that there "is no preference for the use of combination vaccines over separate injections of the equivalent component vaccines." The pros for this option are that it is concise statement, emphasizes choice for provider and patient, provides a clean slate for evaluating safety and efficacy of vaccines in the pipeline, and the vaccine contracting environment already restricts the choice of formulation. The cons for Option 3 include the potential limitation of administration site space, storage space may be limited (single component products take up more space), and reduced availability of combination vaccines leads to more injections.

Following the work group discussion of the advantages, disadvantages, and options, no members chose Option 1, a few chose Option 3, and many providers chose Option 2. Some members of the work group who chose Option 2 were comfortable with Option 3, but a plurality of the work group members who actually expressed a preference favored the general preference for combination vaccines with criteria and caveats. There was considerable discussion and the work group believed that they needed to ask ACIP to weigh in on Option 2 versus Option 3.

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Discussion

Dr. Marcy pointed out that there is another advantage to combination vaccines. There are two studies showing that it takes about a minute plus or minus to draw up the vaccine. A practitioner who has many patients and many vaccines can save a half an hour in the course of a day, which is no small amount. If he gives DTaP, Hep B, and IPV, it is worth $25 in administration fees. If he gives DTaP, Hep B, and IPV separately it is worth $75 in administration fees. Thus, the separate vaccines do have an economic advantage for the practitioner who wishes to use them separately.

Dr. Ehresmann indicated that her personal preference was Option 3 for a number of reasons. From the perspective of a state health department and making vaccines available, there are clear advantages to using combination vaccines for the provider and the patient. The statement in the general recommendations will not likely stop manufacturers from producing combination vaccines, but may stop providers from using them. It “levels the playing field” in terms of choice.

Dr. Sawyer indicated that he was a work group member and an Option 2 advocate. Given that private insurers and others may mandate that providers use separate vaccines, he expressed concern that Option 3 may lead to the unintended consequence that separate vaccines are given even when not intended.

From a practitioner standpoint, Dr. Temte noted that one of the disadvantages regarded the decrease in availability of single component vaccines. Among the members of the American Academy of Family Physicians (AAFP) from whom he had heard, there was a major issue regarding HIB vaccines. Anytime recommendations are changed or interim guidance is offered because of vaccines not being available, it creates significant problems for the vaccine provider community. One of the disadvantages is the seeming decrease of availability of single component vaccines. He wondered whether the work group addressed this.

Dr. Kroger responded that the issue was at least considered when the group discussed the limitations. They did not address issues of shortages per se. There is language that discusses shortages later in the section following the preference statement. That is an important limitation in terms of which particular antigens can be used or not used at a particular time.

Dr. Meissner expressed concern about how combination vaccines might be perceived by the public. The definition is interesting in terms of which vaccines can be conveniently separated. However, people may perceive MMRV as a combination that could be administered as a monovalent vaccine if there is not some statement. For example, in Option 3 the recognition is completely removed of the advantages of the combination vaccines. This could become a slippery slope and there will be more interest among certain segments of the population about using monovalent vaccines.

Dr. Judson suggested that the solution was to remove any economic advantage to giving separate antigens, or conversely to potentially reward giving combinations because of the complexity and additional counseling that has to take place.

Given that there are probably arguments both ways, Dr. Morse pointed out that a cost-benefit analysis may be needed to make determinations either way.

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Dr. Englund indicated that she favored Option 2, pointing out that there had been a major effort by pediatricians over the past 20 years to move toward combination vaccines because of the updates showing that this is patient and family preference. To move away from the direction practice had been moving for 20 years seemed to be a major step backwards.

Dr. Baker also favored Option 2; however, she did not believe anyone would understand it as written. It could be solved generally by revising it to "preferred over individual components." It could remain with the rest of the language in the text, by leaving "generally preferred" at the end of the sentence, or including a quick "but" with a quick phrase.

Dr. Cieslak also expressed a preference for Option 2, but because of the number of conditions, he thought it amounted to not being a recommendation. He suggested truncating it after "age."

Dr. Meissner suggested reviewing the combination vaccine section in the 2009 Red Book, which was recently distributed, as a potential template for phrasing this recommendation.

Dr. Sumaya noted that the work group did not achieve consensus; however, a larger portion of the group preferred Option 2. While he agreed with truncating it after "age," it would really then become Option 1. Perhaps they could truncate it and pick one or two priority items to be explicit.

Dr. Sawyer suggested keeping the patient and provider preference statements, which would encompass the rest of them. The provider should take adverse events into account, while the patient will take number of injections into account. He thought it should be truncated at "depends on provider and patient preference."

Dr. Morse inquired as to why the work group felt it was necessary to include "if licensed and indicated for the patient's age" because it seemed like that was general.

Dr. Kroger responded that it was a holdover of the status quo statement. He thought it was important to emphasize this point because of the position, timing, and spacing section. They want to ensure that vaccines are being administered at the ages for which they are recommended and if licensed for a particular dose and a particular age.

Dr. Ehresmann made a motion to support Option 2 with modification to the wording. She suggested rather than saying "provider and patient preference" to state that it is the patient's preference, but the provider's preference based on their deliberation over a scientific evaluation.

Dr. Baker seconded the motion for Option 2.

Dr. Chilton was opposed to saying just "patient preference." While respect for patient preference is good, the language would require the physician to stock all of the available vaccines, which is neither possible nor reasonable.

Dr. Duchin (NACCHO) favored Option 2 in that combinations are generally preferred; however, he thought it was very important for ACIP to annotate the recommendation with the specific considerations that health care providers might take into account when they decide whether or not they want to use a given combination vaccine. There are many different combination vaccines, each with its own plusses and minuses. Vaccines will also appear in the future after this recommendation is issued that may have unforeseen cost and benefits. He wondered if, when ACIP statements are issued on individual vaccines, there will also be a preference

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expressed in those statements for combinations and how that would relate to this recommendation and the general recommendations as a whole.

Dr. Leonard Freidland (GSK) clarified that the shelf life for both INFANRIX® and PEDIARIX™ is 36 months. Providers will not find shelf life dates in product inserts. Instead they are directed to look at the expiration data on the vaccine being used, and not to use the vaccine has expired. He also indicated that the follow-up on the adverse event profile for PEDIARIX™ has been completed. He directed the committee to an article in *Pediatrics* in December 2008. A post-marketing study was conducted in which over 60,000 infants received PEDIARIX™ and close to 60,000 control subjects received separate vaccines. 120,000 doses of each vaccine were followed. Short reviews were conducted for 22,500 infants who received PEDIARIX™ and similar numbers of the separate vaccines. There was no increased evidence of medically attended fever within 4 days after vaccination after any dose in the infants who received PEDIARIX™ versus the separate vaccines.

Dr. Phil Hosbach (sanofi pasteur) said that sanofi pasteur was pleased to see that Option 2 was being consider, given all of the investment. The policy drove manufacturers to spend hundreds of millions of dollars to develop combination vaccines for the benefits that were outlined. He begged the chair's indulgence to make a recommendation for the wording that might help simplify this, "Use of licensed combination vaccines are generally preferred to reduce number of injections and missed opportunities. Vaccine-specific considerations that might modify this general preference are discussed in the recommendations for specific recommendations for individual vaccines."

Dr. Mark Feinberg (Merck; NVAC) stressed that the discussion ACIP was having carried with it long-term implications. Manufacturers do respond to the guidance offered by providers and importantly by ACIP in terms of what vaccines to develop in the future. One of the components under discussion by the National Vaccine Program Office (NVPO), NVAC, and a number of other partners is the National Vaccine Plan. One of the components of the National Vaccine Plan is focused on stimulating the development of optimized and appropriate vaccines for the future. A clear determinant to what manufacturers do and how quickly they do it has to do with the clarity of guidance provided by important groups like ACIP. Therefore, he encouraged ACIP members to take their discussions very seriously. If they could not achieve clarity and consensus during this meeting about the guidance they wanted to provide, he suggested that they take this back to the work group and present it at a later time when a clear recommendation that would provide the best guidance for public health in the future was developed.

Deborah Wexler (Immunization Action Coalition) raised an issue that troubles nurses with regard to combination vaccines in that some vaccines are not licensed for use in certain age groups. PEDIARIX™ is recommended for doses 2, 4, and 6 months of age or the first 3 doses. Some nurses need to give those three doses, DTaP #4, IPV #3, and Hepatitis B #3 at 18 months of age. PEDIARIX™ is not licensed for that use. Many children need KINRIX™, DTaP, and IPV at age 3 who are behind on immunizations. Most nurses would prefer giving a combination vaccine to those children. With that in mind she wondered whether ACIP would make a recommendation outside of FDA licensure, which ACIP has a history of doing, to make it easier to facilitate giving those three doses of vaccine somewhat outside of the FDA recommendations for the use of PEDIARIX™ or the use of DTaP / IPV vaccine.

Dr. Ehresmann said her concern about the wording was that "provider preference" did not give enough credit to the provider for their assessment and evaluation of the patient.

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Dr. Baker thought they agreed to insert “licensed” in the statement for licensed combination vaccines, given some combination vaccines are not licensed for certain ages.

Dr. Sandy Fryhofer (American College of Physicians) indicated that she is a practitioner who treats the mothers of children. Given that vaccines are in the spotlight, she expressed her hope that some language would be included about adverse events. Her fear was that if only a combination vaccine was available, many mothers may opt out entirely not have their children vaccinated. This is also an ethnic and racial disparities issue because some of these individuals might not have the option of going to a private facility to acquire their vaccines if they cannot obtain it through public means.

Dr. Morse clarified that from the discussion, it appeared that there was significant consensus for Option 2, but that the actual wording had not been solidified. He thought they should define exactly what they were voting for, or at least the general principle of the vote, and then return the next day with specific language.

Dr. Lett pointed out that one variable which must be kept in mind was vaccine availability.

Dr. Kroger clarified the proposed revisions: add “licensed” before the first combination, change “provider preference” to “provider evaluation,” keep “patient preference,” leave “vaccine availability,” and perhaps remove “vaccination status of the patient.”

Dr. Baker suggested the following language, “The use of a licensed combination vaccine generally is preferred over separate vaccine components or component vaccines, but depends on patient preference and evaluation or assessment.” She preferred “provider assessment” rather than “evaluation,” although she was willing to accept “evaluation."

Dr. Judson thought the goal was to shorten this as much as possible, but it now seemed that they had 5 or 6 options on the table. He thought that critical for the first sentence was the statement that the “combination vaccine is preferred and if licensed for the patient’s age,” which would be helpful to a skilled practitioner. However, if indicated did not seem useful because it did not seem that anyone would use a vaccine if it was not indicated. He thought the second part really was about provider preference because patients would likely not make that decision separate from or even in opposition to the provider.

Dr. Baker stressed that patient preference was an increasingly important issue.

It struck Dr. Beck that the issue really regarded how they modified the word “provider.” Everything else seemed to be fitting into place. He agreed that patient preference was important, but that there must be a way of describing the involvement of the provider in this joint decision.

Dr. Sawyer agreed that one or two words were needed to describe provider involvement. He reminded everyone that in the text would be all of the advantages and disadvantages that were outlined, which the provider is supposed read and evaluate for each patient.

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Motion: General Recommendations for Combination Vaccines

Dr. Ehresmann made a motion to approve Option 2 with modifications to be made to the wording by the work group as discussed. Dr. Baker seconded the motion. The motion carried with 15 affirmative votes, 0 abstentions, and 0 negative votes.

The following Option 2 clarification was presented to the ACIP members during the second day of the June 2009 meeting:

The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment*, patient preference, and the potential for adverse events.

*Provider assessment should include storage costs, number of injections, vaccine availability, vaccination status, likelihood of improved coverage, and likelihood of patient return visits.

Dr. Kroger then directed the members' attention to the recommendation regarding Special Situations, which is a laundry list of topics faced by providers on a regular basis, including:

- Concurrently Administering Antimicrobial Agents and Vaccines
- Tuberculosis Screening and Skin Test Reactivity
- Severe Allergy to Vaccine Components
- Latex Allergy
- Vaccination of Preterm Infants
- Breast Feeding and Vaccination
- Vaccination During Pregnancy
- Persons Vaccinated Outside the United States
- Vaccinating Persons with Bleeding Disorder and Persons Receiving Anticoagulant Therapy

Two of these sections, Tuberculosis Screening and Skin Test Reactivity and Vaccination of Preterm Infants, required minor updates to address new vaccine-specific recommendations that have been published. For tuberculosis screening and skin test reactivity, the general recommendations have not recommended an interval between the live viral vaccine and a tuberculosis test. It is known that diseases such as measles can suppress the response to a tuberculosis test and generate false negatives. There is a need to adjust the general recommendations to take into account new tuberculosis-specific recommendations that have been published for two-step testing, which involves basically two doses of the purified protein derivative. A recommendation is also needed to clarify whether the risk of test suppression from a live vaccine also exists for a new TB test. Since the last recommendations were published, there is a newly available test known as the interferon-gamma release assay. Based on consultation with the TB subject matter experts (SMEs), the recommendation should be for the same spacing intervals with live vaccines and the new tuberculosis tests. This is basically a minor update.

Vaccination of preterm infants requires an update as well. ACIP has generally recommended vaccinating preterm infants following the same chronologic age recommendation as term infants, but there have always been a few exceptions to this. Additional language will be added to emphasize testing of HBsAg-unknown mothers for HBsAg even after HepB is administered. This is an important part of determination to use HBIG within 7 days of birth. Another minor

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clarification is the recommendation to defer rotavirus vaccination of infants 6 weeks old and still in neonatal nursery (or neonatal intensive care unit).

Two special situations, Vaccination During Pregnancy and Persons Vaccinated Outside the United States, require fairly major revisions. A reference has been added to Vaccination During Pregnancy for ACIP's *Guiding Principles for Development of ACIP Recommendations for Vaccination during Pregnancy and Breastfeeding*, which was published in May 2008. New concepts have also been added from the Tdap pregnancy-specific document, also published in May of 2008 that recommend: Deferral of Tdap (ACIP Vaccine-specific recommendations), use of Td, limited situations when Td can be deferred (new reference *MMWR* May 30, 2008), and use of Tdap postpartum regardless of interval from last Td. Based primarily on expert opinion, the risk of infant pertussis disease from withholding a dose of Tdap from a post-partum woman outweighs the risk of a local reaction to the Tdap vaccine from a post-partum woman who may have received Td in pregnancy. The work group acknowledged that there may be future on-going discussion of this topic. It was not clear how specifically to word this in the general recommendations statement. Further consideration should be given to this issue, given that there is a considerable amount of language in the 2006 document specifically regarding the use of tetanus toxoid-containing vaccines in pregnancy.

The work group wanted to clarify ACIP's counseling recommendations for pregnant women that may have inadvertently been administered MMR vaccine. The 2006 document mentions a theoretical risk, but does not describe in detail why the risk exists. The new language is as follows:

> Data from studies of children born to mothers vaccinated with rubella vaccine during pregnancy demonstrate rubella antibody levels that probably represent passive transfer of mother's antibodies during pregnancy. No cases of congenital rubella or varicella syndrome or abnormalities attributable to fetal infection have been observed among infants born to susceptible women who received rubella or varicella vaccines during pregnancy, although a theoretical concern exists . . . If vaccination of an unknowingly pregnant woman occurs or if she becomes pregnant within 4 weeks after MMR or varicella vaccination, she should be counseled about the theoretical basis of concern for the fetus; however, MMR or varicella vaccination during pregnancy should not be regarded as a reason to terminate pregnancy (6, 8, 189).

This language originated in the leads from the *MMWR* series published in *JAMA* in June 1989, so this much specificity has not been carried forward through all of the documents since then, but it is cited in all of those documents, so it was presented here as part of the general recommendations.

Another topic in special situation that requires some changes is Persons Vaccinated Outside of the United States (US). The 2002 document was originally written to focus exclusively on internationally adopted children, but it has been broadened to include all persons vaccinated outside of the US, which means that ACIP needs to take into account the new vaccines since 2006: rotovirus vaccine, human papilloma virus vaccine, and zoster vaccine.

The Vaccination Records section revisions consist primarily of clarifications and updates. Strong emphasis is placed on the role of a vaccination record in avoiding extra doses. The language that has been added reads:

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> Appropriate and timely vaccination documentation not only helps ensure that persons in need of one or more recommended vaccine doses receive them, but also that adequately vaccinated patients are not administered excess doses. Curtailing the number of excess doses administered to patients aids in controlling costs incurred by patients, providers, insurers, vaccination programs, and other stakeholders. Additionally, there are isolated examples of excess doses increasing the risk of an adverse reaction (e.g. excess reduced doses of tetanus toxoid and frequent dosing of pneumococcal polysaccharide vaccine causing local reactions).

The effect of this language is primarily to emphasize the importance of provider records and provider responsibility. Language is included to stress that providers should document serology results, vaccination doses, et cetera. Additional language is included to encouraging post-partum mothers to receive a record on discharge from the hospital because Hepatitis B vaccine should be given in that venue. Language is also included to describe potential capabilities of immunization information systems (IIS) with respect to vaccine management and documentation of adverse events, and there is an update on statistics pertaining to IIS enrollment.

Discussion

Dr. Chilton pointed out two minor differences between the general recommendations and the rotavirus statement. There is a statement in the rotavirus policy statement saying that some experts would prefer the vaccine that does not contain latex or that does not have a latex stopper for those patients who are at high risk of later having a latex allergy (e.g., spina bifida patients). The rotavirus policy statement also includes a proviso that if there are epidemiologic considerations that dictate use of rotavirus vaccine in a newborn intensive care unit, it could be done using local some expert opinions. He wondered whether this language could be included in the general recommendations as well.

Dr. Kroger agreed that it would be a good idea to add language along those lines.

Dr. Morse wondered whether everything had to be included in the general recommendations or if the general guidelines could refer to the other guidelines.

Dr. Englund was concerned that if they changed the general recommendations they would have to change the rotavirus recommendations as well. Perhaps referring to the specific guidelines was a better idea for the deferral of rotavirus vaccination of preterm infants 6 weeks old.

Dr. Temte noted that while for vaccination records some language was included about immunization information systems, there appeared to be nothing about electronic medical records (EMRs). He uses EMRs regularly with virtually every adult patient. Their EMRs have a tab to the Wisconsin immunization registry. Given the effort on the part of the current administration toward the use of EMRs in general, it should be in the forefront of ACIP's recommendations to fully integrate EMRs with immunization information systems.

Dr. Kroger suggested making a reference under provider responsibilities to the fact that these products exist.

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With respect to recommending the interferon-gamma release assays, Dr. Marcy thought there was limited data for children under 4 or 5 years of age. In terms of measles vaccine, he suggested including a caveat regarding the age limitation for data. A second data-driven part is on page 21, "regardless of recent history of Td vaccination, pregnant women should receive a dose of TDaP as soon as possible after delivery." If Td has been given to a woman at the beginning of the second trimester and following delivery, this is about six months. He knew of no data showing the safety of TDaP less than 18 months after Td. Scott Halpern's data goes down to 18 months.

Dr. Pickering responded that a recent article was published showing the period of 1 month with no adverse events. However, the numbers were small

The discussion reminded Dr. Morse of the annual discussions of the children, adolescent, and adult guidelines when additional ideas were proposed. He thought they must look at this as a continuous quality improvement and that all of the excellent ideas proposed should go back to the work group so that they could continue to upgrade and improve this document each time. He stressed that it was not necessary to complete the final product at each meeting because they would never complete it. He had thus far heard no arguments against the recommendations which include minimum additional language and / or minor clarifications. Therefore, he suggested moving forward with a caveat that they would continue to improve the revisions with the next iteration.

Dr. Baker agreed with Dr. Marcy that there was no convincing data on safety; however, it is a risk-benefit issue because of the incredible risk to the baby of acquiring pertussis, which is likely to be fatal if the mother and everyone around the baby are not immunized.

Motion: Special Situations and Vaccination Records

Dr. Baker made a motion to approve the recommendation of the work group regarding Special Situations and Vaccination Records. Dr. Sawyer seconded the motion. The motion carried with 15 affirmative votes, 0 abstentions, and 0 negative votes.

Dr. Judson noted that while they voted to approve, he wondered whether there were statements as there were for Tb Screening and Skin Test Reactivity that may conflict with or connect to other recommendations. For instance, booster skin testing or double skin testing is generally for people over 40 in whom immunity may have waned. If this is stated to pediatricians trying to give doses to infants or children, this will be confusing as it does not apply to them. There are no data for infants and children for QuantiFERON ®, let alone where practitioners might order it.

Dr. Morse requested that Dr. Judson put this in writing and refer it back to the work group so that it could be included in the deliberations.

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Rabies Vaccine

Background

Dr. Paul Cieslak
ACIP, WG Chair

Dr. Cieslak briefly reviewed the background information pertaining to rabies vaccine. Given that the human rabies vaccine supply has been tenuous since 2007, ACIP formed a work group to draft interim recommendations regarding how the supply should be managed in the event of a shortage. Draft interim recommendations in the event of a shortage of rabies biologics were previously distributed to ACIP in which alternative schedules during a shortage were proposed. The work group proposed alternative schedules, including a 4-dose schedule, and it was the opinion of the work group that the 4-dose schedule would not result in reduced efficacy in the post-exposure setting. Therefore, the work group was asked to evaluate alternative schedules, specifically for more routine use.

There are two rabies vaccines available in the US. The Novartis vaccine is the purified chick embryo cell vaccine, which is available for post-exposure and pre-exposure immunization without any current limitations. The sanofi pasteur vaccine, the human diploid cell vaccine, is available only for post-exposure prophylaxis at this time. Due to supply issues, there must be a local public health risk assessment and a password restricts its use [www.sanofipasteur.com].

The terms of reference for the ACIP Rabies Work Group were to review the evidence for a reduced schedule of rabies vaccine in the post-exposure setting; provide the available evidence to ACIP for discussion of dropping the 5th dose; and revise the existing statement accordingly.

Human Rabies Biologics: Consideration of a Reduced Vaccine Schedule in Post-Exposure Prophylaxis

Dr. Charles Rupprecht
CDC / CCID / NCZVED / DVRD

Dr. Rupprecht reported that the sources of evidence the work group has reviewed included basic studies of rabies virus pathogensis, overall immunization principles and kinetics specifically regarding rabies vaccines, available data from human clinical trials, national and international epidemiological surveillance data. Members of industry and international subject matter experts, particularly with regard to the WHO collaborating centers, have been consulted as well.

The supply limitations developed during late 2007 when the 2008 ACIP rabies statement was already well into its editorial deliberations with the *MMWR*. The work group felt strongly that there should be discussions with ACIP and preparation of recommendations well before the onset of a true shortage. Besides increases in vaccine availability, a reduced schedule would possibly result in minimization of adverse biomedical events, will limit additional health expenditure, and provide a rational legacy for development of future biologics. With the onset of

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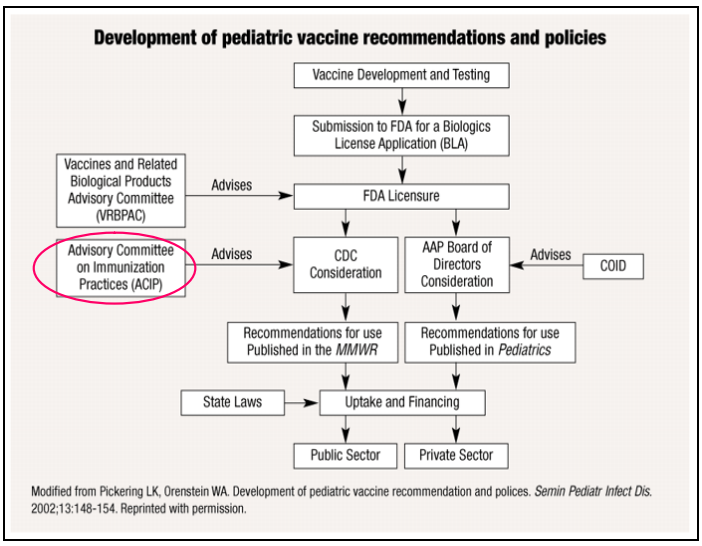
the application of comparative health effectiveness data, the work group felt strongly that the current institution of the ACIP evidenced-based approach would be a sound one for the objective rationale application toward rabies immunizations.

The work group also recognizes that this would be a departure from the claim of the product insert. However, using the following figure from a prior publication by Pickering and Orenstein, Dr. Rupprecht reminded ACIP members that this body does not simply "rubber stamp" label claims:



Obviously, immunization practices differ from what the claims are specifically. It is also important to recognize that, on the basis of the available data, there were no comparative clinical trials that specifically assessed the administration of human rabies immune globulin in 1, 2, 3, or 4 doses. The product inserts were developed on the basis of the existing 5-dose schedule.

Historically, rabies immunizations have undergone changes in schedules, routes, and the formatted material that was used going back to the 1885 premier work by Pasteur when 14-21 doses of sequentially desiccated spinal cord of rabid rabbit was homogenized and used as a vaccine. Originally, in 1980s the human diploid cell vaccine was suggested for an optional 6th 90-day dose which was then later dropped without any experimental comparative studies as well as in the US and a 5-dose series was used and similarly incorporated with the purified chick embryo vaccine, the PCEC vaccine. Similarly, there has been a 4-dose series in long use from a global standpoint, the 2-1-1 series in which 2 doses of vaccine are administered on day 0 (requires availability of both vaccine doses on day 0, limits IM sites for HRIG, et cetera). The work group did not consider this particular schedule for several reasons, not the least of which was that they felt strongly that there was no utility of 2 doses being administered on day 0 compared to the single dose. In addition, there was concern that because of the possibility for complications or mistakes, administration of 2 doses on day 0, with having to have an infiltration site for immune globulin, further negated the utility of having a 2-1-1 schedule as opposed to simply dropping of the 5th dose for a 4 dose total regimen. In regard to rabies virus pathobiology, the work group believes that what occurs in the first few days is critical by a current modern understanding of this acute, progressive encephalitis. The rationale for all post-exposure prophylaxis is to prevent viral invasion from the locality to the nervous system. All of

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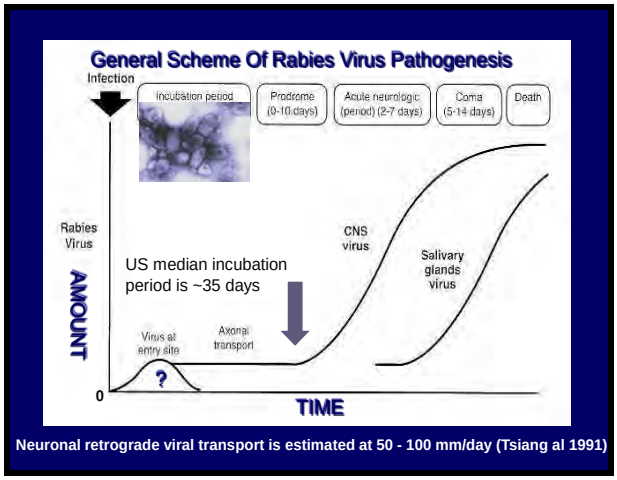
the ACIP recommendations from inception to date have emphasized early wound care, passive immunity (e.g., infiltration of rabies immune globulin at the bite site), and rabies vaccine to stimulate the development of active immunity via a prime-boost strategy.

The following model of rabies virus pathogenesis was first proposed in the 1960s, and from experimental studies to date strongly suggests that the reason post-exposure prophylaxis works in the hours to days after exposure is because the virus is retained in the periphery:



When comparing incubation periods of human rabies cases that occurred in the US in past decades, a median is approximately one month. Clearly the administration of a 5th dose on day 28 after exposure has little if anything to do with the amelioration of basic rabies virus pathogenesis and similarly has probably no saving utility for severe exposures on the face, head, or direct inoculation into the brain itself.

Based on a variety of clinical studies, rapid induction of rabies virus neutralizing antibodies is accepted as a critical surrogate of successful intervention. In clinical trials of rabies vaccination, all healthy individuals developed detectable rabies virus neutralizing antibodies by day 14. No significant differences were documented between a 4- versus a 5-dose rabies vaccine schedule in the relative amount of neutralizing antibodies produced. In comparison of studies using 4 doses of vaccine, when given in a regimen that included rabies immune globulin, equivalent outcomes were observed. It is clear from these clinical studies that there is a relatively rapid induction of rabies virus neutralizing antibodies, which has been accepted as a critical surrogate of successful intervention since there is no defined seroprotective level per se. A combination of these studies over time, regardless of the type of the two vaccines licensed in the US, is compared in the following graph:

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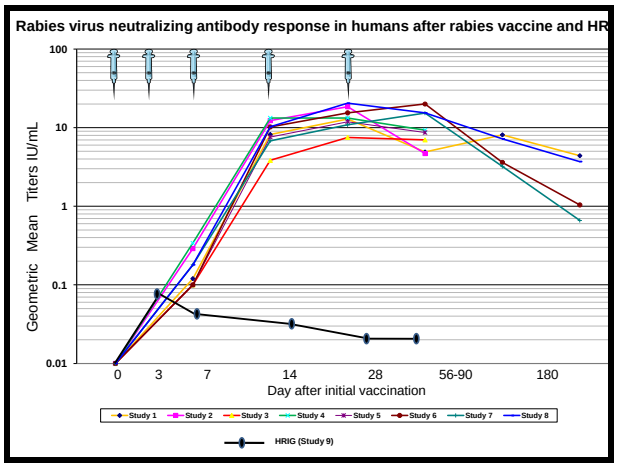

As reflected in the graph, rapidly from day 0 to day 14, everyone develops rabies virus neutralizing antibody. Relatively shortly thereafter, the antibodies begin slowly to decline regardless of the administration of the 5th dose on day 28. Based upon epidemiological surveillance, in the US no failure of human post-exposure prophylaxis has been identified during the past 30 years (since use of modern cell culture vaccines and RIG). Outside of the US, rabies has occurred in human patients who had no prophylaxis, substantial delays in initiation of prophylaxis, or significant deviations from recommended prophylaxis. The work group could find no failures attributable to an absence of the fifth and last vaccine dose on day 28.

In terms of public compliance, cross-sectional studies at the state or county level indicate that public adherence to the existing human PEP schedule is not 100%. One study of human PEP in New York (1998-2000) found that approximately 13% of persons did not complete the full schedule, and approximately 2% only completed 4 vaccine doses, 2 of which involved documented exposures to laboratory-confirmed rabid animals, without incident.
Grossly extrapolated, approximately 1,000 persons likely receive only 3 to 4 doses of vaccine in the US each year, of which approximately 30 to 40 would involve exposures to rabid animals.

In addition, unpublished epidemiological data collected by CDC during a 2008 investigation of frequencies of animal exposures and a correlation with prophylaxis in Puerto Rico demonstrated that a 4-dose vaccine regimen provided an immunological response comparable to the standard 5-dose regimen. In this limited survey 30 (16%) of 191 patients exposed to suspected rabid animals received fewer than 5 doses of vaccine. Consent and sera were obtained from 18 patients, from whom three had received only 1 vaccine dose, 6 had received 2 doses, 5 had received 3 doses, and 4 had received 4 doses. Eleven (61%) of the 18 sera (two of the 2-dose patients, all 5 of the 3-dose patients, and all 4 of the 4-dose patients) exhibited complete virus neutralization at the 1:5 dilution using the RFFIT assay. Adequate titers were detected in the sera of all 9 patients who received only 3 or 4 doses of vaccine, 118, 144, 146 and 153 days after the 3rd (and last) doses and 126, 143, 168 and 215 days after the 4th doses of vaccine were administered. To date, none of these patients have developed rabies. [K. Robertson et al., 2009 (unpublished)].

From the time of Pasteur, animals have been used as important surrogates in preclinical testing of rabies vaccines. Such research on basic immune response and vaccine efficacy in a variety of species have provided significant inferences to human clinical trials. Models from laboratory rodents to non-human primates demonstrate that the absolute number of doses of a potent vaccine is not critical if timely intervention occurs after experimental infection, including the

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combined use of immune globulins. For example, in a recent mouse model in which all 10 animals in the control group succumbed, and in which post exposure prophylaxis was instituted 24 hours after exposure, in the 4 comparative groups of animals that either received 1 dose, 2 dose, 3 dose, or 4 doses of vaccine, the number of animals surviving in each of those groups respectively was 8 of 10, 9 of 10, 9 of 10, and 7 of 10. The survivorship rate was irrelevant to the number of doses administered. The animals in each group were bled 3 months after the exposure and initiation of PEP. Similar to the human data obtained from Puerto Rico, as the number of doses increased from 2, to 3, to 4, there were no significant differences of survivorship.

In another animal model using Syrian hamsters, it was also demonstrated that regardless of the absolute number of vaccine doses in PEP initiated 24 hours after animals were infected with rabies virus compared to controls, there was no significant difference in survivorship of those animals. From the standpoint of randomness in this experiment, there was 100% protection in a group where animals that received 4 doses as opposed to 89% survivorship in a group where 5 doses of vaccine were administered [R. Franka et al., 2009, Vaccine, submitted].

With respect to health economics in the US, there may potentially be some minimal cost decreases to health care payers and the health care system if the regimen was reduced from 5 to 4 doses. The work group recognized that there were not going to be any new clinical trials, nor any insipient changes in the label insert regardless of the ACIP recommendation. The number of visits by patients would decrease as a consequence of eliminating that last visit which is quite important, particularly in rural areas where individuals have to travel a number of miles. Insured patients are unlikely to see an increased cost per dose (cost per complete series of vaccine should remain unchanged). Preliminary assessments support the positive national health benefits associated with a reduced schedule of rabies vaccination. Overall, there is no anticipation that changing the current recommended schedule of 5 vaccine doses to 4 vaccine doses during rabies post-exposure prophylaxis would substantially alter the health economics of rabies prophylaxis.

In summary, no direct post-exposure efficacy trials have compared 5 doses to 4. The work group review included published and unpublished studies of rabies virus pathogenesis, experimental animal studies, human clinical trials, and epidemiologic surveillance data. The work group concluded that taken *in toto*, the evidence suggests that no rabies case would result from reducing the post-exposure vaccination schedule from 5 doses to 4. Based upon feedback, a draft document was prepared by the rabies working group for ACIP review and vote.

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Discussion

Dr. Baker thought the new document was highly improved and she supported the work group's recommendation.

Dr. Meissner pointed out that human nature being what it is, if there is a small percentage of exposed individuals who do not obtain all 5 doses and receive only 4, presumably if 4 doses are recommended, there will be a small percentage who will receive only 3 doses. Based upon the data, it appears as though that this is still likely to provide adequate protection. He also noted that the 2009 Red Book still recommends 5 doses and references the 2008 ACIP guidelines, which is likely to engender a great deal of confusion for pediatricians.

Dr. Rupprecht confirmed that Dr. Meissner was correct in his assumption on the basis of the comparative data. Most of the critical functions occur between day 0 and 14.

While Dr. Chilton appreciated the very good wording in the new document, he wondered what the ramifications may be of handing the manufacturer a de facto 20% windfall increase in profits by stating in the document that the cost of 4 vaccine doses is likely to be as great as that of 5.

Dr. Meltzer, a senior health economist and a member of the work group, took responsibility for that comment. It was based on a comment made to ACIP in the public forum last session during which one of the manufacturers said that they currently sell this as an entire treatment rather than a per dose treatment and they are unlikely to change the price per treatment. In the notes and in the write up, this is referenced. He did not believe anything ACIP said gave license in and of itself to any manufacturer to raise or reduce the prices, given that they work based on market forces.

Dr. Rupprecht added that it was their attempt to be transparent on the basis of the remarks that were made during the last meeting.

Dr. Morse noted that in the report it was noted that a substantial review of the Zagreb 2-1-1 regimen was not included. However, he wondered what evidence was included as supportive. The regimen approved by WHO in 1992 has continued to be in practice.

Dr. Rupprecht responded that those original studies were actually suggested in the 1980s and reviewed by WHO subsequently. From some of the work that was done, as well as some other comparative data, it has been shown there is an maximum amount of effective antigen that can be presented to the immune system at any one time, after which no further increases occur in antibodies, GMTs, protection, et cetera. That can be demonstrated experimentally and clinically, which is one of the reasons the work group felt strongly that there really was no utility of 2 doses of vaccine administered on day 0. Similarly, there were some suggestions clinically that when the Zagreb schedule was used, there was some strong suggestion of interference of immune globulin with those 2 doses of vaccine that were administered on day 0. Hence, on the basis of the clinical suggestions of potential interference and the lack of any utility of providing what is already a very potent product on day 0, and because of the implications during a shortage of not necessarily having 2 doses present on day 0, the work group believed that inclusion of the Zagreb schedule would only lead to additional confusion.

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Dr. Judson noted that 20 to 30 years ago, there was a statement some place that there was no evidence that rabies post-exposure prophylaxis started after 72 hours, or 3 days, or 4 days was effective. Now they were saying that there have been no cases of rabies if post-exposure prophylaxis was used. He wondered whether the prior impression had been modified.

Dr. Rupprecht replied that the review of the cases in which human rabies developed in spite of post-exposure prophylaxis suggested that immune globulin was not used, immune globulin was inappropriately used, or there was a significant delay in use. The excellent review by Wilde and others showed that there were some other complicating factors. The majority of failures were in cases in which heterologous products were suggested. The work group made note of and brought to the committee's attention some of their concerns about the unavailability of intact immune globulins (IG). For example, if one used F(ab)2 prime products in which the Fc fraction is removed from the IG, that will significantly alter the kinetics, biological half life of circulating fragments and outcome of intervention. There have been no failures with timely use of one of the human rabies immune globulin products licensed in the US. The last major epidemiological study of post-exposure prophylaxis was the one by Helmick et al that suggested that there was a median delay of approximately 5 days between when a person was exposed and when they presented for post-exposure prophylaxis. That does not mean people should delay that long or misconstrue the numbers and present at their leisure. Obviously, this is an urgent emergency. Delay could result in death. They do not want the 5-day or 72-hour numbers to suggest that people should be turned away. In fact, there was a notable case in the US of a person exposed abroad. When she presented to her clinician, due to the amount of time that had passed from exposure, she was told that she should have already had prophylaxis and that it is too late to give it now. Probably the best would be to say that it is an urgent emergency and that timely application is highly recommended.

Dr. Duchin (NACCHO) agreed with this recommendation, but had a lingering concern about the fact that health care providers may be troubled by the discrepancy in the package labeling with the FDA recommendation versus the ACIP guidance. He wondered if ACIP could provide standardized language that health jurisdictions across the country could use when responding to these concerns so that they would all be speaking with one voice. He also wondered whether there was any precedent of a discrepancy of this type.

Dr. Rupprecht indicated that in the preamble of the recommendation, there should be some discussion along those lines as to the evidence-based approach and whether it supports the utility of 4 versus 5 doses, what the basis of that evidence is, and that clearly it would be in conflict with what the product claim would be. There had already been a considerable amount of outreach to health departments in 2009 due to the on-going supply issues. Depending upon the recommendations of ACIP, new outreach efforts would likely begin immediately.

In terms of other discrepancies between labeling and ACIP recommendations, Dr. Morse noted that in 2008 Hepatitis A vaccine could be used in lieu of immunoglobulin for basic post-exposure prophylaxis.

Dr. Rupprecht added that historically, from the standpoint of the rabies vaccine, the last time there was the discrepancy was when ACIP first recommended intradermal vaccination for pre-exposure purposes before the product was licensed. Discussion of times when there have been

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discrepancies would be useful in the preamble for better health communications and clarity with practitioners.

Dr. Baker noted that another example was the label on influenza vaccinations, which do not include pregnant women as a target population.

Ms. Stinchfield pointed out that another cost consideration is the amount of nursing time that goes into reminder recall and follow-up. A reduction of 20% in that effort would be substantial.

Clement Lewin (Novartis Vaccines) indicated that the supply constraints that existed in 2008 no longer represented a problem. Novartis has invested approximately $100 million in increasing the capacity of and upgrading the facility in Marburg. He also re-emphasized a point that he made at the last meeting, which was that the ACIP recommendation would essentially be an off-label recommendation. Novartis does not recommend the use of its vaccines off label; therefore, if any provider or health care personnel contact the company, the answer would be that 5 doses are recommended in accordance with the label. This is likely to lead to considerable confusion. Many people have highlighted that ACIP recommendations have not always been aligned with the package insert. While that was true, in the 10 to 15 years he had been working in vaccines, he could not recall ACIP actually making a broad recommendation. This would be like saying they decided HPV vaccine should be 2 doses based on the evidence, but the FDA has not approved that indication. This very broad decision was highly likely to cause a significant amount of confusion amongst the medical community.

Dr. Ehresmann noted that during the last ACIP meeting there was also a comment that the manufacturer did not intend to request a change for the package insert. She wondered whether there was a way that someone other than the manufacturer could do so.

Dr. Baylor (FDA) A change must be requested by the US license holder, which would be the manufacturer. Although there are examples of safety issues in which the FDA could request that manufacturers submit safety data, the FDA did not perceive dropping a dose as a safety issue per se.

Dr. Temte did not foresee a problem. If there is clear ACIP guidance, it will be translated to state partners, practitioners, and other experts. From a clinician's point of view, he said he rarely consults a product insert on a vaccine.

Dr. Morse was struck by the fact that the Zagreb 4-dose regimen has been approved since 1992 by WHO. He wondered whether there was a second package insert used by manufacturers in other countries or if that was simply not addressed.

Dr. Hosbach (sanofi pasteur) responded that he was unfamiliar with package inserts outside the US. He pointed out that historically, manufacturers were permitted to include ACIP recommendations in the package insert. That was somewhat helpful when there was a conflict. However, that is no long permissible by FDA. As a manufacturer, they do receive many calls from physicians and providers about how to utilize vaccines, including rabies vaccine. They also will recommend what is on the package insert in these cases.

Chris Hahn (CSTE) commented that at the city health department, they receive numerous calls from providers as well. Their response would be that ACIP has recommended 4 doses, but that they should be aware that the FDA package insert still says 5 doses.

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Dr. Morse wondered how the Red Book would handle this.

Dr. Pickering responded that it would be updated in the on-line version immediately.

Dr. Bocchini (AAP) responded that the Committee on Infectious Diseases (COID) would review the recommendations and make a decision, which would be published in the AAP newsletter and included in the Red Book on-line immediately to make practitioners aware as soon as possible.

Dr. Baker requested elaboration on what city, local, and / or state health departments say about ACIP's influenza and Hepatitis A recommendations with respect to pregnant women.

Dr. Hahn (CSTE) responded that if they were aware of discrepancies, they try to give the provider all of the information. They do not receive a lot of calls from providers about influenza vaccination for pregnant women. She thought the ACIP recommendation was fairly well accepted in the provider community and was simply followed.

Dr. Ehresmann said that Minnesota would follow the ACIP recommendations in general as a standard and would explain any discrepancies.

Dr. Morse said that New York would tend to go with the ACIP recommendations. They would also raise the issue with the State Advisory Committee to seek their support.

Motion: Reducing Rabies Post-Exposure Prophylaxis from 5 to 4 Doses

Dr. Baker made a motion to approve the recommendation of the work group regarding a reduced schedule from 5 to 4 doses for rabies post-exposure prophylaxis. Dr. Meissner seconded the motion. The motion carried with 14 affirmative votes, 1 abstention, and 0 negative votes.

Poliovirus Vaccine

Overview

Dr. Lance Chilton
Poliovirus Vaccine Work Group Chair

Dr. Chilton stressed that polio still exists. Poliovirus has spread from Nigeria, India, Afghanistan, and Pakistan where it is still endemic. Therefore, it continues to be a threat to the US and the reminder of the world at this point despite the desire to have solved the problem by the year 2000. By 2010, the problem still will not be solved. There is still a threat of long distance importation to poliovirus into the US and for that reason, the decisions on poliovirus vaccine dosing and intervals remains important. The problem that needed to be solved by the work group and ACIP regarded when a third dose of inactivated polio vaccine should be given, and when or whether a fourth dose is needed. The work group plan was limited. They engaged in conference calls between February and April. At the end of those calls, there was remarkable unanimity of opinion.

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Polio Eradication Program: India 2009 Observations

Robert L. Beck, JD
ACIP Member

Mr. Beck said he was privileged to be part of a group of 45 volunteer Rotarians from around the world who travelled to India in February 2009 to vaccinate children against polio. They worked in the streets and slums in several cities in northern India where they vaccinated more than 1,000 children. He spent about a month in India working with the polio program and then travelling on my his own through northern and central India, based upon which he made several observations. The polio program is successful. One of the three endemic strains of polio in India has been successfully eradicated, and the two remaining strains show great promise that they will be eradicated as well. That is a major step forward.

This program is not a once a year event, but is offered several times a year due to limits within the current oral vaccine and because of migrating populations. It is a very people-intensive project, with thousands of government and volunteers involved to vaccinate millions of children. The program has been in operation for decades and with the successes, personnel are showing signs of wearing out. Mr. Beck believes that Indian state and local personnel need visible, public encouragement and recognition to keep up program momentum. Continued funding remains important, but personnel support is also needed. Thus, one of the comments he brought back to India and the US was that he thought something needed to be done to buoy up the people working at the state and local levels to help them stay the course of their important involvement in the program.

The program is also unique from another standpoint. The Gates family and foundation have contributed hundreds of millions of dollars for support of the program. The Rotary Foundation has also donated hundreds of millions of dollars and is one of the best known US charities. CDC is the primary face of the US government in this project and is also doing a good job. The combination of these three organizations makes this project a uniquely positive American / USA story, and that story should be told.

The program is really also a world class international relations opportunity. To Mr. Beck it is akin to the Marshall Plan following WW II. Its success has the potential for a strategic, macro, impact in this region of the world. It is a non-military program. Implementation is through local people, for benefit of local people. Billions of people in the relevant geographic area will see the benefits from such a program, including 1.5 billion Indians, 3.0 Chinese just over the rather porous border, and billions more residing in Russia and India's Muslim neighboring countries. This program is an immense international opportunity in addition to its wonderful public health benefits.

Mr. Beck extended his personal gratitude to Dr. Jean Smith who is a tremendously dedicated person. Dr. Smith lived and worked in India for many years. Her work included the polio program. She arranged special briefings for him before his India trip to make it more meaningful.

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In summation, Mr. Beck concluded that the Polio Eradication Program is a major public health success in India. It has the potential for becoming a major international relations success in the region, and this program is worth continued support.

Updated Recommendations for Routine Poliovirus Immunization

Gregory S. Wallace, MD, MS, MPH, Medical Officer
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Wallace presented a follow-up to the Poliovirus Work Group's February 2009 presentation regarding the deliberations of the work group on the recommendations for the routine inactivated polio vaccine (IPV) schedule, including a schedule when combination vaccines are used, minimum intervals for IPV, and when accelerated schedules should / should not be used.

The work group proposed no changes to the current routine schedule for poliovirus vaccines. If 4 doses of IPV-containing vaccine are administered prior to age 4 years, an additional dose should be administered at age 4 to 6 years. For instance, with Pentacel, if the first 4 doses for DTaP, Hib, and IPV are given as per the schedule, an additional dose is proposed at 4 to 6 years of age. This is equivalent to Canada's routine IPV schedule. The reason for this proposal from the work group has to do with the continued threat of importation, given that polio has not yet been eradicated, and because incomplete data are available on the duration of immunity into adulthood with last dose at age 15 to 18 months. A footnote is proposed to the recommended schedule to emphasize the 4- to 6-year old dose, which reads, "The final dose in the series should be administered on or after the 4th birthday."

With regard to minimum intervals for IPV, age and dose intervals do affect the seroconversion response. Seroconversion rates are generally better when administered at 2, 4, and 6 months of age with the primary schedule, as opposed to the 2, 3, 4 month, or 6, 10, 14 week schedule. In addition, maternal antibody levels at the first dose are inversely related to seroconversion levels, particularly in the first 6 months of life. Longer intervals are optimal for booster response, and there should be at least 6 month intervals prior to the booster dose as this is optimal for memory cell maturation.

For the proposed catch-up schedule, the only change is the interval between the third and fourth dose being extended to 6 months. It was 4 weeks previously. There is also proposed footnote language about early doses that reads, "In the first 6 months of life, minimum age and minimum intervals are only indicated if the person is at risk for imminent exposure to circulating poliovirus (e.g., traveling to a polio endemic region or during an outbreak). A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months have elapsed since the second dose." That is equivalent to the routine recommendation for adults who have not been previously vaccinated.

With respect to next steps, pending an ACIP vote and deliberations and Notice to Readers, the draft is ready to be sent through clearance to clarify and summarize the recommendations. This will be available for reference and text for 2010 immunization schedule and the updated general recommendations publication. The nearly 10-year old ACIP recommendations and reports will be updated in the near future, but no fundamental changes are proposed. This will potentially be ready for a vote in October 2009.

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Discussion

Dr. Sawyer expressed concern about the minimum interval language. He asked whether the intent was for the same language to be a footnote on the regular schedule in addition to the catch up schedule (e.g., in the first 6 months of life, the minimum age and minimum intervals are only indicated if the person is at risk for imminent exposure). That will not apply to anyone unless they travel outside of the US. He wondered if, for example, a patient presented to their provider only 5 weeks after the previous dose the recommendation was that they not receive the next dose. This did not seem like a very practical recommendation, and he suggested softening of that statement so that it is not interpreted that the provider should not give this vaccine under any circumstances. A soft minimum interval that applies in some circumstances but not in another is really not tenable. It comes into play with some software programs because an immunization registry will program forecasting based on minimum intervals, but there are examples where Comprehensive Clinic Assessment Software Application (CoCASA), a CDC program used to assess immunization coverage, does not respect the same minimum intervals with regard to missing immunizations or invalid doses. That has created confusion in San Diego because clinics are following the immunization registry forecast, and then are being evaluated by the county health department with CoCASA such that they receive two different answers about whether a dose was or was not appropriate.

Dr. Wallace responded that for the general routine schedule, the footnotes do not usually include minimum intervals, and he thought everyone was aware of the space issues for the schedule itself. Certainly, the text can be included in the *MMWR* that announces a schedule that addresses accelerated schedules and minimum intervals. The concern has been minimum intervals being used inappropriately as routine accelerated schedules, which was why the work group felt the need for that and to provide the information on the first 6 months of life; however, the minimum intervals are as they are, so if a 4-week interval is used between dose 1 and 2 and 2 and 3, it would be considered a valid dose by CDC.

With regard to the 4-year old age group dose in light of the Hib shortage, it seemed to Dr. Schuchat that there would be many children over the next year or so who would be receiving their booster dose of Hib-containing vaccine late at perhaps age 3. She wondered if the committee considered whether someone received their 4th dose of IPV-containing vaccine at age 3, they would require another polio dose at 4 to 5 years of age.

Dr. Wallace responded that this issue did arise. While the work group recognized that this is an issue, they did not feel that there was sufficient information to inform that adequately. They had developed footnotes and information with many more caveats, but the work group ultimately decided that this would add to the confusion rather than clear it up.
To provide some level of comfort, David Greenberg (sanofi pasteur) reported that in the clinical trials, the Pentacel doses were given on schedule at 2, 4, and 6 months of age with the 4th dose at 15 to 18 months of age. There was good persistence of antibody with 95% of children maintaining seroprotective levels at 4 to 5 years of age. Not that this would change the language, but just to offer some additional reassurance that there are antibody levels that persist for years.

Dr. Wallace responded that this information was considered by the work group, but the deliberation of the work group pertained more to what is unknown into adulthood. In the pre-

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eradication era, they wanted to err on the side of making sure that coverage and protection was as complete as possible. This may become less of an issue as more data become available about protection in adults.

Dr. Sawyer remained somewhat uncomfortable with the modification of a catch-up schedule. The intent of a catch up schedule is to catch children up. It seemed as though they were recommending that children could be caught up for everything else except polio. Translating that into practice is very challenging for a provider. Providers will give children their DTaP but not give their polio and will hope to get them back in for that. Given the potential for confusion, he suggested changing the language from "only indicated" to "only recommended" or "usually recommended." The implication of the word "indicated" is that it is contra-indicated in other circumstances.

Dr. Wallace agreed that the language could be changed from "indicated" to "recommended" or "routinely recommended". To be clear, he stressed that the point of the footnote was not to tell people not to catch children up. It was to offer information so that people did not accelerate a routine schedule only in the first 6 months of life. This would involve potentially one or two doses at the most. However, it is important not to have a routine 6-, 10-, 14-week schedule.

Motion: Poliovirus Vaccine

Dr. Temte made a motion to approve the recommendation of the work group regarding poliovirus vaccine with the slight modification suggested by Dr. Sawyer. Dr. Ehresmann seconded the motion. The motion carried with 13 affirmative votes, 1 abstention, and 1 negative votes.

Dr. Sawyer clarified that he voted "no" because he remained concerned about the concept of a minimum interval, which they did not really mean in certain circumstances. To him, if they were not comfortable with the minimum of 4 weeks, it needed to be changed to whatever they were comfortable with. Practitioners will have to deal with this question a lot in deciding what truly constitutes a valid dose.

Dr. Seward thought there was additional wording in the *MMWR.* There are scientific data showing that there is quite inferior immune response if three doses are given of IPV on the accelerated schedule, so the routine recommendation is 2, 4, and 6 months. What they were thinking about with combination vaccines is the tendency for the catch-up vaccination schedule to become routine. Therefore, they wanted fairly strong wording to indicate that it should not be used on a routine basis. Acceleration should only be used under very rare situations. Catch-up is a separate issue. If a child is one year old and they have not had any vaccine, the risk of no protection is being weighed in terms of achieving some immune response as quickly as possible.
Given the global epidemiology of polio as it has been known for some years, Dr. Judson wondered why the US still started so young. Many of these questions would not arise if not starting at such a young age. That obviously excludes people who would be travelling or in very special situations.

Dr. Morse thought it was linked to other immunizations, which is a longer discussion.

Regarding the issue of catch-up versus regular schedule, Dr. Sawyer pointed out that the current language was in conflict with the general principles of immunization, which says to give

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every vaccine that can be given at a visit as long as they are within the recommended age limits. Contradiction in this language compared to other language raises the potential for problems.

VFC Resolution Update: Polio-Containing Vaccines

Dr. Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases

Dr. Santoli reviewed proposed changes to the VFC resolution that would address the minimum interval issue that was just discussed, as well as continuing to streamline the resolutions through references to published links.

Going through the components of the VFC resolution, the eligible group is defined as infants and children at least six weeks of age for the recommended schedule for 2, 4, and 6 to 18 months, and 4 to 6 years. The resolution refers to the current polio statement found at:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4905a1.htm

For the dosage intervals, specific information is included based on the day's discussion. The minimum interval from doses 3 to 4 is extended from 4 weeks to 6 months. The minimum interval from dose 1 to 2 and dose 2 to 3 remains at 4 weeks, and the minimum age for dose 1 remains 6 weeks of age. In addition, because each product has particular characteristics, the following links to the ACIP recommendations and notices that are related to each product are included:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4905a1.htm
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5210a8.htm
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5739a5.htm
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5739a4.htm

For the recommended dosage and the contraindications, the resolution refers to the FDA webpage through which package inserts can be found:

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

When a new recommendation and / or notice related to the changes that were voted upon is published, the language and links in this document that can be replaced by that new link. This is similar to the pneumococcal resolution discussed in February 2008.

Motion: VFC Resolution Update for Polio-Containing Vaccines

Dr. Chilton made a motion to approve the VFC resolution as stated. Dr. Baker seconded the motion. The motion carried with 14 affirmative votes, 1 abstention, and 0 negative votes.

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Discussion

Dr. Katz said that given the remarks by Dr. Chilton, Mr. Beck, and Dr. Judson, he thought there was an element of reality which had not quite been portrayed. The polio eradication effort was supposed to have ended in 2000, making the effort 9 years behind. Each year, the reported numbers of cases are almost the same. For 2008 it was 1,562 cases. He stressed that those were paralytic cases. For every paralytic case, there can be anywhere from 100 to 1,000 individuals excreting virus silently and causing transmission. Nigeria has had the same numbers of polio cases almost every year for the last 7 years because of failure to deliver vaccine. In contrast, children in India (Uttar Pradesh and Bihar) receive 7 to 10 doses of oral vaccine and they still have not eliminated polio. Thus, there may be a problem with the overall approach. As Mr. Beck pointed out, there is volunteer and donor fatigue. He reminded everyone that both CDC and WHO have committees on polio research and it is quite apparent that the programs followed since 1988 are simply not bringing polio to an end. There must be changes in the initiative, imagination, and funding of CDC and WHO to determine better ways to eradicate polio. Otherwise, they would have to accept it as a disease that will never be eliminated.

Measles, Mumps, Rubella Vaccine

Overview

Ms. Kristen Ehresmann
ACIP Member

Ms. Ehresmann pointed out that the ACIP measles, mumps, rubella (MMR) vaccine policy statement had not changed since 1998, with the exception of some changes related to the mumps outbreak in 2006. During the 10 years since the last policy statement was published, there was a shift into an era of post-elimination for measles and rubella. It is important to remember this in making decisions and discussing this topic. Decisions should be made that include aggressive follow-up to maintain this post-elimination status. There was vigorous discussion among the MMR Vaccine Work Group members. Within the work group, she was the lone vote with a public health perspective. Therefore, the proposed changes that the CDC staff provided the group did not go over very well and she I was solemnly voted down. The concern of her colleagues was feasibility and cost-benefit for institutions if a fairly strong approach was taken to recommending two doses of vaccination all of the time for persons born before 1957. Thus, they worked with CDC staff to develop excellent compromise language that addressed the concerns of the clinical and public health sectors. The new language was unanimously accepted. It was also presented to the Healthcare Infection Control Practices Advisory Committee (HICPAC) and was approved during their recent meeting.

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Proposed Changes of MMR Vaccine Evidence of Immunity Requirements for Healthcare Personnel

Dr. Kathleen Gallagher
Division of Viral Diseases, NCIRD

Dr. Gallagher presented an update on the proposed changes to the MMR vaccine evidence of immunity requirements for healthcare personnel. With regard to background, today's healthcare workers are at increased exposure to a variety of infectious diseases, including vaccine preventable diseases. There are specific recommendations to address vaccination or the corresponding proof of immunity requirements for healthcare workers. The two documents that address those issues were published in the *MMWR* in 1997 (*Immunization of Healthcare Workers*) and 1998 (*Measles, Mumps, and Rubella—Vaccine Use and Strategies for Elimination of Measles, Mumps, Rubella, and Congenital Rubella Syndrome and Control of Mumps*). During the national mumps outbreak in 2006, vaccine policy recommendations for children and high risk groups, including health care workers, were revised including the addition of 1 to 2 doses of the mumps or MMR vaccine.

Although these diseases are rare, measles and mumps in health care facilities continue to occur. Virtually all measles cases will visit at least one health care facility during their infectious period. Quite frequently, because measles is not the initial diagnosis suspected, they have multiple health care exposures. A study conducted in Washington State in the late 1990s showed that health care workers had a much greater increased risk of acquiring measles when compared with adults of their own age with the relative risk of 19 (95% CI 7.4, 45.4, $p < 0.01$) [Steingart KR, Tomas AR Dykewicz CA, Redd SC. Transmission of measles virus in healthcare settings during a communitywide outbreak. Infect Control Hosp Epidemiol. 1999; 20: 115-19]. It is known from measles epidemiology that in the late 1980s and early 1990s, many health care workers were reported with measles (n=643), 27% of whom were born before 1957 [CDC. MMWR. 1998; 47{RR-8}:1-57]. During the 2006 mumps outbreak in the US, there were numerous health care related exposures.

It is also known that nosocomial transmission of measles and mumps occurs in health care facilities and has been documented. In the post-elimination era for measles, from 2001-2008 there were 27 reported measles cases that were transmitted in health care facilities, which is about 5% of all US measles cases. In 2008, this was 11% of cases. There is considerable economic expense and a large public health effort involved with trying to contain these exposures and outbreaks. In 2008, Arizona had the largest US nosocomial outbreak of measles in over 20 years (n=14). There were many health care related exposures, not just in the original hospital. In three hospitals in this Arizona community, almost 8000 health care workers were exposed, of whom 25% had no documentation of immunity to measles in their occupational health records. These workers were serologically screened and 5% of the employees born before 1957 and 11% of those born after were susceptible to measles based on serologic testing. Nosocomial transmission of mumps can occur as well. The last well-documented occurrence of this was in Tennessee in 1986 and 1987 when there was nosocomial transmission of mumps in two hospital emergency departments that infected six health care workers and in two long-term care facilities where nine patients were infected.

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The current ACIP recommendations state that health care personnel without other evidence of immunity should routinely receive two doses of MMR vaccine for measles and mumps and one dose of MMR vaccine for rubella. These recommendations also stress the importance of vaccination to protect healthcare personnel and their responsibility to avoid transmitting these diseases and thereby causing harm to patients. These recommendations also include a permissive recommendation for one or two doses of MMR vaccine for unvaccinated health care workers born before 1957.

The current ACIP MMR vaccine presumptive evidence of immunity requirements for health care workers indicate that health care workers are considered to be presumptively immune if they have met one of four conditions: documentation of administration of appropriate vaccination against measles, mumps, and rubella; laboratory evidence of immunity; documentation of physician diagnosed disease for measles and mumps (this is not allowed for rubella); or birth before 1957. The latter three evidence of immunity criteria are what health care personnel are required to provide as far as documentation to be exempt from being vaccinated. There are also numerous footnotes in this language:

> *May vary depending on current state or local requirements.
> + Health-care facilities should consider recommending a dose of MMR vaccine for unvaccinated workers born before 1957 who are at risk for occupational exposure to measles and who do not have a history of measles disease or laboratory evidence of measles immunity.

The footnotes allow variability with regard to state and local requirements and again provide some permissive vaccination consideration for health care personnel born before 1957.

The language for measles and mumps outbreaks states, "During outbreaks, health-care facilities also should <u>strongly consider</u> recommending a dose of MMR vaccine to unvaccinated health-care workers born before 1957 who do not have serologic evidence of measles or rubella immunity or a history of measles disease." [CDC. *MMWR* 1998;47{RR-8}:1-57]. The language for a mumps outbreak states, "During an outbreak, health-care facilities should <u>strongly consider</u> recommending 2 doses of a live mumps virus vaccine to unvaccinated workers born before 1957 who do not have evidence of mumps immunity." [CDC. *MMWR* Notice to Readers. 2006;55(22):629-630].

The changes proposed during the February 2009 ACIP and HICPAC meetings included the addition of laboratory confirmation of disease, elimination of documentation of physician diagnosed disease for measles and mumps, and elimination of birth year before 1957 to state, "Currently, healthcare personnel are considered immune if they have one or more of the following: 1) Appropriate vaccination against measles, mumps, and rubella (i.e., administration on or after the first birthday of two doses of live measles and mumps vaccine separated by greater than or equal to 28 days and at least one dose of live rubella vaccine); 2) Laboratory evidence of immunity or laboratory-confirmation of disease."

During those two meetings feedback was received from both groups that suggested mixed support for the removal of birth year before 1957 as proof of immunity. Members of HICPAC and ACIP felt that requiring unvaccinated health care workers born before 1957 to be either serologically screened or vaccinated was not cost-effective, especially given the current low burden of disease. Thus, the issue was further discussed with the ACIP Adult Vaccine Work

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Group along with some external invitees, including some members of HICPAC. Based upon these deliberations, proposed language was developed. The proposed language was presented during the June 2009 HICPAC meeting and was voted on and approved by that body.

The first proposed change is the addition of laboratory confirmation of disease as adequate proof of immunity for measles, mumps, and rubella. The rationale for this is that this change is being made for completeness and consistency. Although they are rare, cases of measles, mumps, and rubella still occur. Naturally acquired immunity is robust and long-lasting; therefore, it is reasonable to conclude that if a health care worker can provide laboratory evidence of disease, they should be considered immune. For surveillance purposes, this type of data is routinely relied upon to define whether or not a person is a case of measles, mumps, and rubella. This proposed change will also be consistent with the varicella recommendations which already include laboratory confirmation of disease [CDC. *Prevention of Varicella. Recommendations of ACIP. MMWR.* 2007;56{RR-4}:1-37].

The second proposed change is to delete the documentation of physician diagnosed disease as adequate evidence of immunity for measles, mumps, and rubella. The impetus behind this change comes from many state and local public health colleagues who anecdotally report situations in which this criterion is not being adhered to as intended. For example, there have been anecdotal reports of scenarios in which physicians on staff at a facility where they are exposed report that they remember having measles as a child, which serves as their documentation of physician-diagnosed measles. In practice, it has become increasingly difficult for any health care worker who may have had clinical measles or mumps to be able to contact their childhood provider as they are either no longer in practice or are deceased. In addition, the accuracy of a clinical diagnosis of disease without laboratory confirmation has declined substantially, especially with vaccine modified disease (mumps).

Numerous studies have documented the decline in the predictive value positive of clinical diagnosis (in the absence of lab confirmation) with declines in disease incidence. In the case of mumps, it is known that there are numerous etiologies for non-epidemic parotitis. A study conducted in the early 1970s demonstrated that only 40% of vaccinated patients with parotitis could be lab confirmed as having mumps [Brunell, 1972]. Another study conducted over 30 years later showed that only 2% of 800 clinical mumps cases were lab confirmed and alternative etiologies could be found for 14% of these cases [Davidkins, 2005]. Studies conducted to assist with the documentation of measles elimination in the US showed the PVP declining from 74% to 1% [Hutchins, 2004]. Additionally, 87% of cases of rash illness that met the measles clinical case definition during 1997 / 1998 were ruled out with appropriate lab test [Harpaz, 2004].

Changes are also proposed to the footnotes to the tables, which refer to both routine circumstances and outbreak situations. For routine circumstances, the wording recommended is, “For unvaccinated personnel born before 1957 who lack laboratory evidence of measles, mumps and/or rubella immunity or laboratory confirmation of disease, healthcare facilities should strongly consider recommending two doses of MMR vaccine (for measles and mumps) and one dose of MMR vaccine (for rubella), respectively.” The change here from the current wording would basically be to change the wording from “consider” to “strongly consider” and from one to two doses of MMR for measles and mumps. The recommendations for rubella would remain unchanged. For outbreaks, the wording would read, “For unvaccinated personnel born before 1957, who lack laboratory evidence of measles, mumps and/or rubella immunity or laboratory confirmation of disease, health care facilities should recommend two doses of MMR vaccine during an outbreak of measles or mumps and one dose during an outbreak of rubella.”

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The change here is a wording change that from “should strongly consider recommending” to just “recommending” and from one doses of MMR to two doses of MMR.

The rationale for changing the language in these footnotes is that it allows health care workers born before 1957 to still be considered immune, but also allows facilities that have been screening and / or vaccinating these individuals to have ACIP and HICPAC support to continue this practice. Health care facilities can weigh for themselves the risk of an exposure to measles, mumps, or rubella in their facility and the cost associated to them if such an exposure were to occur. It also allows for aggressive vaccination of health care providers, including those born before 1957, when an outbreak occurs.

It is known from anecdotal reports and from surveys conducted in convenience samples that some health care facilities are already screening and / or vaccinating health care workers for measles, mumps, and rubella regardless of age. Of 38 respondents to a survey sent out on an occupational health listserv for health care facilities earlier this year, 26% reported that they conducted serologic screening and / or vaccination of all their employees, regardless of age. An additional 21% reported that they screened and vaccinated all new employees, regardless of age. The footnote wording proposed for routine circumstances will provide the support of ACIP and HICPAC for these facilities to continue these practices.

The anticipated burden to health care facilities in implementing these policies is likely to be low. A few health care workers will likely have lab confirmation of disease and there should be little or no cost associated with this change. It would basically be the health care worker having to acquire documentation from their medical provider. The proportion of health care workers with a history of disease as their only documentation of evidence of immunity is likely small, and many of these employees are likely to have been born before 1957. These policies could be implemented with other annual routine disease prevention measures, such as influenza vaccination and tuberculosis (TB) testing. Implementation could be started soon and phased in within a few years.

In conclusion, current policy was established more than a decade ago and needs to be updated. In the era of both measles and rubella elimination, the goal is 100% immunity in high risk populations. The tolerance for any cases or exposures has decreased. Health care personnel are at high risk for exposure, so it is important to protect them preemptively. Given the current epidemiology of measles worldwide, it is likely that there will be continued importations in the US, and measles exposures and outbreaks are likely to continue in health care facilities. Future mumps exposures in health care facilities are also likely. Some facilities already have policies in place that are consistent with the proposed changes.

Discussion

Dr. Baker requested further information about the intent of “strongly recommended” from “recommended” for routine.

Dr. Gallagher responded that the original proposal was to remove the 1957 requirement entirely. This was a compromise to provide stronger language in support of facilities that were already doing this even though it was not the current recommendation.

It was not clear to Dr. Baker why, if some facilities were already doing this, they needed ACIP’s support.

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Ms. Ehresmann replied that the rationale was that ideally they would like a statement reading, "It is recommended, even in a routine setting." However, the work group recognized from the feedback received from clinicians and the membership that this would not be practical or financially feasible for many institutions.

Dr. Chilton sympathized with the Tucson hospitals where this occurred, given that this was the largest outbreak in the last 20 years. However, the fact that it involved 8000 health care workers, some of whom were born before 1957, was not persuasive to him that the entire country should be immunizing everybody his age or thereabout. The costs associated with that seemed to be much greater than the benefit associated with adopting a changed policy for that throughout the country.

Dr. Gallagher agreed, indicating that this comment was also made during the February 2009 ACIP and HICPAC meetings. The proposed revision would actually allow birth before 1957 to remain as proof of immunity. The caveat was that if facilities were so inclined, the recommendation would support that. The work group heard people's concern about the cost and benefit of vaccinating everybody before 1957, especially considering that few health care workers have been affected by this. It is also known anecdotally and from the surveys that some facilities are already doing this preemptively because they have made a choice for risk-benefit or other reason in their facilities to vaccinate everybody born before 1957. The work group felt that the proposed language would help support that.

Dr. Judson agreed with Dr. Baker that there should probably be only one level of recommendations: recommended or not recommended. He also noted that he was involved in some of the discussions through the Adult Vaccine Work Group on hospital workers, and was head of a hospital infection control committee for about 20 years at Denver General Hospital. There have only been a handful of cases in the US. No cases have been endogenously transmitted for a very long time. All of the outbreaks have stemmed from importations. When he reviewed the state health department records in Colorado, he found that there have been no cases of measles in health care workers and only one or two exposures. Thus, the recommendation is speaking to a problem that does not exist in most places. In another 10 years, this will be completely irrelevant because nobody working then will likely have been born before 1957.

Dr. Seward said she perceived these as minor changes to the existing recommendations. She pointed out that it is currently standard of care to vaccinate during an outbreak. Over the last 10 years, she had never come across a health department that did not screen and vaccinate every healthcare worker born before 1957 during outbreaks. That is the current standard of care.

Dr. Judson agreed and thought that this was why there was no problem. He did not plan to vote against this. He found these to be very minor issues and that measles control in the US has been highly successful.

With regard to Dr. Judson's comment about one level of language, Dr. Temte reported that two days earlier the Evidence-Based Work Group strongly advised against doing anything other than "recommend" or "do not recommend." He thought it was also confusing to see "should consider" and "recommend" in quick success. This seemed to be saying, "We should do this, but we are going to back away from this because we are only considering it." He cautioned that using three partial words together really watered down the recommendation.

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Dr. Sawyer said that the term “health care facility” suggested to him larger entities that have policy making bodies, which most single private offices probably do not have. It was not clear to him whether this recommendation extended to all places where health care is delivered.

Dr. Gallagher responded that when she used the term “health care facilities” in her presentation, frequently it was because the groups surveyed represented larger health care facilities. However, the recommendations would apply to all health care workers.

Dr. Sumaya said he had no preference for saying “strongly considered” versus “considered” or “strongly recommended.” He wondered what the difference was in true contraindications.

Dr. Marcy wondered why documentation of physician diagnosed rubella was not one of the criteria.

Dr. Gallagher replied that rubella cannot be well-diagnosed clinically.

Dr. Marcy pointed out that the same was true for measles and mumps, so “physician diagnosed” should be eliminated for them as well. The last three cases he saw of mumps were of neumoparatitis and lymphadenitis. “Physician diagnosed” is simply meaningless. This is still included for international travelers and students at post-high school. He supported use of “should consider” versus “may wish to consider.”

Dr. Gallagher responded that the recommendations they were discussing focused only on health care workers. When the full 1998 recommendations are updated, consideration could be given to eliminating “physician diagnosed for international travelers and post-high school students.

Dr. Morse pointed out that some agreed upon, standardized criteria should be developed to avoid problems within individual discussions and negotiations.

Dr. Meissner inquired as to whether they should say “laboratory evidence of immunity” or if they should be more specific. With the 2006 mumps outbreak, they learned that cellular immunity did not correspond to protection against disease.

Dr. Gallagher requested clarification about whether Dr. Meissner was suggesting that something specific be included about types of laboratory confirmation that are acceptable.

Dr. Meissner responded that people do not look at cellular immunity as a measure. It is a complicated assay, and cellular immunity is not necessarily a marker of immunity. The question regarded whether to be specific about what constitutes immunity. He was thinking specifically in terms of those born before 1957.

Dr. Seward suggested defaulting to the guidance in the surveillance manual for the case definitions and what constitutes confirmation of disease, which is immunoglobulin M (IgM), polymerase chain reaction (PCR) culture, and rise in immunoglobulin G (IgG).

Ms. Ehresmann summarized that it appeared that there was agreement for some of the proposed changes. Eliminating physician diagnosis of measles, adding laboratory confirmation, and outbreak seemed to have consensus. They appeared to be stuck on routine circumstances and the language issue (strongly consider, et cetera). She wondered whether it would be

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possible to make a recommendation to vote on less than everything or address the issues upon which they seemed to be stuck.

Dr. Gallagher put up the proposed wording, upon which ACIP members were to vote:

Proposed Wording: Table 1

Acceptable presumptive evidence of immunity to measles, rubella and mumps for persons who work in health care facilities* (Table 1)

1) Documented administration of …(2 doses of live measles virus vaccine, one dose of live rubella vaccine, two doses of live mumps)†, *or*
2) Laboratory evidence of immunity or laboratory-confirmation of disease, or
3) Born before 1957 [& £ @]

For rubella, the following statement is included "(*except women of childbearing age who could become pregnant ++)*"

Proposed Language: Footnotes

(*For persons born before 1957*)
Footnote for ROUTINE circumstances:

> [£] "*For unvaccinated personnel born before 1957 who lack laboratory evidence of measles, mumps and/or rubella immunity or laboratory confirmation of disease, healthcare facilities should strongly consider recommending two doses of MMR vaccine (for measles and mumps) and one dose of MMR vaccine (for rubella), respectively*."

Footnote for OUTBREAKS:

> [@] "*For unvaccinated personnel born before 1957 who lack laboratory evidence of measles, mumps and/or rubella immunity or laboratory confirmation of disease, healthcare facilities should recommend two doses of MMR vaccine during an outbreak of measles or mumps and one dose during an outbreak of rubella*."

Discussion

Dr. Seward reminded everyone that the wording in existence from the 1998 iteration is "should consider" for the routine recommendation, and a lot of people are already doing this.

Dr. Neuzil wondered whether they wanted facilities to "consider recommending" or "to vaccinate."

Dr. Seward replied that this was pretty standard language that implies vaccinating.

Dr. Neuzil thought this should be very clear, "Should strongly consider administering or vaccinating with 2 doses."

Dr. Judson noted that the positive predictive value of a clinical diagnosis of mumps and rubella was never very good, except in an epidemic or a very common situation, so it was probably worthless. Most physicians could diagnose measles very well when the disease was occurring frequently; however, now they cannot. Positive predictive value becomes virtually meaningless for measles which barely exists except for the occasional importation. Citing studies from the

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1990s or 2000s really has no meaning to current deliberations. He thought "clinical diagnosis" should be removed in all cases as evidence of immunity.

Ms. Ehresmann pointed out that they appeared to have reached consensus on everything but the routine circumstance. The 1998 language says "should consider recommending," for which a suggestion was made to more clearly specify vaccinating versus recommending. With that in mind, she wondered if they could move forward with a vote. She was unclear on the use of the term "strongly" because there was a lot of discussion that it was not appropriate to use modifiers.

Dr. Pickering thought that the evidence-based medicine guidelines were not quite finished, but there is a move toward evidence bases for everything. Most evidence-based guidelines do not include adverbs as descriptors.

Dr. Katz wondered whether "two doses of MMR vaccine," could be stated as "two properly spaced doses."

Dr. Gallagher replied that this wording is in the table, but they could add it to the footnote or refer back to the table to define what "appropriately administered" means.

Motion 1: MMR Vaccine Evidence of Immunity for Healthcare Personnel

Ms. Ehresmann made a motion to approve the recommendation of the work group for evidence of immunity for healthcare personnel with the suggested changes. Dr. Baker seconded the motion. No vote was take, given that the discussion continued.

Following up from the HICPAC perspective, Dr. Elward pointed out that in the discussion during the February 2009 ACIP meeting, concern was expressed about making across the board recommendations of vaccination in routine circumstances due to the cost implications and the unfunded mandate it might impose on health care facilities in the absence of evidence that there are problems with measles control outside of outbreak situations. She indicated that HICPAC approved the language shown with these footnotes.

Dr. Morse noted that consideration should be given to whether ACIP was comfortable with having a different recommendation from HICPAC.

Dr. Seward said it would be preferable for the ACIP recommendation to be the same as HICPAC.

Dr. Schuchat reminded everyone that HICPAC and ACIP are advisory committees to CDC. CDC will utilize the committees' recommendations to develop and issue final recommendations. Therefore, it is unlikely that there would be two different recommendations. CDC is trying to harmonize with itself.

Dr. Cieslak proposed that they remove the footnote for routine circumstances from the motion.

Dr. Gallagher wondered whether, based on the wording changes suggested for the first footnote, a change needed to be made to the wording on the second footnote to make the language consistent (e.g., change the word "recommend" to "vaccinate").

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Dr. Neuzil stressed that they were not making the recommendation for facilities to consider recommending. She believed they were making a recommendation to vaccinate, which was her interpretation of what she was voting on.

Dr. Chilton pointed out that based on the data presented, it appeared that only 5% of those born before 1957 would be susceptible. Therefore, the cost to prevent cases to those born before 1957 who are exposed to measles, mumps, or rubella is about $2,800 per person. That seemed unacceptable.

Dr. Judson added that an arbitrary cut off had been established for immunity for which there is no real basis. He thought 5% may be a very high figure. That is, probably well less than 5% would actually be susceptible.

Motion 2: MMR Vaccine Evidence of Immunity for Healthcare Personnel

In light of the comments made by Drs. Schuchat and Seward, Ms. Ehresmann revised her motion to approve the recommendation of the work group for evidence of immunity for healthcare personnel as it was written to be consistent with HICPAC. Dr. Baker withdrew her second and Dr. Sawyer seconded the revised motion. The motion did not carry with 4 affirmative votes, 0 abstentions, and 11 negative votes.

Motion 3: MMR Vaccine Evidence of Immunity for Healthcare Personnel

Dr. Baker made a motion to accept the footnote for outbreaks as listed and modify routine circumstances to read “for unvaccinated personnel born before 1957 who lack laboratory evidence of measles, mumps and / or rubella immunity or laboratory confirmation of disease, health care facilities should consider vaccinating personnel with two doses of MMR vaccine at the appropriate interval.” Dr. Neuzil seconded the motion. The motion carried with 11 affirmative votes, 0 abstentions, and 4 negative votes.

Dr. Cieslak requested clarification regarding whether this actually represented a change. The old language did not discuss the number of doses for routine vaccination.

Dr. Seward replied that the old language was one dose for measles and one dose for rubella and until 2006, it was one dose for mumps. In 2006 it was changed to two doses for mumps, which is the current routine recommendation. The measles is the most severe of the three illnesses, so they thought it was logical to make the routine recommendation consistent for outbreaks and give two doses for measles as well. For routine, it was a change from one dose to two for measles. It is currently two doses for mumps. That was changed in 2006. It has always been one for rubella because rubella is basically a one-dose policy. This is just making it consistent for measles and mumps.

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Dr. Judson said there was a scientific dissidence. For the outbreaks having two doses, he did not believe there was any evidence or immune-competent adults to suggest that a second dose would do anything to respond to an outbreak. By the time this second dose is administered, the outbreak is over and the population is generally immune, especially for measles.

It was noted that the outbreak in Arizona lasted for about 5 months.

Human Papillomavirus (HPV) Vaccines

Overview

Janet Englund, MD
Chair, ACIP HPV Vaccine Workgroup

Dr. Englund indicated that during this session, members would be hearing about two issues that would soon be coming up for an ACIP vote: 1) bivalent HPV vaccine in females, last discussed with ACIP in October 2008; and 2) quadrivalent HPV vaccine in males, not previously considered by ACIP.

The bivalent HPV vaccine is a two-component HPV vaccine. The biologic license for application was first submitted with interim data from the phase III vaccine trial in 2007. Following feedback from the FDA, GlaxoSmithKline (GSK) decided to wait for end-of-study data, which was submitted to the FDA in March 2009. The HPV Vaccine Work Group is preparing for an ACIP vote, which may take place in October 2009. Therefore, data are being presented to the full ACIP membership during this session so that they would be prepared for the potential upcoming vote. Also, a supplementary BLA was submitted for the quadrivalent HPV vaccine in males in December 2008. The HPV Vaccine Work Group is likewise preparing for a potential ACIP vote in October 2009.

Workgroup activities throughout the past several months have included a great deal of discussion about the bivalent HPV vaccine and the quadrivalent HPV vaccine. Bivalent HPV vaccine discussions have included ASO4 adjuvant mechanism of action / meta-analysis of adverse events, final Phase III efficacy results and cross protection data, comparative bivalent / quadrivalent immunogenicity, co-administration with other adolescent vaccines, and potential recommendations. Quadrivalent HPV vaccine in males discussions have included safety and efficacy in males, acceptability of male vaccination, cost-effectiveness, and recommendation options.

Update on GSK Cervical Cancer Candidate Vaccine (Cervarix®) Including Final Efficacy Results

Gary Dubin, MD
GlaxoSmithKline

Dr. Dubin provided the committee with an update on new clinical data available for the GSK cervical cancer candidate vaccine Cervarix®, including an update on the current regulatory status of the vaccine.

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The GSK vaccine is formulated with HPV 16 and HPV 18 virus-like particles and the AS04 adjuvant system which includes aluminum hydroxide salts and monophosphoryl lipid A. AS04 is included in the vaccine because in early clinical development, it was shown to enhance immune responses to the virus-like particles. GSK has conducted an extensive clinical development program, including approximately 30,000 women ages 10 years and up. Cervarix® is now licensed in over 95 countries, including the 27 countries of the European Union (EU). In some of these countries, there are on-going post-licensure activities to generate additional information in the real-world use setting. There are new clinical data that were submitted to the FDA in March 2009. The Center for Biologics Evaluation and Research (CBER) review clock is now re-started. The primary new clinical data include final efficacy data from the pivotal trial of HPV-008, which was presented previously as interim data.

There were a number of previous ACIP presentations between 2005 and 2009, which included the following:

- Phase 2 data: vaccine efficacy, safety and immunogenicity (including long-term follow-up) [Harper DM et al. Lancet 2004; 364:1757-65; and Harper DM et al. Lancet 2006; 367:1247-55]
- Interim results of pivotal Phase 3 efficacy trial in 15-25 year olds [Paavonen J et al. Lancet 2007;369:2161-70]
- Age bridging data in 10-14 and 26-55 year olds [Pedersen C et al, J Adol. Health 2007, 40(6):564-71; and Schwarz T et al. Vaccine 2009; 27(4):581-7]
- Integrated safety analysis from 11 trials involving ~30,000 women (~16,000 receiving active vaccine) [Descamps D et al. Vaccine 2009, 5(5) [Epub]]
- Meta-analysis of autoimmune diseases with ~68,000 subjects in clinical trials (~37,000 receiving AS04-containing vaccines) [Verstraeten T et al. Vaccine 2008, 26(51):6630-8]
- Adjuvant system mechanism of action

The new data upon which Dr. Dubin focused during this session included the following:

- Final efficacy analysis of pivotal Phase 3 trial (HPV-008)
- Comparative study of immunogencity and safety of GSK vaccine and Gardasil® (HPV-010) [Gardasil® is a registered trademark of Merck & Co Inc.].

The HPV-008 study enrolled over 18,000 women in 14 countries. It was a double blind randomized trial in which subjects received either the HPV vaccine or Hepatitis A vaccine as a control. It was an event-triggered study in that the interim analysis was event-triggered and the final analysis was triggered by the requisite number of cervical intraepithelial neoplasia (CIN)2+ events that were pre-specified in the study protocol. Subjects were followed for 48 months in this study. When the interim analysis was conducted, the mean follow-up time completed at that point had been 15 months for follow-up on average following the first dose of vaccine. With the final analysis, the mean follow-up time was about 39 months following the first dose of vaccine. Thus, there was a considerable amount of additional follow-up time and many more end points accrued that made this analysis much more statistically powerful than the interim analysis. An end-of-study analysis will be conducted when all subjects complete the 48 months of plan study follow-up.

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The primary objective of the study was to assess efficacy against CIN2+ associated with HPV16 or 18. This was assessed in the according to protocol (ATP) cohort and importantly, the endpoint was evaluated in women who were DNA negative and CR negative at month 0 and DNA negative at month 6 for the HPV type considered in the analysis, so very much an ATP analysis. There are important secondary and exploratory objectives assessed in this study, which included the assessment of efficacy against CIN2+ and CIN3+ lesions, irrespective of the HPV type detected in the lesion; efficacy against persistent infections and CIN2+ lesions associated with non-vaccine oncogenic types; evaluations on the vaccine impact in reducing the need for colposcopy and on cervical excision procedures (including LEEP, laser knife, or cone biopsy); and vaccine safety.

The interim analysis was triggered when 23 cases of the primary endpoint were observed in the total vaccinated cohort, which was met in November 2006. The results from that interim analysis were published in 2007 [Paavonen et al, Lancet, 2007;369:2161-70]. The final analysis was to be triggered when at least 36 cases of the primary endpoint, CIN2+ associated with HPV-16 or 18 were observed in the ATP cohort. This trigger was met in October 2008. The CIN2+ endpoint assessments used HPV DNA detection methodology that was published previously. This detection system allows detection of 14 oncogenic HPV types, including HPV16 & 18. Two types of analyses have been performed. One analysis was the pre-specified analysis, which evaluated the association of virus and the CIN2+ lesions just by simple DNA detection. An additional analysis using an HPV Type Assignment Algorithm (TAA) to assign likely causality in cases where multiply infected lesions were detected was also performed.

Understanding the cohorts that were evaluated in the HPV-008 trial is important because there are a number of different evaluations. The total vaccinated cohort (TVC) included all women who received at least one dose of vaccine regardless of their baseline cytologic, serologic, or HPV DNA status. This cohort included over 18,000 women and case counting started on day 1. Another cohort evaluated was the according-to-protocol cohort. This cohort included all women who complied with the protocol, received all 3 doses of study vaccines and had normal or low-grade cytology at month 0. An additional cohort evaluated is referred to as the TVC naïve. This is a subset of the TVC, which included all women who received at least one dose of vaccine and who, at baseline, had normal cytology, were HPV DNA negative for all 14 oncogenic types detected in GSK's assays, and were seronegative for HPV 16 and HPV18 at study entry. These two cohorts are believed to be important because they approximate groups that have public health relevance. The TVC cohort approximates the general population, which includes sexually active young women with prevalent infections and lesions. The TVC naïve cohort approximates the primary target population for universal vaccination programs, mostly young women before onset of sexual activity or before sexual debut.

With respect to the results of the primary objective, vaccine efficacy against CIN2+ lesions associated with HPV16 and 18 was high and statistically significant using either the composite endpoint of the two HPV types considered in the analysis, HPV16 or 18, or considering the two types individually. The analysis using the Type Assignment Algorithm (TAA), was to assign causality in lesions with multiple infections, also showed very high level of efficacy—about 98% protection for the composite endpoint. As mentioned earlier, the primary endpoint only considered lesions in women who were seronegative as baseline for the respective type considered in the analysis. GSK, therefore, evaluated the primary objective in women irrespective of their baseline serostatus. This is a larger group of women, including women who

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were seropositive or seronegative at entry. The high level of efficacy is maintained in this broader cohort with point estimates that are actually quite similar than the estimates seen in the more restricted primary endpoint analysis. Vaccine efficacy was also evaluated against HPV 16 and 18 CIN2+ lesions in the TVC naïve and the TVC cohorts. Vaccine efficacy was very high in the TVC naïve cohort at over 98%. In the TVC cohort, vaccine efficacy was 53%. It should be noted, however, that the CIN2+ lesions in this analysis included lesions associated with pre-existing infections—an important point to consider.

Another important analysis in the assessment of vaccine efficacy was evaluating efficacy, not only against CIN2+ lesions associated with HPV16 or 18, but evaluating efficacy against lesions irrespective of the HPV type in the lesions. These analyses are important because they provide perspectives on the overall public health impact that the vaccine is expected to provide against clinically relevant lesions irrespective of whether it is a vaccine type. In the TVC naïve cohort, the vaccine prevented about 70% of CIN2+ lesions and about 87% of CIN3+ lesions overall. An epidemiologic estimate of the proportion of CIN2+ and CIN3+ lesions associated with HPV 16 and 18 suggests that the vaccine efficacy extends beyond what would be expected of a vaccine that would provide protection only against vaccine types. Regarding the results in the TVC cohort, efficacy against CIN2+ and CIN3+ lesions was 30% and 33% respectively. Again, however, it should be noted that the majority of these endpoints were the result of pre-existing infections. That point is emphasized in terms of the cumulative incidence of lesions over time in the TVC. Lesions development occurs at the same rates in both the vaccine and the control groups until about month 18 when there begins to be separation of the curves. This is because most of the lesions that develop early in the trial, during the first 18 months, were derived from pre-existing infections. It is only after there is a wash out of these lesions that the prophylactic affected the vaccine becomes apparent, during the latter part of the follow-up. The efficacy of the vaccine was also evaluated in the prevention of colposcopy referral and cervical excision procedures, which included LEEP, laser knife, or cone biopsy. These endpoints have public health relevance. Additionally, cervical excision procedures may be linked to subsequent issues like cervical incompetence. In both the TVC naïve and the TVC cohort, substantial reductions are observed in these important endpoints.

In regard to efficacy data against CIN2+ lesions associated with non-vaccine oncogenic HPV types, efficacy was evaluated using composite endpoints for a number of oncogenic HPV types. Efficacy was also evaluated individually for a few of the most important vaccine types. Vaccine efficacy against HPV 31 and 45, considered as a composite endpoint in the TVC naïve cohort, was 100% and in the TVC cohort was 52%. Again, many of the lesions in the TVC were the result of pre-existing infections. There were substantial and significant reductions in CIN2+ lesions associated with composites of HPV types that constitute the A9 species. The A9 species is the family of viruses that are phylogenetically related to HPV 16. Significant reductions were also seen in CIN2+ lesions associated with viruses in the A7 species, which are viruses phylogenetically related to HPV 18. With regard to the 10 most frequent HPV types associated with cervical cancer, there was a significant reduction in CIN2+ lesions associated with these types, evaluated as a composite endpoint. Pertaining to HPV 31 and HPV 45,, there was a high level of protection against 6 month persistent infection and CIN2+ lesions for HPV 31. For HPV 45, there was a high level of protection against 6 month persistent infection in the TVC naïve. While there were a limited number of CIN2+ cases associated with HPV-45, there were no cases in the vaccine group. In the TVC cohort, there was statistically significant evidence of efficacy against lesions associated with both HPV 31 and HPV 45 CIN2+ lesions and also persistent infection.

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Most of the safety data from the trial were published at the time the interim analysis was conducted. However, long-term outcomes, such as the occurrence of serious adverse events, medically significant conditions prompting physician visits, new onset autoimmune diseases, and pregnancy outcomes were assessed through the long-term follow up phase of this study. For each of these safety endpoints, the occurrence rates were quite similar between the vaccine (N = 9,319) and the control (N = 9,325) groups. Serious adverse events (SAE) were 7.5% in each the vaccine and control group. Medically significant conditions (e.g., prompted a physician visit) were 31.8% in the vaccine group and 32.4% in the controls. New onset autoimmune disease was 0.8% in each group. In terms of selected pregnancy outcomes, congenital anomalies were 0.7% in the vaccine group and 0.5% in the controls, and spontaneous abortions were 9.1% in the vaccine group and 8.7% in the controls.

To conclude on HPV-008, the trial confirms vaccine efficacy against CIN2+ associated with HPV 16 and 18 as a composite endpoint or with the two vaccine types considered separately. The study also showed significant impact on CIN2+ and CIN3+ lesions overall, irrespective of the HPV type found in the lesion, and irrespective of the baseline DNA status of subjects. Efficacy was observed against CIN2+caused by specific non-vaccine types. A significant impact was seen on colposcopy referrals and cervical excision procedures. Consistent with what was observed in the interim analysis of this study, the final analysis confirms a favorable safety profile.

Regarding the HPV-010, this is the first head-to-head study comparing the GSK vaccine and Gardasil® with respect to immunogenicity and safety. High efficacy has been observed for both vaccines in the pre-licensure setting. Any differences in the long-term protection between the two vaccines, if they exist, are unlikely to become apparent for many years. Additionally, apparent differences in the cross protection profiles of the vaccines could potentially be related to immunologic responses against vaccine antigens. It is important to note that published immunogenicity data on the two vaccines cannot be compared directly because of differences in study methodologies and differences in serologic assays. This study is the first head-to-head comparative study evaluating the two licensed vaccines. GSK's vaccine is not licensed in the US, but is licensed in other countries using the same methodology to assess immunogenicity and safety.

The composition of the two vaccines is an important consideration in thinking about the results. The GSK vaccine contains 20 micrograms each of HPV 16 and HPV 18 virus-like particles. The antigens are expressed in a baculovirus expression vector system and the vaccine contains the AS04 adjuvant system. Gardasil® contains 40 micrograms of HPV16, 20 micrograms of HPV 18, and additionally the vaccine contains HPV 6 and 11 virus-like particles. The virus-like particles are expressed using a yeast system and the vaccine contains an aluminum hydroxyphosphate sulphate adjuvant.

The primary objective of the study was to compare the geometric mean antibody titers (GMTs) for HPV 16 and 18 using seroneutralizing antibodies as the measure at month 7. That is one month after completion of the three-dose series for both vaccines in women aged 18-26 years. This testing was performed at the GSK biologicals labs using a pseudovirion-based neutralization assay (PBNA) developed by the National Cancer Institute (NCI) [Pastrana et al. Virology 2004;321:205-16]. There were some important secondary endpoints assessed in the study, which included serum neutralizing geometric mean antibody titers in month 7 in women in

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2 other age strata: 27 to 35 years and 36 to 45 years. Neutralizing antibody levels were assessed in cervico-vaginal secretions (CVS) using PBNA. The frequency of antigen-specific memory T-cells and B-cells were assess, as were reactogenicity and safety.

The HPV-010 study was conducted in 40 US study centers using observer blind methodology, which is the highest level of blinding possible given the use of commercial supplies of Gardasil®. Over 1100 women between the ages of 18 and 45 years were randomized to receive vaccine according to the schedules either 0, 1, 6 months for the GSK vaccine or 0, 2, 6 months for Gardasil®. A single dose of aluminum hydroxide placebo was administered either at month 2 in the GSK vaccine group or month 1 in the Gardasil® group to maintain the study blind. Enrollment was stratified into 3 age strata between 18 and 45 years of age. Importantly, statistical criteria to assess immunologic differences between the vaccines, including tests of statistical superiority for the immunogenicity endpoints, were all pre-specified.

Regarding the primary and secondary age stratified analyses, in each of the three age strata, the GMT for the GSK vaccine group compared to the Gardasil® group were statistically significantly higher in the GSK group versus the group of women receiving Gardasil®. The HPV 16 neutralizing antibody geometric mean antibody titers, assessed at month 7, were between 2- and 5-fold higher in the GSK vaccine group depending on the age strata. The HPV 18 neutralizing antibody geometric mean antibody titers, assessed at month 7, were between 7 and 9 fold higher. Remember, the antigen content of the two vaccines differs for HPV 16 in that Gardasil® has 40 micrograms of HPV 16 virus like particles and the GSK vaccine has 20. For HPV 18, the two vaccines have the same relative antigen content. Positivity rates at Month 7 for HPV-16 and -18 antibodies measured in cervico-vaginal secretions (CVS) by PBNA (women 18-45 years) was higher with GSK Vaccine than with Gardasil®. The frequency of circulating antigen-specific memory B-cells at Month 7 was 2.7-fold higher with GSK vaccine than with Gardasil® for HPV-16 and HPV-18 . The frequency of CD4+ T-cell responses at Month 7 was significantly higher with GSK vaccine than with Gardasil® for HPV-16 and HPV-18.

Turning to the safety evaluations, a higher percentage of women in this study who received the GSK vaccine reported solicited local symptoms within the 7 days after any vaccine dose. Symptoms in both groups tended to be transient, and all of the solicited symptoms resolved within the 7 day observation period. Solicited general symptoms were generally comparable, except for fatigue and myalgia which occurred at a somewhat higher rate in the GSK vaccine group. Again, these symptoms were transient, and resolved. Unsolicited symptoms, including serious adverse events, occurred at similar rates in the two groups. Importantly, when compliance with completion of the three dose course in the two groups was assessed, the compliance levels were high and comparable. Both groups had about 84% of subjects completing the three-dose schedule.

In conclusion, in the HPV-010 study in month 7 after vaccination, immune responses were significantly higher with the GSK vaccine compared to Gardasil®. This included parameters such as serum neutralizing antibody responses and antibody positivity rates in CVS, memory B-cell frequencies, and T-cell frequencies. The vaccine safety profiles were consistent with previous studies of both vaccines. The differences observed in reactogenicity did not impact compliance with completion of the 3-dose course. GSK believes that long-term follow-up evaluations in the post licensure setting will be helpful to assess the duration of protection with the two vaccines, and will also help to determine the clinical relevance of the observed differences in immune responses from this study.

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Overall conclusions and observations are that HPV-008 efficacy data confirm the efficacy of the vaccine against CIN2+ associated with vaccine types, and extends the efficacy profile of the vaccine including demonstration of an impact on the CIN2+ overall and associated with non-vaccine types, including HPV 31 (HPV-16 related) and HPV 45 (HPV-18 related). The HPV-010 data confirmed that the GSK vaccine and Gardasil® induced different immunologic responses. The differences in responses were observed for both HPV 16 and 18 components, although the largest differences observed were for HPV 18 where the two vaccines have the same virus like particle (VLP) dosage. Although the importance of these differences is unknown, they may represent determinants of duration of protection against HPV16 or 18 and / or protection against non-vaccine types. GSK thinks it is important to recognize that disease modeling will help to determine how the observed differences in vaccine profiles might ultimately translate into differences in the public health impact of the vaccines. These data, taken together with long-term data from Phase II efficacy studies, indicate that the GSK HPV vaccine is likely to provide long-lasting protection against cervical cancer.

Discussion

Dr. Judson asked whether there was any reason to think that the superior neutralizing antibody response in the GSK vaccine was related to a difference in adjuvants.

Dr. Dubin replied that although it was difficult to know for sure. most of the evidence suggested that it was the adjuvant that resulted in the difference. This comes from previous studies that have compared different formulations of GSK vaccines using AS04 or aluminum hydroxide as an adjuvant, in which the results were very similar to those observed in the 010 study. Significantly higher neutralizing antibody titers were observed with the AS04 adjuvant compared to aluminum hydroxide, and a slightly higher rate of reactogenicity is observed. It is hard to know whether they are mechanistically related, although they certainly could be.

In the analysis of the reduction in CIN2+ due to the non-vaccine serotypes, Dr. Marcy wondered how many of the infections ascribed with non-vaccine serotypes were dual infections with 16 and 18, such that some of that response could be due to the 16/18 response.

Dr. Dubin responded that it was now very clear when data from these large studies are evaluated that it is not uncommon to have lesions where multiple HPV types are detected. The analyses shown were pre-specified in which they assessed only the types that were considered in the analysis. That being said, GSK has conducted additional analyses in which lesions that contain HPV-16 or 18 co-infections have been removed and there is still evidence of statistically significant protection against CIN2+ lesions. Some of this data will be available in the public domain soon. It was not presented here because there was limited time to go through the complexity of multiple infections. It is hard to know when there are multiple infections which type is actually is driving the lesions, so an analysis that excludes co-infected lesions is considered to be a very conservative analysis. An analysis that does not exclude them is considered to be the other end of the spectrum. Therefore, the results from these two kinds of analyses represent a range that probably reflects the spectrum of cross-protection.

Dr. Meissner noted that the concentration of antibodies necessary to neutralize 31 and 45 presumably was higher than the concentration necessary to neutralize 16 and 18 because those

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were in the vaccine itself. As time goes by, with waning titers, he wondered whether the ability of those antibodies to neutralize the non-vaccine serotypes may be reduced or even disappear.

Dr. Dubin stressed that it was important to point out that, with respect to the mechanism of cross protection, it is not clear whether it is an antibody-mediated phenomenon or whether it is related to induction of T-cell responses. That is one of the reasons that some of the GSK studies not only assessed antibody responses, but also, as in the 010 study, they assessed T-cell reactivity. In the HPV-008 study, there are now data out through 3 ½ years, so what he showed was a cumulative estimate of efficacy over that time period. There are also data, not shown here, from another study in which efficacy has been assessed out through 7.4 years (not using CIN2+ as the endpoint, but in one of the Phase II studies) in which incident infection was an endpoint. There is evidence of sustained protection against both HPV31 and 45 through that entire follow-up period, which GSK believes will predict protection against associated lesions as they continue to engage in follow-up in this program.

Dr. Neuzil thought that the best information regarding the public health impact of this vaccine on cervical cancer was the overall vaccine efficacy against CIN2+ and CIN3+ irrespective of HPV type in the lesion [Slide 12].

Dr. Dubin agreed. Two cohorts are analyzed. The broadest is the TVC cohort that includes all women enrolled in this study regardless of their baseline serostatus and regardless of what type was ultimately detected in a lesion. The point estimate of efficacy, again CIN2+ of 30%, is what would be expected if the vaccine were introduced into a population of women that includes women who have pre-existing infections and pre-existing lesions. The TVC naïve cohort is a subset of that cohort and includes only women who had no evidence of oncogenic infection at entry into the study. Other than that, there are no restrictions.

Regarding the data on local adverse effects, Dr. Duchin (NACCHO) inquired as to whether Dr. Dubin could show them the data on general adverse effects, which he mentioned was higher in the GSK vaccine for fatigue and myalgia.

Dr. Dubin responded that the solicited general symptoms were generally comparable for both vaccines except for fatigue and myalgia

Dr. Baker asked about syncope for each group.

Dr. Dubin replied that in the larger study there were 18,000 subjects. In that study, there were reports of syncope, but they occurred at the same rates in the two groups. In fact, he thought the numbers were exactly balanced with a total of 11 subjects in the HPV group and in the Hepatitis A control group that had syncope develop after vaccination and one subject in each group who developed pre-syncope.

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GARDASIL® Update: Safety & Efficacy in Boys and Men

Richard M. Haupt, MD, MPH
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Dr. Haupt reminded everyone that he had presented a lot of these data during the February 2009 ACIP meeting. In addition to presenting data on boys and men from the safety and efficacy study, Protocol 20, designed specifically to assess disease and infection endpoints, Dr. Haupt presented immunogenicity data in 9 to 15 year old males. These data were collected over 5 years ago from an immunobridging study, which was submitted to the FDA with the original biological license application. During this session, Dr. Haupt focused on the immunogenicity data in male subjects 9 to 15 years of age, and the efficacy and safety data in 16-26 year-old men.

In the clinical program for men and boys there are two adolescent studies, Protocols 16 and 18. Protocol 16 was an immunobridging and safety study in which immune responses were examined using the Merck competitive Luminex immunoassay. This was assessed in 10 to 15 year old adolescent girls and adolescent boys and compared to a control group of 16 to 23 year old women as a means to bridge the efficacy being observed in women 16 to 23 years of age to that of the adolescent population. Protocol 18 was an immunogenicity and safety study of GARDASIL in 9-15 year-old boys and girls. This protocol also included a saline placebo arm to evaluate reactogenicity. It was a safety study that examined immunogenicity and safety, and included both the aluminum adjuvant as a control arm and a saline placebo only. That study was extended to a 36-month follow-up, and has subsequently been extended to a long-term effectiveness study. Merck is following both girls and boys in that study for 10 years to assess long-term effectiveness and safety. Disease endpoints are being collected over time from that population.

Protocol 20 is the male study. It is a randomized, double-blind, placebo-control trial. It was designed to be a 36-month study. Earlier on 2009, based on the very high efficacy demonstrated and the safety profile, Merck's data and safety monitoring review board recommended that this study be ended early and that vaccination of the placebo recipients be started. Based on that recommendation, the 36-month study plan will be shortened. The study enrolled heterosexual as well as men having sex with men (MSM), for a total of about 4000 subjects of whom about 600 are in the MSM population. For men enrolled in this trial, Day 1 polymerase chain reaction (PCR) and serology result were obtained for the 4 types in Gardasil® (6/11/16/18). Men were excluded who had more than 6 lifetime sex partners, so a lower risk population is represented. However, they could still have had as many as 5 lifetime sex partners. The point is that when men were examined across the board in this study, about 83% were naïve at baseline to all four types. That offers a sense of the susceptibility of a sexually active male population to the vaccine types that are in Gardasil®. There is a great opportunity to prevent infection / disease caused by these four types—even in men who are sexually active.

Regarding disease endpoint efficacy, the primary endpoint was a 6/11/16/18 related external genital lesion (EGL). EGL was a composite endpoint that included genital warts and PIN of any grade. PIN is defined as penile, perineal, or perianal intraepithelial neoplasia. Primary endpoint efficacy was very high at 90%, which is highly statistically significant. This is driven

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predominately by genital warts. There were three cases in the Gardasil® group, 28 for genital warts in the placebo, for vaccine efficacy of 89.4%. There was 100% efficacy against PIN, although there were very few numbers. PIN is a fairly rare condition and this study was never powered to demonstrate efficacy against PIN. It was designed as an extension to examine infection and disease endpoints and to demonstrate efficacy in males for specific disease endpoints.

There were two secondary objectives that were infection endpoints. One was efficacy against the persistence of infection. Much like in the women's studies, that is defined as persistent infection with two or more consecutive positive samples with the same HPV type 6 months apart. There was also an anytime DNA detection, which is a large category that includes any one-time positivity whatsoever (swab, biopsy, et cetera). Persistent infections are very important as a predictor for disease development. There was approximately 86% efficacy. The efficacy against individual types in that analysis was high for all four types, and there was modest efficacy in the endpoint of anytime DNA detection.

Immune response was examined measured with Merck's competitive Luminex immunoassay, which is an assay that measures one specific neutralizing antibody against a known neutralizing epitope. The bottom line is that much like what has been observed in women, the virus-like particles (VLPs) in Gardasil® are highly immunogenic. There was virtually 100% seroconversion as measured in the peak response at month 7. There were very high geometric mean titers (GMTs). As with GMTs in women, over time as measured by Merck's assay, some individuals reach a point at which their antibody level cannot be measured. However, continued efficacy is observed even in the face of that.

In terms of general safety, and much like was seen in women, the most common adverse events observed in men were local injection site reactions. It was the most common vaccine-related adverse event as well. In the boys and men, very rare serious adverse events were seen and none were observed that were vaccine related. Very few men who discontinued, and they certainly had very few discontinued to what was considered to be vaccine related.

In addition, Merck examined immune response in 9 to 15 year old adolescent boys. There are times when efficacy studies in certain sub-populations cannot be conducted. This is one of those experiences where it would be unfeasible to conduct an efficacy study because of issues of sexuality and genital sampling. In discussions with the FDA, it was agreed that immunobridging to this population was an appropriate way to infer efficacy in the 9-15 year old population to demonstrate that immune responses to GARDASIL® in 9- to 15-year-olds are non-inferior to those in 16- to 26-year-olds and to demonstrate that GARDASIL® is well-tolerated in 9- to 15-year-olds. The data from 9 to 15 year old adolescents across all four vaccine types demonstrated a non-inferior immune response. In fact, an immune response in the adolescent boys was 2- to 3-fold on average higher than what was observed for adult males. In terms of immune response to HPV 6, there is a higher level in the younger adolescent and then it declines as the boys go through puberty and reaches a similar level across the older age groups studied. This profile is virtually identical for the other three types (11, 16, 18). The same profile has been observed in women as well. There is nothing different about the adverse event profile in the younger adolescent boy populations. The most common adverse event was local injection site reactions to the vaccine. There were very few serious adverse events and very rare discontinuations due to vaccination.

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In summary with respect to safety and efficacy in boys and men, genital HPV infections lead to a significant burden of disease in men. HPV 16 and 18 are important cancer-causing HPV types in men and are responsible for the majority of HPV-related penile, anal, and oropharyngeal cancers and their associated pre-cancers. HPV types 6/11 cause over 90% of genital warts and RRP. GARDASIL® is highly efficacious against HPV 6/11/16/18-related persistent infections and genital warts in men. This efficacy may also translate to reduced transmission of vaccine type HPV strains between sexual partners. Immune response in 9 to 15 year-old boys is non-inferior to the immune response in16 to 26 year-old men. GARDASIL® was generally well-tolerated in 9 to 26 year-old boys and men. Vaccination of boys and men will contribute to an additional public health benefit of GARDASIL®.

Dr. Haupt concluded with the following list of completed and on-going studies:

- 018-20 (Adolescent Long-Term Safety & Effectiveness)
  - → Duration of efficacy of GARDASIL®
  - → Impact of GARDASIL® on rates of disease caused by non-vaccine HPV types
  - → Long-term safety & immunogenicity of GARDASIL®

- 021(HIV-Infected Children)
  - → To evaluate the safety & immunogenicity of GARDASIL® in HIV-Infected children
  - → To determine the impact of nadir CD4 counts (prior to institution of ART) on peak immune responses to GARDASIL®

- 024 (Concomitant REPEVAX™ [Tdap-IPV])

- 025 (Concomitant ADACEL™ & MENACTRA™)
- 036 (HIV-Infected Men [AMC])
  - → Safety & immunogenicity of GARDASIL® in HIV-infected men

- 046 – Sub-Saharan Africa
  - → Safety & immunogenicity study

Discussion

Dr. Meissner inquired as to whether Dr. Haupt cared to respond to the data that was presented by GSK showing antibody titers 2- to 9-fold higher against 16 and 18 at 7 months follow-up, and what clinical significance he thought this had, particularly in terms of long-term immunity and need for booster doses.

Dr. Haupt concluded what it is certainly interesting data, but it is not clear that those differences really correlate with any difference in efficacy or duration of protection. At this point, it is known that both vaccines are highly immunogenic and a lot of antibody is produced by both vaccines depending upon which assay is used and how it is measured. Whether those differences are clinically meaningful is completely unclear at this time.

Dr. Marcy inquired as to whether genital warts were divided into circumcised and uncircumcised men.

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Dr. Haupt responded that they captured circumcision data on male subjects who participated and examined efficacy for all endpoints based on different baseline covariates. Efficacy was assessed based on baseline circumcision, and no difference was observed. It did not appear that circumcision impacted efficacy. There are some other natural history data pertaining to the impact of circumcision and use of condoms. However, from a pure efficacy perspective, the vaccine is highly efficacious no matter what baseline determinant somebody has.

Dr. Judson asked whether there had been any demonstrated differences of any type between the Merck and GSK VLPs.

Dr. Haupt responded that the vaccines are manufactured very differently. It is very likely that even though they are 16 / 18 VLP's, there will be some minor amino acid differences. The VLPs of GSK are truncated at the C-terminal end.

Dr. Dubin added that the genetic sequences used to express the VLPs are different. Presumably that might translate into some differences in the conformation of the VLPs. There has not been any direct comparison that he was aware of regarding the conformation or epitope mapping looking at the two VLPs. Given the differences in the genetic sequences used to produce the VLPs, he expected that there may be some differences in conformation.

Dr. Haupt noted that this was part of the problem. Even if there is known amino acid sequence difference, it is not clear how that translates into the conformation of differences. Conformation is important for immune response.

Cost-Effectiveness of HPV Vaccination of Boys in the US

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Dr. Kim reiterated that human papillomaviruses (HPV) impose a significant burden on population health. Infections with high risk oncogenic HPV are associated with 100% of cervical cancers, the majority of anal cancers, and a smaller proportion of other anogenital, oropharyngeal, and oral cancers. The majority of these HPV related cases are caused by types 16 and 18. Infections with low risk, non-oncogenic HPV are associated with cervical lesions as well as the vast majority of genital warts, and juvenile onset recurrent respiratory papillomatosis (JORRP), a rare but severe respiratory condition in children. The majority of these cases are attributable to HPV types 6 and 11.

The objective of this analysis was to evaluate the cost-effectiveness of including pre-adolescent boys in a routine HPV vaccination program of pre-adolescent girls in the US. The analytic approach was similar to the analysis of catch-up vaccination that was presented to ACIP in June 2008. A series of mathematical models were employed that simulate the natural history of disease. Epidemiological, clinical, and economic data were synthesized from various sources such as cohort studies, clinical trials, and national surveys. Because not all model parameters can be informed directly by the available data, the models were calibrated to achieve good fit to empirical data. Model validation exercises were then undertaken to ensure that the predicted outcomes were consistent with observations from independent data that were not used in model development. The models were used to simulate different interventions and estimate their

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consequences, such as quality-adjusted life expectancy and costs. The final step was to explore the influence of alternative scenarios, assumptions, and parameter values.

Because of the inherent tradeoffs associated with different model types, multiple models were used for this analysis. The first was a dynamic transmission model of HPV type 16 and 18 infection among males and females, which captures the direct and indirect benefits of vaccination. This model was used to calculate the percent reductions in HPV 16 and 18 incidences associated with different vaccination strategies. These estimates of HPV incidence reduction were applied directly to a microsimulation model of cervical carcinogenesis, which captures cervical outcomes associated with all HPV types and detailed screening strategies. This model was used to assess the cost-effectiveness of HPV vaccination and cervical cancer screening in the US. Separate Markov cohort models were developed to simulate the incidence of other HPV 16 / 18 related cancers and HPV 6 / 11 related genital warts and JORRP to capture the potential benefits of the vaccine on other health conditions.

Briefly, the dynamic model for females reflects sexual transmission of HPV 16 and 18 only. Those who are uninfected can acquire an HPV 16 or 18 infection, develop pre-cancerous lesions classified as CIN1 and CIN2,3 and over time may develop invasive cancer. Women who clear their infection or lesion develop natural immunity to that same type, and then they can subsequently reacquire the same type of infection at a reduced rate or acquire a new infection with the other type. The history of prior infection is tracked throughout the analysis. Once vaccination is introduced, women enter a corresponding vaccinated state. The model has a similar structure for males reflecting HPV infection only. The dynamic model is age-structured and stratifies the population into four sexual activity levels. Females and males form sexual partnerships over time, depending on age and sexual activity level. HPV incidence is a function of number of sexual partners, HPV prevalence in the population at a given time, and the transmission probabilities of HPV type 16 and 18.

The microsimulation model is an individual-based model that has detailed screening and vaccination modules and tracks the history of each individual woman. All HPV types are included in this model, stratified as HPV 16, 18, other high risk types, and low risk types. We leverage the strengths of both models by using the dynamic model to estimate reductions in age-specific HPV 16 and 18 incidence with vaccination, and then applying those reductions to the corresponding inputs in the microsimulation model. This linkage between the two models allows investigators to reflect herd immunity as well as all HPV types, detailed screening scenarios, and individual level heterogeneity. Natural history parameters in both models were from epidemiological studies, cancer registries, and demographic statistics primarily from the US. After initial parameterization, the models were calibrated to ensure a good fit to empirical data using a likelihood-based approach. Selected data on females and males were as follows:

Selected Data on Non-Cervical Conditions
(Females)

	Annual Incidence (per 100,000)	5-year survival (%)	Utilities	Cost per case ($)
Vulva cancer	0.2-19.6	77.8	0.68	20,430
Vaginal cancer	0.1-6.0	55.7	0.68	23,440
Anal cancer	0.1-5.6	66.2	0.68	31,300
Mouth cancer	0.2-13.9	62.6	0.68	37,370
Oro-pharynx cancer	0.1-1.1	62.6	0.68	37,370
Genital warts	7.0-620.0	100.0	0.91	430
JORRP (age 0-14)	4.3	100.0	0.69	62,010

Selected Data on Non-Cervical Conditions
(Males)

	Annual Incidence (per 100,000)	5-year survival (%)	Utilities	Cost per case ($)
Penile cancer	0.1-7.6	75.0	0.68	17,110
Anal cancer	0.1-4.3	64.1	0.68	31,300
Mouth cancer	0.1-17.7	57.6	0.68	37,370
Oro-pharynx cancer	0.1-2.9	57.6	0.68	37,370
Genital warts	13.0-501.0	100.0	0.91	430

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The primary analysis included outcomes related to cervical disease as well as other HPV 16- and 18-associated cancers for both females and males relevant to both the bivalent and quadrivalent vaccines. Secondary analyses included HPV 6 and 11 genital warts as well as 6 and 11 associated JORRP, relevant to the quadrivalent vaccine only. Analysis was conducted from the societal perspective, including direct medical and non-medical costs regardless of payer. As recommended for cost-effectiveness analysis in the US, health and economic outcomes were discounted at a rate of 3% per year.

Health outcomes were expressed in terms quality-adjusted life years (QALYs), which is life expectancy that is adjusted to reflect diminished quality of life due to disease. Health state utilities, which generally range from 0 reflecting the worst health state to 1 reflecting perfect health for invasive cancer, genital warts, and JORRP were obtained from the published literature. Economic outcomes included lifetime costs of interventions, including direct medical costs such as vaccination, screening, diagnosis, and treatment as well as direct non-medical costs such as patient time participating in the intervention and transportation. Patient time costs due to lost productivity were not included in this analysis. In the base case, it was assumed that the cost per vaccinated individual was roughly $500 inclusive of three doses, supplies, administration, and patient time and transport.

Results were expressed as incremental cost-effectiveness ratios measured by the net increase in healthcare costs divided by the net gain in health effect when comparing one intervention to another. These ratios are a measure of value for resources and are used to compare this value across different interventions and diseases. The strategies in this analysis included routine vaccination of 12 year old girls and routine vaccination of 12 year old girls and boys. All strategies included screening with cytology based on current screening rates. The lifetime health and economic outcomes were captured for all birth cohorts over a 10-year period of the vaccination program.

With respect to vaccination, it was assumed in the base case analysis that coverage for both girls and boys with the full three dose series was 75%, that efficacy for girls and boys was 100% over the lifetime among those without prior infection with vaccine targeted HPV types, and that the cost per vaccinated individual was $500. Alternative assumptions were evaluated and sensitivity analysis included lower vaccination coverage, lower efficacy, duration of protection and vaccine cost. With respect to cervical screening, the base case analysis assumed cytology screening starting three years after sexual debut, consistent with current guidelines. Screening frequency was based on coverage rates reported by the National Health Interview Survey (NHIS). PAP test sensitivity ranged from 70% to 80% for detecting CIN with a specificity of 95%. The cost of $85 included the test costs, the office visit, and patient time and transport. In secondary analysis, alternative screening strategies were explored including HPV DNA testing for primary screening starting at later ages every 1 to 3 years.

In the primary analysis, the cost-effectiveness of including boys in an HPV 16 /18 vaccination program was assumed. These results reflect female outcomes only and the first set of results includes benefits related to cervical disease only. Under assumptions of 75% coverage and complete lifelong vaccine protection, routine HPV vaccination of 12 year old girls who were screened at current rates in adulthood had an incremental cost-effectiveness ratio of $40,310 per quality adjusted life expectancy (QALY) gained compared to screening alone. Adding 12 year old boys to the vaccination program provided benefits for higher costs and had a cost-effectiveness ratio of roughly $180,000 per QALY compared to vaccinating girls only. These ratios decreased or became more attractive when the vaccine's benefits on other HPV 16 and

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18 related female cancers were included. For example, under an assumption of 50% efficacy against non-cervical cancers, vaccinating girls alone decreased to $33,000 per QALY and vaccinated both girls and boys costs $157,000 per QALY.

Under a more optimistic scenario of the 100% efficacy against the other female cancers, the ratios decreased to less than $30,000 per QALY for vaccinating girls alone and $140,000 per QALY for vaccinating girls and boys; when including cancer benefits for both females and males, these cost-effectiveness ratios fell to $30,000 per QALY and $131,000 per QALY, respectively, when assuming 50% efficacy against non-cervical cancers, and to $24,000 and $103,000 per QALY when assuming 100% efficacy. To evaluate the quadrivalent vaccine, cervical disease and genital warts only were included. When including genital wart benefits for females only, the ratio for vaccinating girls decreased to $32,000 per QALY and vaccinating both girls and boys decreased to $158,000 per QALY. When including warts benefits for females and males, the ratios decreased even further as expected to roughly $28,000 and $124,000 per QALY for the two vaccination strategies.

Scanning the results across the scenarios of other health outcomes, the cost-effectiveness ratio for vaccinating girls alone remains comfortably below $50,000 per QALY even when outcomes include cervical disease only. The ratio for the strategy of including boys, on the other hand, depends on the health conditions included and falls near or below $100,000 per QALY when all cancers or all outcomes are included. When vaccine efficacy was reduced to 75% in boys only, the ratio associated with the strategy of vaccinating boys increased by 80% to 117% depending on outcomes included. For example, when reflecting only benefits associated with cervical disease, the cost-effectiveness ratio of vaccinating both girls and boys increased from $180,000 to $325,000 per QALY when efficacy decreased from 100% to 75% in boys. When reflecting all health outcomes, this ratio increased from $78,000 to $170,000 per QALY.

Additional sensitivity analysis included reduced vaccination coverage with scenarios of cervical outcomes alone, all outcomes assuming 50% efficacy, and all outcomes assuming 100% efficacy. When strategies were evaluated in the context of 50% vaccination coverage, the corresponding ratios for both strategies improved due to slightly higher levels of herd immunity benefits. The strategy of including boys in the vaccination program was roughly $100,000 per QALY under an assumption of 50% efficacy and remained below $100,000 per QALY with 100% efficacy.

The impact of the vaccine cost, which in the base case was $500 per vaccinated individual, was also examined. Using a vaccine cost of $360, when all outcomes are considered, vaccinating girls and boys decreased to $89,000 per QALY under an assumption of 50% efficacy and $53,000 per QALY with 100% efficacy. In contrast, when the vaccine costs increased to $600, the ratios became less attractive than the base case. In this scenario, the strategy of vaccinating girls and boys remained well above $100,000 per QALY when efficacy was 50% and approached $100,000 per QALY when efficacy was 100%. Results were also sensitive to assumptions of waning vaccine protection; when vaccine protection was assumed to be 10 years, both vaccination strategies had ratios that exceeded $100,000 per QALY. In contrast, changes in screening practice involving less frequent screening with HPV DNA testing and primary screening made vaccination strategies more attractive. Results were insensitive to changes in health state utilities associated with genital warts or duration of warts, and also when a higher proportion of oral and oropharyngeal cancers attributable to HPV type 16 and 18 were assumed.

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As with all model-based analyses, this analysis had several unavoidable limitations, including uncertainties with respect to natural history, especially the non-cervical diseases. There are also uncertainties with respect to the vaccine properties for females and especially for males. With respect to the analytic assumptions, decrements in quality of life associated with detection and treatment of pre-cancerous lesions that result from screening were not included. Inclusion of these utilities would favor vaccination strategies since HPV vaccination is expected to reduce the prevalence of vaccine type lesions. Conversely, diminished quality of life was also not included due to potential adverse events associated with vaccination, which would favor the screening strategies. Also, this analysis did not evaluate catch-up programs. It is expected, however, that in the context of catch-up vaccination among young females, extending vaccination to boys would be even less attractive than suggested by the current analysis.

In summary, provided vaccine efficacy was high and long-lasting, routine HPV vaccination of 12-year-old girls was stably less than $50,000 per QALY across a wide range of assumptions compared to screening alone. This result is consistent with most previous cost-effectiveness studies. Including pre-adolescent boys resulted in higher costs and benefits, and generally had cost-effectiveness ratios that exceeded $100,000 per QALY. This was especially true when vaccine efficacy was differentially lower in males than females. Only when all potential health benefits from the vaccine were included under optimistic assumptions of 100% efficacy, for both females and males over the lifetime, or 50% lifelong efficacy with lower vaccine cost, did vaccinating both girls and boys fall below $100,000 per QALY.

Overview of Cost-Effectiveness Models of Male HPV Vaccination in the United States

Harrell Chesson, PhD
NCHHSTP / CDC

Dr. Chesson began with a review of what is known about the cost-effectiveness of HPV vaccination in general. Vaccination of 12 year old girls has been shown to be cost-effective, with cost-effectiveness estimates ranging from $0 to $50,000 per QALY gained. This result has been consistent across a wide range of models. However, there is more uncertainty and less precision in the cost-effectiveness estimates for vaccination of females over the age of 12 and for vaccination of males. He then presented a summary of the published cost-effectiveness studies of male HPV vaccination, and compared and reviewed two unpublished models.

In a study by Taira and colleagues (2004), the cost per QALY of male vaccination was about $440,000 in the base case scenario with 70% coverage. However, when vaccine coverage of females was reduced to 30%, the cost per QALY was reduced as well to about $40,000. This finding that the benefits of the male vaccination increase and the cost-effectiveness becomes more favorable with lower vaccine coverage has been found in several models of cost-effectiveness and the impact of male vaccination. It was also shown in the model by Elbasha and colleagues, who in the base case found a cost per QALY of $40,000 at 70% coverage. However, with higher coverage, the cost per QALY increased but with lower coverage of females, the cost per QALY decreased. The Jit study was based in the UK. These investigators found a cost per QALY gained for male vaccination of about $1,000,000 with 80% coverage and lifelong duration of vaccine protection. The key themes from the published studies are that male vaccination has less impact and is less cost-effective as vaccine coverage of females increases. However, vaccine coverage is not the only factor that affects cost-effectiveness. There is considerable uncertainty in the natural history, disease cost and quality of life assumptions, and vaccine characteristics. Because of these uncertainties, there is a wide

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range of cost-effectiveness ratio across models and within models. The published models have focused on the prevention of cervical intraepithelial neoplasia (CIN) cervical cancer and genital warts; however, the recent trends in the cost-effectiveness models for HPV have been to include additional HPV related outcomes that might be prevented through vaccination such as non-cervical cancers and recurrent respiratory papillomatosis (RRP).

Two preliminary models have been expanded to include all of these health outcomes. These include the Kim / Goldie model that Dr. Kim just summarized, as well as the Merck model which looks at adding vaccination of males 9 to 26 years old to a vaccination program for females 9 to 26. Both models examine the cost-effectiveness of adding male vaccination to a female only vaccination program in the context of current cervical cancer screening in the US. To review the Merck model briefly, they assumed effective vaccine coverage by age 18 of about 35% in females and 23% in males. First dose coverage assumptions were higher, but they assumed that only about 50% of those vaccinated with the first dose would complete the series. Vaccine efficacy against infection and disease was based on the clinical trials. They assumed lifelong duration of vaccine protection and assumed that there would be no benefit for those who do not receive all three doses. They assumed the vaccine cost would be $133 per dose, inclusive of administrative costs. They used the US health care system perspective in which vaccine costs as well as disease treatment costs were assessed without regard to who paid these costs. Cost and benefits of vaccination were evaluated over a 100-year time horizon with future cost and benefits discounted at 3% annually.

The incremental benefit, in terms of reducing cervical cancer, for male vaccination is quite small and it takes about 40 years to even see this difference. Although the additional benefit of male vaccination is more noticeable for the male anal cancer outcome than for cervical cancer, it still remains that the majority of the benefits that can be obtained from vaccinating both sexes can be obtained from vaccinating females only. In the Merck model, the cost per QALY of female only vaccination was about $2,000. The incremental cost per QALY of adding male vaccination was about $25,000. In terms of the gain and changes in cost and QALYs,per person in the population, adding males costs about $22 as opposed to the incremental cost of female vaccination, which is about $9. The change in benefits was much lower for male vaccination, and was roughly 1/6 the marginal benefit in terms of QALYs gained as compared to female only vaccination.

The estimated cost per QALY depends on which health outcomes are included in the model. When including cervical outcomes only, the cost per QALY of male vaccination is over $200,000. However, as more outcomes are included, the cost per QALY decreases to $25,000. When the impact of genital warts on quality of life is reduced by 50% and the duration of genital warts is reduced to three months, these changes in the genital warts assumptions make a fairly big impact on the cost per QALY estimates when including only a few of the health outcomes. However, when all health outcomes are included, the changes in genital warts assumptions do not have as much of an impact. It is important to point out that just focusing on the diseases for which there is evidence of vaccine impact, the cost per QALY of male vaccination is $70,000 per QALY or above and is very sensitive to changes in the model assumptions, such as those related to genital warts.

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In terms of the results of the two models, when including only cervical outcomes, both models suggest a cost per QALY of male vaccination in the neighborhood of $200,000; however, when including all health outcomes, the cost per QALY of male vaccination is about $25,000 in the Merck model, which is lower than the estimates from the Kim / Goldie model that Dr. Kim just presented in which the cost per QALY of male vaccination can range from $78,000 to $170,000 depending on the vaccine efficacy assumptions. However, this is not really an apples to apples comparison because there are several differences in the questions being addressed by the models. For example, the vaccine coverage is much higher in the Kim / Goldie model and the Kim / Goldie model focuses only on vaccination of 12 year olds. With respect to similarities and differences in the models, both models included a wide range of health outcomes. The only difference is that the Merck model included vaginal pre-cancers. Both models were able to include the indirect effects of vaccination or herd immunity. Both models did incorporate current cervical cancer screening, although the methods they used to do so differed. They also examined a long time horizon, although again, the methods they used to do so differed. Both models assumed at least some degree of natural immunity following HPV infection and clearance. As noted, the effective coverage in the Merck model was much lower than in the Kim / Goldie model.

The Kim / Goldie model used a higher cost of vaccination and this is partly because they included patient time and travel costs—not only in their cost of vaccination, but in the cost of the disease treatment. The Merck model included the quality of life impact of CIN, and the Kim / Goldie model did not. The models could be made more comparable by aligning three key assumptions: Cost of vaccination, including administration costs (Merck $400 per series base case, Kim / Goldie $360); vaccine coverage and adherence (Merck 75% coverage / 100% adherence; Kim / Goldie 75% coverage / 100% adherence base case); and ages vaccinated (Merck 9 to 12; Kim / Goldie 12 base case). In the sensitivity analyses, assumptions were changed from the base case. The scenario in which the Kim / Goldie cost was changed to $360 per series was selected for this comparison as it was more comparable to the Merck assumptions. The scenario of the Merck model in which 100% vaccine adherence was assumed was selected for this comparison as it was more in line with the Kim / Goldie model. Under this scenario, the cost per QALY of HPV vaccination, adding males to the female only vaccination program, was about $90,000 in the Kim / Goldie model and about $40,000 in the Merck model. When the models were aligned on these three assumptions, the disparity in the outcomes was greatly reduced, although the estimates are still somewhat different.

To summarize, male vaccination costs more than $100,000 per QALY in most scenarios in the Kim / Goldie model. Cost per QALY was < $100,000 only when all health benefits were included with 100% lifetime efficacy, or with 50% lifetime efficacy at lower vaccine cost. Male vaccination cost less than $50,000 per QALY in the most scenarios in the Merck model. Cost per QALY was >$100,000 when including only cervical, vaginal, and vulvar cancers and genital warts in the scenario of 75% effective coverage in females. The differences across these models were reduced, but not eliminated, when selected assumptions were aligned.

To conclude, estimates of the cost-effectiveness of male vaccination can vary across models and even within models when key assumptions are changed. This is due to the uncertainty in the influential factors that impact the cost-effectiveness of male vaccination including the HPV diseases included in the model, vaccine coverage and efficacy, and other assumptions.

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Discussion

Dr. Temte thought first time HPV coverage in adolescent females was approximately 25%. From a programmatic standpoint, he wondered whether it was better to push forward to immunize all girls or have a recommendation in which they try to immunize both boys and girls with the idea that perhaps by trying to reach both they would achieve better results than with just the female recommendation.

Dr. Kim responded that while she did not have a definitive answer, she could offer a qualitative one. All of the models are consistent in finding that the cost-effectiveness of vaccinating girls is certainly higher than vaccinating boys. Dollar for dollar, the goal would be to achieve coverage in girls based on the data there is currently on vaccine efficacy. To answer the question, it really depends on what the cost is of achieving the increase in coverage in females in terms of whether there is an added cost to that and how that relate to the improvements that might be achieved in health related to boys. Her group has personally not assessed any cost threshold analyses to say that going from 50% to 75% coverage would add X cost for reaching another 25% of girls compared to what it means to go from 0% to 25% coverage in boys. A head-to-head analysis has not been done.

Dr. Dasbach (Merck) indicated that Merck has conducted some of those analyses. What they have tried to do with the model that Dr. Chesson just presented was to reflect current coverage levels to at least what is being observed in the US currently, and what would happen if male vaccinations were added on top of that. If coverage levels are low, it makes a lot of sense to increase coverage either by vaccinating more females or more males.

Dr. Temte asked whether that was dollar for dollar as female coverage was increased. It looked like the models were pretty consistent in that as female coverage increases, the cost-effectiveness ratio, the cost per QALY for males, skyrockets. This raised a question about what the best value would be.

Dr. Kim responded that this is precisely what they were trying to help inform. It is true that the models are consistent in that as coverage is increased in girls, the value of adding boys decreases. However, there might be other reasons that are not included in these models, such as whether including boys actually helps reach more girls or whether opening up vaccination to boys helps gain more coverage in girls. That type of scenario has not been included her their analyses to date.

In terms of how things play out in public health protective “bank for the buck” Dr. Judson pointed out that one variation not used was that very often the interventions are gotten into the people who may least need them and are most able to pay for them. Thus, one way of looking at this would be that if 50% coverage is reached in girls at 12, they only account for 10% of all eventual cervical cancer. That is a major public health concern. He also requested clarity on what it cost to prevent a penile wart for one year in a man in terms of quality of life assumptions were used.

Dr. Kim responded that they were using consistent results (e.g., the same QALY assumptions as the Merck model). She said she could not personally vouch for the quality of life decrement associated with penile warts. Returning to Dr. Judson’s first question, although they did not look

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at the impact of disparities in vaccination coverage among females or males in this particular analysis, they did include that analysis in the catch-up analysis and found that their results were very sensitive to correlations between vaccination coverage and screening coverage. If restricting vaccination coverage to women who will eventually get screened, the cost-effectiveness of vaccination at any age becomes highly unattractive and that worsens as the correlation becomes stronger. For genital warts, a decrement in quality of life of .09 was assumed. The scale of health utilities is usually from 0 to 1, 0 reflecting death or the worst health state, and 1 reflecting perfect health. A .09 in theory would be indifferent to a 9% risk of death to get rid of the genital warts at that time period.

Dr. Dasbach indicated that the cost of genital warts was about $500 to $600 per episode of care. Just within the US alone, the economic burden is about over $200,000,000 per year in terms of treatment. In terms of the QALYs, a similar estimate is used in terms of the disutility or the quality of life weight associated with warts, and that was also about .09 on a scale of 0 to1. What that means with respect to cervical cancer is that decrement is assumed to be closer to.25 to .5 depending on whether it was local or distal cancer. Also important in terms of looking at this QALY is the duration of the event, so within the Merck model it was assumed that the median length of a genital wart was about 6 months.

Dr. Cieslak pointed out that these models were somewhat of a black box because everything that was going into them was not known to the ACIP members. Given that he always thought of the burden of HPV as being a question of the incidence and severity of cervical cancer, he was surprised to see the large decrements in cost per QALY gained as lesser incidence of diseases in males were added. This was counterintuitive to him. He wondered if Dr. Chesson could offer further insight.

Dr. Chesson responded that the female vaccination has a major impact on cervical cancer, so that does not leave as much room for the male vaccination to do as much good in terms of reducing the cervical outcomes. Change in cervical cancer was very small by adding male vaccination.

Dr. Cieslak said he understood, but as other things were added, there were profound drops in cost per QALY.

Dr. Chesson responded that a major reason for the genital warts drop was that even though the cost per case was about $500 when multiplied that by all cases, is was a substantial burden than could be offset. So not only is it a change in the QALYs that is driving this, but also it is a change in the cost associated with the disease outcomes, particularly in genital warts.

Dr. Dasbach added that in terms of what they did with respect to male disease as well as female disease, all of the data were calibrated to current levels that are being observed in the US with respect to incidence. They then assessed the reductions that vaccination would provide in terms of the benefits of preventing those diseases. The reason decreases are seem in males is that, as Dr. Chesson was mentioning, there are now direct benefits to males in the female diseases and those are all indirect benefits that male vaccination provides. So in vaccinating males, there are indirect and direct benefits.

Dr. Sumaya wondered whether the time and effort of the vaccine process was or could be included. There may be cost differentials on the acceptability of the vaccine with at risk populations. In other words, he thought there would be greater acceptability / interest in the

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vaccine as opposed to men and he wondered whether there was any cost differentiation with that phenomenon.

Dr. Kim responded that this would depend on the level of the coverage actually achieved in both genders. The cost-effectiveness and the value of vaccinating either girls or boys is very sensitive to assumptions of coverage, so they would have to evaluate specific scenarios. Additional cost would be tacked on to implementing or trying to get that coverage for the vaccination strategies. That would differentially disadvantage the vaccination strategies compared to, for instance, screening alone.

Dr. Morse pointed out that it appeared that age at immunization would have a major influence on the model, especially as immunization levels increase. Thus, the cost of immunizing an older group of the cohorts 20 to 26 years of age might be much more expensive.

HPV Vaccines: Issues for ACIP Consideration

Lauri Markowitz, MD
ACIP HPV Vaccine Workgroup
NCHHSTP / CDC

Dr. Markowitz provided a brief overview of issues that ACIP will likely need to consider during the October 2009 meeting. These include the two issues heard during this meeting (e.g., quadrivalent vaccine in males and bivalent vaccine in females).

A variety of issues need to be considered for HPV vaccine in males. These include the burden of disease in males, vaccine efficacy, immunogenicity, safety, vaccine acceptability, and impact and cost-effectiveness. It is known that HPV prevalence and incidence are high in sexually active men. HPV incidence in men is similar to that in females. There are still unknowns regarding the transmission and natural history of HPV, particularly in males. In terms of HPV-associated disease in males, HPV types 16 / 18 cause the majority of HPV-associated anal, penile, and oropharyngeal cancers (~7000 invasive cancers / year). HPV types 6 / 11 cause RRP and over 90% of genital warts (.25 -.5 million / year). There are some high risk groups, such as MSM, which has not been discussed with ACIP. This group has high rates of HPV infection and HPV related outcomes. The quadrivalent vaccine is generally well-tolerated in males. There is high efficacy for protection against vaccine-type persistent infection (VE = 86%) and genital warts (VE = 89%). Of note, there are no data yet on efficacy for prevention of pre-cancers in males, although studies on these endpoints are on-going.

In terms of the modeling and economic analyses, male vaccination provides little additional benefit for prevention of cervical cancer if there is high vaccine coverage in females. Cost-effectiveness estimates are more favorable as more health outcomes are included. In the Kim / Goldie model, male vaccination cost > $100,000 per QALY in most scenarios. The incremental cost effectiveness was < $100,000 per QALY only when all health benefits were included with 100% lifetime efficacy, or with 50% efficacy and lower vaccine cost. In the Merck model, the cost per QALY was < $50,000 in almost every scenario in which all health outcomes were included. The cost per QALY was in the $75,000 range when including only cervical, vulvar, and vaginal cancers and genital warts.

With regard to a recommendation for quadrivalent HPV vaccine for males, several questions must be considered: Should there be data on efficacy for prevention of pre-cancer lesions in males before making recommendations? How much should health economic models impact

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decisions? What endpoints should be included? What about vaccine coverage in females? Considerations for supporting a recommendation for vaccination of males include the fact that HPV does cause disease in males as well as females. The vaccine has high efficacy for prevention of genital warts and a strong likelihood for prevention of cancers in males. There is also high efficacy for prevention of persistent infection in males. In some models, which included the most favorable assumptions and high efficacy, the cost per QALY was less than $50,000. There are also issues of equity; that is, should the vaccine be made available to males as it is for females? There are also programmatic considerations. Would a gender-neutral vaccination program facilitate vaccine delivery? The work group realizes at the present time there are really no data to support that hypothesis.

Considerations for not supporting HPV vaccine recommendations for males include the fact that there are no data on the efficacy for prevention of pre-cancer lesions, and in the Kim / Goldie model, the cost per QALY for male vaccination exceeded $100,000 under most scenarios examined. In the Merck model, the cost per QALY was about $70,000 or $75,000 when focusing only on health outcomes for which we evidence of impact.

The options for HPV vaccine recommendations in males that have been discussed in the work group include a routine vaccination at age 11-12 with a permissive recommendation or a catch-up to some older age. The reason a permissive recommendation only was supported by many work group members was the need to wait for more efficacy data against other endpoints and / or the fact that the model showed that the vaccination of males is not cost-effective. There was also discussion of specific recommendations for high risk groups, particularly men who have sex with men. It was recognized that this would be difficult to implement and that many MSM would already have been infected at the time they self-identified.

Regarding the work group's discussions related to the bivalent vaccine in females, considerations were previously presented to ACIP in October 2007. In addition to making specific recommendations for use of this vaccine, there is a need to consider issues related to having two licensed HPV vaccines in the US—the focus of this session. The following table reflects the characteristics of the two vaccines, both of which are L1 virus-like particle or VLP vaccines:

	Quadrivalent (Merck)	**Bivalent (GSK)**
VLP types and Composition	20 µg HPV 6 40 µg HPV 11 40 µg HPV 16 20 µg HPV 18	20 µg HPV 16 20 µg HPV 18
Producer cells	*Saccharomyces cerevisiae* (bread yeast) - expressing L1	*Trichoplusia ni* insect cell line infected with L1 recombinant baculovirus
Adjuvant	Alum: 225 µg Aluminum Hydroxyphosphate Sulfate	AS04: 500 µg Aluminum Hydroxide 50 µg 3-deacylated Monophosphoryl Lipid A
Schedule	0,2,6 months	0,1,6 months

Some issues to consider related to having two licensed HPV vaccines for use in females include: Should a preference be stated for one vaccine? Are there differences related to protection against HPV 16 / 18, other oncogenic types, and / or HPV 6 / 11? Are there differences in cost-effectiveness? Can the vaccines be used interchangeably in the vaccination series for protection against HPV 16 / 18? The current understanding of both vaccines is reflected in the following table:

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Attribute	Quadrivalent	Bivalent
Protection against HPV 16/18 related CIN2/3 and AIS*	≥98%	≥93%
Protection against HPV 6/11 related genital lesions	100%	-
Cross-protection against CIN2/3 due to high risk types other than HPV 16,18	Some 16 related types?	Some 16 and 18 related types?
Seroconversion to vaccine types	~100%	~100%
Geometric mean antibody titers	bivalent > quadrivalent	
Duration of protection	Unclear if any differences	Unclear if any differences
Local Reactogenicity	bivalent > quadrivalent	
Cost of vaccine dose**	$130 private $105 contract	?

Both vaccines may offer some protection against non-vaccine types and there may be differences. Seroconversion to the vaccine types occurred in almost all vaccines, and after a three dose series for both vaccines. The data from the comparative trial illustrates that the bivalent vaccine does produce higher titers than the quadrivalent vaccine, but both vaccines produce titers that are substantially higher than those after natural infection. The implications of this, in terms of differences in duration of protection, are unclear. There is higher local reactogenicity after the bivalent vaccine; however, both vaccines have good tolerability profiles. At present, the cost in the US is only known for the quadrivalent vaccine.

In terms of cross protection, based on data from a meta-analysis of HPV types associated with cervical cancers worldwide, HPV 16 and 18 account for 70% of cervical cancers. Some non-vaccine oncogenic types account for a smaller percentage of cervical cancers. Two of the more common types of these non vaccine types are 45 and 31 [Smith J. et al, Int J Cancer 2007].

In terms of protection against type 31 and 45 related CIN2/3 and persistent infection among women who were in the naïve group, they were naïve to 14 types at baseline. There was 100% protection against CIN2/3 or AIS due to 31 or 45 and this was significant for 31. There was also significant protection against 6 month persistent infection with both of these types. For the quadrivalent vaccine, previously published data earlier this year show protection against type 31 related CIN2/3 and persistent infection, but not for type 45. This analysis for the quadrivalent vaccine was among women who were naïve to 12 oncogenic types at baseline. Efficacy has also been examined for CIN2/3 due to groups of non-vaccine oncogenic types. In these analyses, there were some protection from lesions due to types due in the A9 species (these are types related to HPV 16) for the bivalent vaccine and for the quadrivalent vaccine as well. For types related to HPV 18, there is significant protection for the bivalent vaccine but not the quadrivalent vaccine. For a combined endpoint of CIN2/3 due to any of 10 non vaccine types, efficacy was 68% for the bivalent vaccine and 33% for the quadrivalent vaccine [Paavonen et al, presented at IPC, Malmo Sweden (May 2009); Brown et al, JID 2009;199]. A note of caution about these analyses of cross protection is that the analyses shown earlier did not exclude lesions in which there was also infection with a vaccine type, so it is possible that some of the observed protection could have been due to the vaccine types. Also, it is quite difficult to

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directly compare results from the trials for a variety of reasons in terms of the way the populations were selected and the way the analyses were conducted.

Taking into account the available data, the work group has discussed options regarding making recommendations for two licensed vaccines and whether a statement of preference should be made for one vaccine or the other. While there was not complete consensus, the majority of members on the work group felt that a statement should include the following elements: There should be a statement of the differences in protection provided by the vaccines, specifically differences with regard to protection against HPV 6 and 11. The quadrivalent vaccine provides protection against genital warts. There could potentially be a statement about differences in cross protection. There should be an encouragement to providers to understand differences between the two vaccines. For protection against 6, 11, 16, or 18 related outcomes, the quadrivalent vaccine is recommended. For protection against HPV 16 and 18 related outcomes, either the quadrivalent or the bivalent vaccine is recommended. Concerning the issue of interchangeability of the vaccines, it was acknowledged that there would be no data at the time recommendations would need to be made regarding this issue. A possible statement could be, "Whenever feasible, the same brand of HPV vaccine should be used for all doses of the vaccination series. If vaccination providers do not know or have available the type of HPV vaccine previously administered to a female, any vaccine should be used to continue or complete the series to provide protection against types 16/18." There are many other issues that would need to be addressed for the bivalent vaccine recommendations, which will be addressed during the October 2009 meeting.

The future plans for the HPV vaccine work group are to continue to review data, refine the understanding of the cost-effectiveness analyses, discuss options for recommendations for these two issues, and prepare draft recommendations and options for the October 2009 ACIP meeting if there is FDA approval.

Meningococcal Conjugate Vaccine (MCV4)

Overview of Work Group Activities

Carol J. Baker, MD
Advisory Committee on Immunization Practices

Dr. Baker indicated that during this session, the following topics would be presented upon:

- ❑ Update on immunogenicity and safety of a second meningococcal conjugate vaccine (MenACWY-CRM) for 11 to 55 year olds
  - → No VFC vote required; no proposed changes to recommendations for vaccination
- ❑ Early estimate of vaccine effectiveness of meningococcal conjugate vaccine (MCV4)
  - → 3 years after vaccine implementation: unable as yet to evaluate duration of protection
- ❑ Proposed revaccination recommendations for persons at high-risk for invasive meningococcal disease

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With regard to why revaccination needed to be considered, the 2005 ACIP recommendation for revaccination after MCV4 states the following:

> "ACIP expects that MCV4 will provide longer protection than MPSV4; however, studies are needed to confirm this assumption. More data will likely become available within the next 5 years to guide recommendations on revaccination for persons who were previously vaccinated with MCV4."

Although they are only at the 4-year mark, some considerations need to be made. First, it is likely that the early meningococcal conjugate vaccine (MCV4) vaccinees likely will have been persons in high risk groups for invasive meningococcal disease. They probably received vaccines the earliest, and probably represent a very small part of the total vaccine target. There has also been a shift in thinking about the duration of protection regarding conjugate vaccines, because immunologic memory or boost ability may not actually correlate with protection.

To prepare the committee for the future, Dr. Baker reported that the work group would be considering a recommendation for revaccination of adolescents vaccinated 5 years ago who would be entering college. This is a very large cohort of approximately 600,000 students annually. According to the data, a very small proportion of entering college students will have been vaccinated 5 years ago (e.g., coverage <4% in 2005; 11% in Fall 2006). Cost-effectiveness of revaccination of college freshmen living in dormitories needs to be assessed. An additional year may allow for more definitive effectiveness evaluations to be completed.

In addition, a recommendation for routine vaccination of infants and / or toddlers with meningococcal conjugate vaccines must be considered. There is a potential for three vaccines to be licensed in 2010-2011: MCV4-D 2-dose series (9,12 months), HibMenCY 4-dose series (2,4,6,12 months), and MenACWY-CRM 4-dose series (2,4,6,12 months). The work group will also continue to evaluate data on the burden of disease and cost-effectiveness of vaccines in infants.

The work group anticipates a revision of the 2005 ACIP meningococcal conjugate vaccine statement in the Fall of 2009. The revision is expected to reaffirm the current 2- to 10-year old and adolescent recommendations, which are for high risk 2- to 10-year olds and all adolescents; include additional safety data, especially regarding Guillain-Barré Syndrome (GBS) monitoring; add the MenACYW-CRM vaccine information; include data concerning duration of protection; and include recommendations for revaccination of high risk groups. In 2010-2011, the work group will begin to present data that will lead to a recommendation for infant vaccination.

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MenACWY-CRM (Menveo®) Clinical Trial and Product Overview

Peter Dull, MD
Head Development Meningococcal Vaccines
Novartis Vaccines

Dr. Dull offered a brief, broad overview regarding the Novartis Vaccines Meningococcal Vaccine Program with respect to vaccine characteristics, the overall clinical program, and the specific data on adolescents currently under review.

Novartis Vaccines, as a company, has a longstanding interest and scientific expertise in meningococcal disease prevention. The program is intended, rather ambitiously, to control disease in all disease-causing serogroups and all age ranges beginning from two months of age. The history of the Novartis Vaccine Program begins with a monovalent MenC vaccine, which was a CRM conjugate vaccine, which was originally licensed in the United Kingdom (UK) in response to a serogroup C outbreak in late 1999. MenACWY-CRM was built upon the successful MenC-CRM vaccine platform and is a CRM-based conjugate quadrivalent vaccine with initial indication for adolescents through 55 years of age. The goal is to move into younger age groups, with applications forthcoming submissions planned for 2 to 10 year olds and infants. Ultimately, Novartis expects to provide broadly protective MenB infant vaccine. This vaccine is currently undergoing Phase III studies in Europe in >4000 infants. This vaccine would provide the penultimate cornerstone to complete the meningococcal disease prevention goal.

With regard to MenACWY-CRM, Menveo® is the trade name that will be used. A unique conjugation process is used utilizing the protein carrier, CRM197. CRM197 is a non-toxic mutant of diphtheria toxin that requires no formaldehyde detoxification, which avoids cross-linking to accessory antigens. It has been used successfully in pneumococcal and Hib conjugate vaccines. Other specific unique features of this vaccine include the conjugation chemistry [Bardotti A et al. Vaccine. 2008;26:2284–2296]. Purified polysaccharides are optimally sized then linked to the CRM197 to produce the conjugates. Standardized polysaccharide sizing allows for consistency in the end product, as well as retention of structural identity.

The vaccine has 10 micrograms of MenA with 5 microgram of the C, W, and Y component. It contains no adjuvant and no preservative. The presentation will be “vial-vial”, with the liquid component containing the MenCWY, which is reconstituted into the lyophilized MenA component.

The clinical development dates back to about 2002. The clinical trial database is quite extensive, with 24 clinical trials either completed or on-going. Over 16,000 subjects have now received one or more doses of the final formulation. The objectives of the program are to demonstrate immunogenicity across broad range of age groups, persistence of bactericidal antibodies, safety and tolerability, and concomitant use with routine vaccines. Serology using exogenous human complement has been agreed to with the FDA as being the licensure criteria for this vaccine. The data presented during this session is derived using human complement as a reagent.

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Several Menveo® studies have either completed or are on-going. The following table summarizes the findings of key MenACWY-CRM (Menveo®) Clinical Trials:

Age group	Doses	Phase	Comparator	Key Results
19–55 y	1	III	Menactra®	▪ Well tolerated ▪ Noninferior immunogenicity with statistically higher immunogenicity response for serogroups CWY
		II	Menomune®	▪ Well tolerated ▪ Statistically higher immunogenicity ▪ Persistent immune response
11–18 y	1	III	Menactra	▪ Well tolerated ▪ Noninferior immunogenicity for ACWY with statistically higher immunogenicity response for serogroups AWY
		III	Concomitant	▪ Supports co-administration or sequential administration with HPV and adolescent Tdap
2–10 y	1	II	Menomune	▪ Well tolerated ▪ Statistically higher immunogenicity
		III	Menactra	▪ Study ongoing
0–2 y	1-2 (toddlers)	II	MenC	▪ Well tolerated ▪ Comparable immunogenicity to MenC-CRM
	4 (infants)	III	No comparator	▪ Study ongoing

The MenACWY-CRM (Menveo®) versus Menactra® in Adolescents Phase III Study is a large study performed in 40 study sites throughout the US, with a primary endpoint of non-inferiority with pre-specified superiority analysis if non-inferiority is first satisfied and approximately 2000 subjects. Adolescents were enrolled with a lot consistency study embedded, and were randomized to receive either one dose of Menactra® or one of three lots of Menveo®. Blood was drawn at baseline and 30 days, and there was a 6-month safety follow-up period. Two-year data of persistence with a subset of approximately 400 subjects from the same cohort has recently become available, which Dr. Dull reported on during this session.

Seroresponse was the pre-specified primary immunogenicity endpoint agreed upon with FDA. For a subject with hSBA titer <1:4 at baseline, seroresponse is defined as a post-vaccination hSBA titer ≥1:8. For a subject with hSBA titer ≥1:4 at baseline, seroresponse is defined as a post-vaccination hSBA titer of at least 4 times their baseline titer. With respect to seroresponse one month post-vaccination, across all four serogroups, the non-inferiority criteria were achieved and statistically significant differences were also observed for the A, W, and Y serogroups. That is the regulatory endpoint, but speaking to the public health endpoint, for those who are protected after vaccination regardless of pre-titer a similar theme emerged. Again, non-inferiority was achieved across all four serogroups A, C, W, and Y, and for the A, W, and Y, there were statistically significant differences between the two vaccines. In another post-hoc analysis among those who are seronegative at baseline, across all measures the same theme emerges: non-inferiority for serogroups A, C, W, and Y, with statistically significant differences for A, W, and Y. Regarding the Y response, unique in the US and among much of

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the developed world, there has been an emergence of serogroup Y as a serogroup of interest, constituting upwards of 1/3 of disease in recent surveillance data. Regarding hSBA titers ≥ 1:8 at 22 months post-vaccination in the same subset of approximately 400 adolescents, the same theme emerged. For A, W, and Y a statistically significant difference was maintained between the two vaccines. In terms of local reactogenicity within 7 days of vaccination, both vaccines were well tolerated, with comparable reactogenicity and incidences of local injection-site reactions were similar between groups. With respect to systemic reactogenicity within 7 days of vaccination, rates of systemic symptoms were similar between groups. No serious adverse events were assessed as vaccine-related, and there were no study withdrawals due to adverse events.

Concomitant administration was examined in a large Phase III study conducted in Latin American to examine Menveo® administered alone versus Menveo® co-administered with Tdap and HPV vaccines. There was also an analysis of sequential administration with diphtheria-containing vaccines such as MenACWY-CRM given one month before Tdap. There was no incremental increase in reactogenicity of two diphtheria-containing vaccines. This has been observed in other studies and is not completely surprising. That is, the safety profile was comparable whether given alone, sequentially, or concomitantly with the other study vaccines. Non-inferior immunogenicity was measured by percentage with hSBA ≥ 1:8 for all meningococcal serogroups; percentage with diphtheria and tetanus antibody concentrations ≥ 1.0 IU/mL; and percentage with HPV seroconversion and GMTs. There were robust responses to all pertussis antigens, and the non-inferiority criteria were met for PT. From an immunogenicity standpoint, non-inferiority was achieved for the meningococcal serogroups for the diphtheria, tetanus, and HPV. With regard to pertussis antigen responses, non-inferiority was achieved for pertussis toxin. Robust responses were achieved across all three antigens, but there was a decrement in the response to filamentous hemagglutinin (FHA) and pertactin (PRN).

In summary, the Menveo® program seeks to provide protection beginning from 2 months of age, and there are data from Phase II that support infant vaccination with a 2-4-6 schedule. There is favorable immunogenicity compared with the currently licensed quadrivalent meningococcal conjugate vaccine, MenACWY-D (Menactra®), in adolescents. The percentage of seroresponders and hSBA ≥ 1:8 is statistically significantly higher for serogroups A, W-135, and Y. GMTs are statistically significantly higher for serogroups A, C, W-135, and Y. There is a statistically significantly higher percentage of those who maintain hSBA ≥ 1:8 at 22 months post-vaccination. Menveo® is well-tolerated in all age groups. Data support concomitant use with routine adolescent vaccines. Phase III studies are in progress to support licensure in infants beginning from 2 months of age.

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Estimate of Effectiveness of Meningococcal Conjugate Vaccine (MCV4)

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Centers for Disease Control and Prevention

Ms. MacNeil presented an analysis that provided an early estimate of the effectiveness of meningococcal conjugate vaccine (MCV4), as well as a description of cases of meningococcal disease in persons vaccinated with MCV4.

Regarding the timeline for MCV4 recommendations, MCV4 was licensed in January 2005 for use in 11 to 55 year olds. In May 2005, ACIP recommended vaccination of adolescents at three time points, at 11 to 12 years of age, or at high school or college entry if not previously vaccinated. Expected shortages limited the use of MCV4 in 2005 and 2006. During that time, vaccination focused primarily on persons entering high school and college, while 11 to 12 year olds were asked to defer vaccination until a later time. As supply improved, ACIP revised their recommendations to call for a routine vaccination of all 11 to 18 year olds at the earliest opportunity in June 2007.

MCV4 was licensed on the basis of safety and immunogenicity, and was demonstrated to be non-inferior to meningococcal polysaccharide vaccine (MPSV4), the vaccine then licensed for use in the US. Previous studies have shown that polysaccharide vaccine is 85% effective against serogroup C meningococcal disease [[1]*Rosenstein N, Levine O, Taylor J, et al. "Efficacy of meningococcal vaccine and barriers to vaccination." JAMA 1998;279:435-9*]. In pre-licensure clinical trials with MCV4, 92% of subjects demonstrated seroresponse to serogroup C, while 82% seroresponded to serogroup Y. The incidence of meningococcal disease was at a historic low prior to the implementation of MCV4, and this has delayed efforts to conduct a vaccine effectiveness analysis using case-control methodology.

However, through efforts to conduct a case-control study, CDC became aware of a number of cases of meningococcal disease in MCV4 recipients. The cases Ms. MacNeil presented during this session all occurred between January 2005 and December 2008, and were identified by Active Bacterial Core Surveillance Sites (ABCs) and MeningNet sites, which are participating in an on-going MCV4 effectiveness case-control study. Surveillance for meningococcal disease in these sites is a mixture of both active and enhanced passive surveillance. Data were collected for each of these cases through case report forms and medical record reviews. The following map reflects the ABCs and the MeningNet sites included in this analysis. Together, the ABCs and MeningNet sites cover 54% of the US population:

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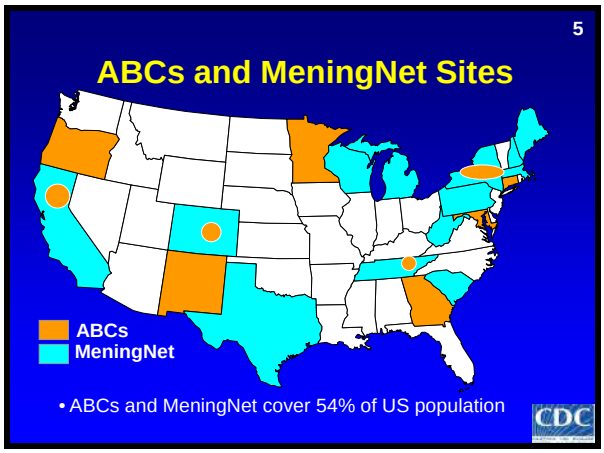

Cases were included in this analysis if they had isolation of a vaccine preventable serogroup of *Neisseria meningitidis* (serogroup A, C, Y, or W-135), or detection of DNA from a vaccine preventable serogroup in a clinical specimen taken from a normally sterile site, more than 10 days after vaccination with MCV4. From 2005 to 2008, 14 cases of meningococcal disease were identified in MCV4 recipients. Of these, 13 (93%) were culture confirmed, 1 case was polymerase chain reaction positive (PCR+) with clinically compatible illness, 8 (57%) cases were caused by serogroup C, and 6 (43%) cases were caused by serogroup Y. All 14 cases had received MCV4, and no common lot of vaccine was identified among the cases. The median time from vaccination to disease onset was 395 days (range 43 to 1,021) and cases in vaccinated persons were identified in 6 of the 20 participating case-control study sites. Of these, 7 (50%) cases were male, 7 (50%) cases were attending college, and 2 (14%) cases were military recruits. The median age at vaccination was 18.4 years (range 12.6 to 20.5), the median age at time of disease was 19.9 years (range 15.2 to 21.6 years). Nearly half of the cases occurred within the first year following vaccination, with other cases occurring 1 to 2 years or more 2 years post-vaccination. In interpreting these data, it is important to note that MCV4 coverage was low in 2005 and 2006. Only cases who were vaccinated early had time to be observed 2 to 3 years post-vaccination. With time, this distribution is expected to change.

With regard to the clinical description of the cases, 13 (93%) cases were hospitalized. The median hospitalization time was 3 days (range 0 to 46 days). There were 3 fatal cases (21% case fatality). Meningitis was reported in 6 (43%) cases and bacteremia in 8 (57%) cases. Regarding underlying conditions, Case 1 had a pulmonary embolism and deep vein thrombosis; Case 2 had Type 1 diabetes and mitro valve prolapse; Case 3 had irritable bowel syndrome and eczema; Case 4 was a current smoker; Case 5 had a history of pyelonephritis; Cases 6, 8, 10, 11, and 12 had no reported underlying conditions, Case 7 had seasonal allergies; Case 9 had a prior history of bacterial meningitis and recurrent infections; Case 13 was taking a medication that inhibits complement; and underlying medical conditions were unknown for Case 14.

It is expected that cases of meningococcal disease would occur in vaccinated persons; however, as CDC began to receive reports of cases in vaccinated persons, they wondered whether the 14 observed cases were within the range of what would typically be expected. To estimate the expected number of cases in vaccinated persons, a simulation approach was used. The simulation approach is useful for modeling phenomena with significant uncertainty in inputs such as MCV4 coverage in the analysis. The simulations rely on repeated random sampling. The estimates of vaccine effectiveness were varied in the simulations to determine how likely the observed outcome of 14 cases in vaccinated persons was. Because the population under

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surveillance included only ABCs and MeningNet sites, the calculation of expected number of cases was limited to this population as well. In the analysis, an incidence rate of .38 per 100,000 was used, which was the incidence of serogroup C and Y disease among 13 to18 year olds. It was calculated using 2002-2006 ABCs data, and was estimated to the US population. This incidence rate is similar to the observed rates in the unvaccinated that were calculated using data from the 20 participating case-control study sites. National immunization survey (NIS) teen estimates for MCV4 coverage were used when they were available. NIS teen provides coverage estimates for 13 to 17 year olds and at this time is complete for 2006 and 2007. In the analysis, CDC was interested in estimating cases for 2005-2008. For 2005 and 2008, coverage had to be estimated based on the limited distribution and claims data available. In 2005, estimated coverage for 13 to 17 year olds was 4%. In 2008, coverage was estimated to have increased to approximately 50% in this age group.

Because NIS Teen only provides coverage estimates for 13 to 17 year olds, coverage also had to be estimated for 18 year olds. For the primary analysis, CDC used the best estimates of what coverage actually was in 18 year olds and increased coverage over time from 2005 to 2008. Because there was greater uncertainty in the estimates for 18 year olds, a sensitivity analysis was also done for varying coverage estimates among those 18 years of age or older. Determining the coverage in 18 year olds was the most challenging aspect of this analysis because it was complicated by the fact that coverage among all 18 year olds is very different than coverage among college freshmen. Coverage also likely varies between colleges. The following table summarizes the coverage estimates used in the primary analysis:

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Vaccine Coverage Matrix: Primary Analysis

	13-17 years	18 years	19 years	20 years	21 years
2005	4%	25%			
2006	~11%[1]	37.5%	25%		
2007	~32%[2]	50%	37.5%	25%	
2008	50%	62.5%	50%	37.5%	25%

[1]National Vaccination Coverage Among Adolescents Aged 13-17 Years – United States, 2006. MMWR: Aug 31,2007
[2]Vaccination Coverage Among Adolescents Aged 13-17 Years – United States, 2007. MMWR: Oct 10, 2008

These coverage estimates represent the best estimate as to what coverage actually was in each year and each group. The way these coverage estimates are applied also accounts for the fact that those over 18 will not continue to be vaccinated with MCV4 and, therefore, maintains the coverage level reached at 18 years of age for that birth cohort. These 18 year olds are also maintained in the populations, so the total population in the analysis increases over time.

Regarding the methodology used in the simulations, a record was created for each person in the birth cohort. A vaccination status was then assigned to each person, which was determined by a uniform random number in the coverage assumptions for that birth cohort. The disease status was then assigned to each person, which was also determined by uniform random number along with vaccine effectiveness and incidence rate assumptions. Each simulation was run 1,000 times. When it was complete, it produced a range of expected values given the assumptions used. The results of the simulations were used to determine the probability of seeing 14 or more observed cases by determining the area under the curve on the right tail of the histogram. Based on best estimate of coverage in 18 year olds, if MCV4 was 90% effective,

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a median of 7 cases would be expected, and the probability of observing 14 or more cases of meningococcal disease in vaccinated persons would be 2.9%; therefore, based on the best estimates of MCV4 coverage, vaccine effectiveness appears to be greater than 80%. It is unlikely to be 90% effective.

Regarding the sensitivity analysis of the probability of seeing 14 or more cases based each coverage assumption and level of vaccine effectiveness tested, 18 year old coverage was held constant for each birth cohort. If there was 50% coverage (coverage was held constant at 50% for all persons 18 years of age or older during 2005-2008) and MCV4 was 90% effective, there would be a 5% chance of observing 14 cases in vaccinated persons. If MCV4 were 85% effective, there would be a 47% chance 14 cases would be observed. Even with high estimates of coverage in the sensitivity analysis, MCV4 appeared to be between 80% and 90% effective.

To summarize, this is the first estimate of vaccine effectiveness for MCV4. The results of this analysis suggest that effectiveness of MCV4 is between 80% and 90%, which is similar to polysaccharide vaccine. It is also important to consider that all of the observed cases of meningococcal disease in MCV4 recipients occurred less than 3 years since vaccination therefore this estimate of vaccine effectiveness applies to persons less than 3 years since vaccination.

The ACIP Meningococcal Working Group expects more data to be available in 1 to 3 years to further evaluate vaccine effectiveness. Plans are to expand the MCV4 effectiveness case-control study to additional sites with the hope that this analysis will allow CDC to determine separate estimates of vaccine effectiveness for serogroup C and serogroup Y. Additionally, with the introduction of new conjugate vaccines, vaccine-specific analyses will be conducted. At this time, CDC is unable to evaluate duration of protection using this early data; however, they will continue to monitor for cases of disease in vaccinated persons through the case-control study and ongoing surveillance in the US.

Discussion

Dr. Neuzil requested further rationale for why, with respect to effectiveness estimates, a straight case-control study using the ABC and MeningNet sites was not done.

Ms. MacNeil responded that CDC is in the process of conducting that study, but it is not complete. It has been slow because the incidence has been so low in the last few years. What was presented was simply an early estimate using that data. Eased on the case-control study are anticipated within the next year or two.

Dr. Pickering requested clarification between what was recognized and what was actually tested for. That is, were the 12 people who did not have an apparent immunity deficiency tested for terminal complement deficiency or any of the other conditions known to be associated with this disease?

Ms. MacNeil replied that the records reviewed were of the actual hospitalization for meningococcal disease. There were no additional indications of other cases that had complement deficiencies at the time of disease; however, CDC did not have any follow-up records regarding whether they were tested for complement deficiencies later.

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Rationale and Proposed Recommendations for Revaccination of Persons at Increased Risk for Meningococcal Disease

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Dr. Cohn presented the rationale and proposed recommendations for revaccination of persons at increased risk for meningococcal disease. She acknowledged and thanked sanofi pasteur for providing CDC with much of the data to be presented during her presentation. She then explained the working group rationale for recommending revaccination with quadrivalent meningococcal conjugate vaccine (MCV4) for high risk groups, clarifying that at this time, there is still a single licensed vaccine, MCV4, to which she would be referring. However, these proposed recommendations are intended to apply to any quadrivalent conjugate vaccine used, and the language will be adjusted as new vaccines are licensed. In addition, she defined the group of persons at increased risk, reviewed the available data on safety and immunogenicity of revaccination, and reviewed the proposed recommendations.

In 2005, ACIP recommended that persons aged 2 to 55 years who are at increased risk for meningococcal disease be vaccinated with MCV4. MCV4 was licensed in 2005 only for a single dose, and there were no recommendations made for revaccination made at that time. There was an expectation that conjugate vaccines would provide longer lasting protection than polysaccharide vaccine. Since that time, it has become clear that data on duration of protection from primary vaccination and the safety and efficacy of revaccination are limited, and it is unlikely there will be more data available. Given that many individuals in this high risk group are at much greater risk for severe disease, the mortality among these high risk groups can be high. Therefore, the working group believes that protection should be optimized for these high risk groups. There is a precedent for revaccination with meningococcal vaccines as the recommendation to revaccinate with polysaccharide states:

> "Revaccination might be indicated for persons previously vaccinated with MPSV4 who remain at increased risk for infection.
>
> – Children (age <4 years) should be considered for revaccination after 2-3 years
> – For older children and adults, revaccination might be considered after 5 years"

This recommendation was also made in the setting of limited data on duration of protection, and even some concern about blunted response of revaccination; however, revaccination of these groups has become a standard of care. Therefore, the burden of proof needed to be that conjugate vaccines provide substantially greater protection than polysaccharide vaccine five years after vaccination not to recommend revaccination. While these individuals may continue to be protected beyond five years, immunogenicity data are not strong enough for the working group to be assured.

With respect to why the working group believes high risk groups should be revaccinated, the group evaluated data on circulating antibody, but memory and herd immunity are also important benefits of conjugate vaccines. Serum bactericidal activity (SBA) is a measure of functional antibody or the ability of sera to kill a strain of Neisseria meningitidis in the presence of complement. Baby rabbits were used as the complement source. SBA is an accepted marker of immunogenicity, but no there is no clear cut off that indicates long-term protections for individuals after vaccination.

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Dr. Cohn presented the percentage of persons with SBA titers greater than 1:128, because this was the cutoff that was used for licensure trials for MCV4. However, this may be an over-estimate of titers needed for protection. Additionally, the assays are highly variable across laboratories. There are also properties of conjugate vaccines, such as the ability to mount a memory response, that are not quantitated in SBA titers. The contribution to protection of these conjugate properties versus levels of circulating antibody is not well-understood, but there is evidence from the meningococcal group C conjugate vaccine (MenC) experience in the UK that memory alone is not enough to protect against meningococcal disease, perhaps because there is not enough time to mount a memory response before infection becomes overwhelming. Finally, there is not high enough coverage with MCV4 that reduced transmission can be expected, so no additional protection can be presumed through herd immunity at this time.

SBA-BR seroresponse ≥1:128 post-vaccination at years 3 and 5 post-vaccination, serogroup C, Dr. Cohn presented data from studies of subjects in the initial clinical trials. The total number of subjects tested 3 and 5 years out is very small. The 3-year subjects were initially vaccinated at 11 to 18 years of age, and the 5-year year subjects were initially vaccinated at 2 to 10 years of age. Three years after vaccination, the subjects vaccinated with MCV4 had substantially higher titers than those vaccinated with MPSV4 in naïve controls. At five years, only 50% of those vaccinated with MCV4 has titers at or above 1:128, which is greater than the 42% seen in the other two groups, but is still low. There is similar data at 5 years among subjects initially vaccinated at 11 to 18 years of age, but Dr. Cohn did not show that data because the number of subjects in that study was very small. However, the data is comparable and is very similar to the 2 to 10 year olds who were vaccinated 5 years previously [Data courtesy of sanofi pasteur, 3 year follow-up of MTA02 (11-18 year-olds), 5 year follow-up of 603-02 (2-10 year-olds)].

In terms of the GMTs of the SBA, there is better persistence of SBAs in subjects vaccinated with MCV4 compared to MPSV4 and at 5 years. Titers are higher than age matched controls, which is not the case for subjects who were previously vaccinated with MPSV4, but the absolute values of these titers is still low. In the smaller study of 11 to 18 year olds at 5 years, the GMTs were similarly low. To summarize, the 5-year SBA persistence data do not convince the working group that protection, as measured by circulating antibody at 5 years, is substantially higher in subjects vaccinated with MCV4 than in unvaccinated individuals or in subjects who received MPSV4,[Data courtesy of sanofi pasteur, 3 year follow-up of MTA02 (11-18 year-olds), 5 year follow-up of 603-02 (2-10 year-olds)].

The proposed 2009 definition for persons recommended for revaccination includes the following:

- Those at increased risk of infection
  - Persistent complement deficiency
  - Anatomic or functional asplenia

- Those with suboptimal response to vaccination
  - Anatomic or functional asplenia

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- Those with prolonged or frequent exposure
  - Microbiologists who are routinely exposed to isolates of *N. meningitidis*
  - Frequent travelers to or people living in areas with high rates of meningococcal disease (Meningitis belt)

Previous ACIP language implied that only persons with terminal complement component deficiencies are at increased risk. To clarify, the working group would like to change this language to state that persons with persistent deficiencies in the complement pathway are at increased risk, and those deficiencies would be listed in the recommendations. Late complement pathway deficiencies are highly associated with recurrent disease, but other deficiencies put persons at risk as well. For example, 70% of children with primary C3 deficiency have an episode of invasive bacterial disease in a median age of 2 years, and 55% of this disease is caused by Neisseria *meningitidis*. There is a high risk for recurrent disease. In comparison, C1, C2, and C4 deficiencies are rarely associated with invasive disease. Properdin, factor D, and terminal complement deficiencies also cause a high rate of infections (50-60%). These occur in the teenage years, and almost all of this disease is caused by Neisseria *meningitidis*. Complement-independent, antibody-mediated phagocytic killing can occur with high levels of antibody. Therefore, maintaining high levels of antibody in this population is important.

The data on the risk of disease in persons with asplenia is from older case series and studies that showed risk for all encapsulated organisms, including, but not specifically for *Neisseria meningitidis*. So while the working group was unable to offer a precise risk for disease among asplenics, it is widely accepted that persons with asplenia are at risk for invasive infection from *Neisseria meningitidis*. There are also data to suggest that persons with asplenia have a suboptimal response to vaccination. A group of 130 persons with asplenia had a significantly lower response to one dose of MenC vaccine in the UK. Their SBA GMTs were 157 compared to 1448 among non-asplenics, and only 80% of those individuals had titers greater than 1:8 SBA [Balmer, P et al. Infection and Immunity, Jan 2004, 332-337].

In terms of exogenous exposures putting a person at increased risk, microbiologists exposed to isolates of *Neisseria meningitidis* are at increased risk with an estimated attack rate of 13 per 100,000 microbiologists exposed to an isolate of *Neisseria meningitidis* during 1996-2001, compared to a rate of .3 per 100,000 among US adults. There is also a high risk of mortality, which was 50% among a small group of laboratory workers with an n of 16, which is possibly related to this group being exposed to a high bacterial load [Sejvar et al, J. Clin Micro, 2005].

The disease risk in travelers or to persons living in areas with the epidemic meningococcal disease, such as the African Meningitis Belt, is not known. It is likely to only be higher if that person is living in or working with local population; however, given the potential for limited access to medical care while traveling, the working group felt that this was important to include in these recommendations. Additionally, vaccination has a small, but possible ability to reduce risk of colonization and spreads to household contacts of travelers upon the return, such as occurred after the W 135 Hajj outbreak.

In terms of how many people would be included in this recommendation, based on private claims data provided to the working group by sanofi, approximately 20,000 doses annually are given to groups for which vaccine is recommended only for high risk persons. Over the course

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of five years, this would be about 100,000 persons in total who received vaccination, but not all of these individuals would necessarily need to be revaccinated. Travelers may not be included in these estimates, as vaccination is an out-of-pocket cost for travelers, but most travelers will unlikely be traveling five years after to the African Meningitis Belt, so they were unable to estimate how many travelers would be included. Although there are about 60,000 persons with sickle cell anemia in the US, the prevalence of complement deficiencies and other types of asplenia is unknown. So the working group recognizes that this recommendation is off-label use of the vaccine, but they are comfortable with this given the targeted and small number of individuals at increased risk included in these groups.

The working group discussed at length their preference not to include college freshmen living in dorms and military recruits in the groups recommended for revaccination at this time. This is a much larger cohort of individuals, more than 600,000 / year with much broader policy and programmatic implications. In 2009, very few persons in these groups were vaccinated greater than five years prior and coverage in the fall of 2006 was only 11%, so it was likely to even be lower. For the upcoming college year, the number of adolescents vaccinated more than five years ago will be very low. In most colleges, there is relatively high vaccination coverage among college freshmen, and there is close to 100% coverage among military recruits. Therefore, individuals no longer protected by vaccine may be protected by the potential for herd immunity in these institutions. The working group agreed that more time should be taken to assess the degree of transmission in these highly vaccinated populations, and the need for revaccination in these groups.

There are limited safety data available on revaccination. Dr. Cohn reported on data from two studies. The first was from subjects initially vaccinated at 11 to 18 years old and the second was in subjects initially vaccinated at 2 to 10 years of age. The proportion of subjects with local and systemic adverse events was similar whether they received MCV4 or they were vaccine-naïve prior to this initial vaccination. The reactions were similar and there were no serious adverse events in any of the groups. A strong boost response was observed with revaccination for both serogroup C and serogroup Y. In terms of the percentage of seroresponders after revaccination compared to age matched controls, 100% of subjects previously vaccinated with MCV4 had titers at or above 1:128. A strong boost response was also demonstrated by high GMTs among subjects previously vaccinated, compared to vaccine-naïve subjects. The same was true for serogroup Y. More subjects were able to retain titers at or above 1:128 five years after initial vaccination with serogroup Y, compared to serogroup C. A large portion of the vaccine-naïve individuals also had antibody titers above or at 1:128. This may be due to natural immunity due to nasal pharyngeal carriage or it may be related to the assay used. Nevertheless, a boost response to revaccination was clearly demonstrated for serogroup Y compared to the previously vaccine naïve group [Data courtesy of sanofi pasteur, 5 year follow-up of 603-02 (2-10 year-olds at dose 1)].

To summarize, even with the small number of individuals in these studies, the ACIP working group was convinced that revaccination would be safe and would induce a boost response.

The working group also evaluated this five year interval for revaccination among the young children aged 2 to 6 years. Regarding the SBA GMTs by single year of life for 2 to 10 year olds, there are very few persons in each of the age years where it is clear that the initial immune response in the very young children is similar to polysaccharide vaccine. It is known that protection in young children vaccinated with polysaccharide vaccine is not long-lasting [Pichichero M et al. *Pediatr Infect Dis J.* 2005;24:57-62]. Limited antibody persistence data with MCV4 suggests children vaccinated at age 2 to 3 years are not as well-protected three years

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post vaccination. Of children vaccinated at age 2-3 years, 14.6% (n=48) had an hSBA titer >1:4 3 years after vaccination [Granoff, D et al. PIDJ 2005:24, 132-136]. Children at increased risk in this age group are also likely to be asplenic or have complement deficiency, and may have a suboptimal response to vaccine. The working group agreed that an additional dose of vaccine three years after the first MCV4 may benefit this small group of children.

Thus, the working group was proposing revaccination for high risk persons out of an abundance of caution. In the setting of demonstrated disease risk, which is very high in some of these age groups, and a low risk for serious adverse events, the working group felt that it would be useful to have limited off-label use in this small targeted group. There is evidence of waning functional antibody, which may or may not indicated lack of protection; however, it is known that high levels of circulating antibody is important for persons with complement deficiencies. Persons at increased risk are not protected at this point by herd immunity in the population. There is also strong evidence of a boost response. Therefore, the proposed recommendation is:

> "Persons aged 2-55 years who remain at increased risk for meningococcal disease 5 years after vaccination with MCV4 or MPSV4 should be revaccinated with MCV4. This includes:
> - Persons with persistent complement component deficiencies*
> - Persons with anatomic or functional asplenia
> - Microbiologists who are routinely exposed to isolates of *N. meningitidis*
> - Frequent travelers to or people living in areas with high rates of meningococcal disease (African meningitis belt)
>
> *inherited or chronic deficiencies such as C3, properdin, factor D, or late complement components"

Two additional components of this recommendation would be stated as follows:

> "At this time, college freshmen living in dorms who were previously vaccinated against meningococcal disease at age 11-18 years are not recommended to be revaccinated with MCV4.
>
> Children who received their first MCV4 or MPSV4 at age 2-6 years and remain at increased risk for meningococcal disease should be vaccinated with an additional dose of MCV4 3 years after their first meningococcal vaccine."

Discussion

Referring to the safety of revaccination [slide 15], Dr. Neuzil said it would be ideal to see a larger number of subjects who had received a repeat vaccination in the 11 to 18 year old group (n=17). Based on a power calculation, that would not be high enough to detect a difference. She wondered whether Dr. Cohn could tell them anything more about local reactions, even though the total number was close, in terms of whether there was any trend toward greater severity, et cetera.

Dr. Cohn responded that there is one additional study that she did not include in adolescents 11 to 18 years of age who were revaccinated at three years rather than five years. The n in that study was greater and the proportions were similar. She requested that someone from sanofi further discuss the reactions as she did not have specific information beyond whether they fell into one of the specified categories.

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Dr. Hosbach (sanofi pasteur) responded that they have larger numbers at three years which he agreed to provide to the group, although he did not have it with him. There was nothing remarkable.

Dr. Marcy expressed concern about the data Dr. Dull presented for Menactra®, given that subjects barely made it at 1:8 in some cases. Now they were viewing 1:128, and the levels were very high. He was trying to understand the difference, because simply attributing it to different assays was not sufficient.

Dr. Cohn responded that human complement was used in the other assays, while the sanofi and UK studies had used baby rabbit complement for the most part. There are also differences in assays in various laboratories. The level needed for licensure was based on baby rabbit complement, which seems to have changed in the process in that she believed human complement would be required for all future studies. She inquired as to whether anyone from FDA wanted to comment.

Dr. Hosbach (sanofi pasteur) responded that baby rabbit complement was utilized initially in comparing what was licensed for Menomune®, the polysaccharide vaccine. That was utilized as a standard. For studies in infants and toddlers, human complement was used as well.

Referring to the second component of the proposed recommendation, James Turner (ACHA) thought they would find that there would be students coming to school who received polysaccharide when they were teens. The proposed recommendation seemed to state that no revaccination would be recommended if they had been vaccinated against meningococcal disease. He suggested an amendment to read, “Those who were previously vaccinated with MCV4, would not need to be revaccinated with MCV4.”

Dr. Cohn responded that the change could be made to reflect MCV4, and a line could be added to indicate that persons with polysaccharide vaccine should be revaccinated if they have not been vaccinated in five years.

Amy Middleman (SAM) noted that the proposed recommendations indicated that persons aged 2 to 55 who remained at increased risk from meningococcal disease should be immunized again five years later. However, the second component of the recommendation separated out 2 to 6 year olds and indicates revaccination at three years. She wondered whether the first part should actually read “7 to 55 year olds.”

Dr. Cohn said that consideration was given to changing that, but the caveat is that if children are initially vaccinated at age 2 and then they are vaccinated at age 5, by the next time they would be over 7 years old. They did not want people to think that they continually needed to be vaccinated at three years. She agreed that they could change it if it seemed confusing.

Dr. Baker pointed out that the dashes needed to be replaced with “through.”

Dr. Sawyer was not clear whether the working group was proposing multiple revaccinations or a one-time revaccination.

Dr. Cohn answered that as currently written, the recommendation was that persons continue to be vaccinated every five years. This can be readdressed in the future, but the group was thinking that to simplify the recommendations, this language would work well. For this particular

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group of individuals, this may have to be revisited every five years and would likely require the same recommendation given the high risk of disease.

Dr. Baker agreed that it was frustrating, given the limited data. There is a tremendous risk for the individuals to be included. The population and costs are small. Microbiologists are already covered by the Occupational Safety & Health Administration (OSHA) for vaccine, and travelers or their employers pay for the vaccine. The risk of not having protective immunity drove this recommendation. The poorest response in is ages 2 through 4 year. They are more likely to be vulnerable as they turn 5 or 6, depending upon when they have been vaccinated. The Red Book used to say 3-5, but people were confused about whether this meant 3 or 5. Moving to a five-year recommendation as routine for adolescents, but a three-year for children younger than that is consistent with the Red Book.

With regard to the lack of specific safety data, Dr. Sawyer wondered whether Vaccine Adverse Event Reporting System (VAERS) data were assessed to determine whether those who had been following this practice without recommendations had generated any reports to VAERS.

Dr. Cohn responded that there is a VAERS analysis of people who are vaccinated with MCV4 at all. There has not been a specific analysis to examine people who may have received two doses. Aside from the reports of Guillain-Barré Syndrome (GBS), there is nothing specifically about syncope in adolescents. In children who received many other vaccines, the adverse events are similar (e.g., local reactions in other vaccines).

Dr. Cieslak indicated that he had not seen any data on breakthrough cases because of waning immunity, nor had he seen data on the efficacy side suggesting that that population they were proposing to revaccinate was likely to be protected after the second dose. If I had to guess, because they did not respond to the first dose, they would probably be less likely to respond to the second dose.

Dr. Baker responded that the data Dr. Cohn summarized on asplenics led to the UK recommendation that adult asplenics receive two doses two months apart. They immunized and bled subjects one month. It is known that asplenics do not have a good primary response, so revaccinating them may be similar to giving them two doses, which is routine health policy in the UK. Even if one or two microbiologists died of meningococcal disease at five years, she did not want to be the one to find out. While there are very limited data regarding safety, this is driven by the incredible risk for these patients. The difference is 13 per 100,000 for microbiologists compared to .3 per 100,000.

Nancy Messonnier added that the working group discussed balance: Do you wait for breakthrough cases to occur before you make a recommendation? Part of the conclusion that the working group came to was that the standard of care was actually the polysaccharide vaccine recommendation for revaccination, which appeared to be based on a similar lack of data on breakthrough cases. As discussed in the working group, there was not convincing evidence that the conjugate vaccine behaved substantially differently in these age groups than polysaccharide vaccine such that a different recommendation would be warranted than would be made for polysaccharide vaccine.

Dr. Englund noted that there were some data showing that college freshmans' re-immunization was not very robust. She wondered whether the working group was happy with that part of the recommendation.

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Dr. Cohn responded that there are some data to show that individuals who initially received polysaccharide vaccine and were then give conjugate vaccine were able to overcome and boost. Though not to the same extent as persons who previously received conjugate vaccine, it was better than an additional dose of polysaccharide vaccine.

Dr. Judson inquired as to whether this would have to go back through the FDA for a change in indications or labeling, given that they were making a recommendation based on inadequate efficacy data that the FDA might not approve.

Dr. Cohn responded that the recommendation was for off-label use.

Dr. Baker replied that the current label is for one dose. There is no re-immunization labeling at this time, as has been the case for polysaccharide vaccine for years. The initial efficacy was in the military where human complement was used. In the military polysaccharide was developed because of the tremendous outbreaks and the high mortality. There was a great efficacy study in which efficacy was correlated with bactericidal activity in recruits. That was the history of a very bad disease versus a very safe vaccine. With regard to Dr. Englund's question regarding whether the working group was happy, Dr. Baker said she was not happy but this was all the data they had and she was concerned about individuals at high risk.

Dr. Englund felt strongly that the lack of data was very concerning. This is a major problem that will affect a large segment of children who received the polysaccharide vaccine. There are mechanisms to get it funded that ACIP should be encouraging.

Dr. Baker thought the assumption that there is a large population of children who received polysaccharide vaccine who will need to be revaccinated was a tremendously wrong assumption.

Dr. Cohn thought that most children who received polysaccharide vaccine would have received it prior to going to college unless they were in one of the high risk groups. If they were in a high risk group, they would fall under the recommendation to continue to be revaccinated with MCV4. The polysaccharide recommendations were only made for children who were entering college and were living in dorms.

Dr. Hosbach (sanofi pasteur) stated that this is not in the package insert. The older package insert does indicate that the ACIP recommendation says to immunize these populations every three to five years. They do intend to generate additional data.

Motion: MCV4 Revaccination for Persons at Prolonged Increased Risk

Dr. Sawyer moved to approve the revised recommendations as stated in the presentation. Dr. Sumaya seconded the motion. The recommendation will include clarification again MCV4 and dashes with be changed to "through." The motion passed with 13 affirmative, 1 negative, and 1 abstention.

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VFC Resolution Update: Meningococcal Vaccines

Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Santoli indicated that the purpose of this proposed resolution was to update the revaccination recommendations discussed during this session and to streamline the resolution through the use of links to published documents.

The MPSV4 Component of the VFC Resolution, I are:

- ❑ Eligible groups
  - → All children 2-18 years of age.

- ❑ Recommended Meningococcal Polysaccharide Vaccine Schedule
  - → The recommended schedule for meningococcal polysaccharide vaccine can found at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5407a1.htm
  - → See Section B. Conjugate Vaccine to Prevent Meningococcal Disease for potential, limited use of MPSV4 for revaccination.

- ❑ Dosage Intervals for Meningococcal Polysaccharide Vaccine
  - → http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5407a1.htm
  - → See Section B. Conjugate Vaccine to Prevent Meningococcal Disease for potential, limited use of MPSV4 for revaccination.

- ❑ Recommended dosage
  - → The recommended dosage can be found in the package inserts available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

- ❑ Contraindications and Precautions
  - → Contraindications and Precautions can be found in the package inserts available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

MCV4 Component of the VFC Resolution, I are:

- ❑ Eligible groups
  - → All children 2-18 years of age.
  - → Recommended Meningococcal Polysaccharide Vaccine Schedule
  - → The recommended schedule for meningococcal conjugate vaccine can found at:
    - ▪ http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5407a1.htm
    - ▪ http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5631a3.htm
    - ▪ http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5648a4.htm

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- Revaccination is recommended for children at increased risk of meningococcal disease, including:
  - → Persons with persistent complement component deficiencies (inherited or chronic deficiencies such as C3, properdin, factor D, or late complement components)
  - → Persons with anatomic or functional asplenia
  - → Persons infected with HIV
  - → Microbiologists who are routinely exposed to isolates of N. meningitidis
  - → Frequent travelers to or people living in areas with high rates of meningococcal disease (African meningitis belt).

- Dosage Intervals for Meningococcal Conjugate Vaccine
  - → http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5407a1.htm
  - → http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5631a3.htm
  - → http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5648a4.htm

- Children through age 18 years who received their first dose of MCV4 or MPSV4 at ages 2-6 years and remain at increased risk for meningococcal disease should receive an additional dose of MCV4 at 3 years after their first dose.

- Children through age 18 years who received a dose of MCV4 or MPSV4 after age 6 and remain at increased risk for meningococcal disease should receive an additional dose of MCV4 at 5 years after their previous dose.

- MCV4 is preferred for revaccination, but MPSV4 is an acceptable substitute for persons with precautions or contraindications to MCV4 vaccine.

- Recommended dosage
  - → The recommended dosage can be found in the package inserts available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

- Contraindications and Precautions
  - → Contraindications and Precautions can be found in the package inserts available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

The underlined group, persons infected with HIV, was not a group that was discussed. However, that group was previously included in the VFC resolution for vaccination by the ACIP, so it was brought forward into this VFC resolution to give providers who are treating these children the flexibility of vaccinating VFC eligible children with this vaccine.

Then the resolution concludes with the following statement about making updates based on published documents:

> "If an ACIP recommendation or notice regarding meningococcal vaccination is published within 12 months following this resolution, the relevant language above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the publication URL.

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Motion: VFC Resolution Update for Meningococcal Vaccines

Dr. Baker moved to approve the revised recommendations as stated in the presentation. Dr. Sawyer seconded the motion. It was noted that all dashes should be replaced with "through." The motion passed with 14 affirmative, 0 negative votes, and 1 abstention.

Japanese Encephalitis Virus

Introduction

Paul Cieslak, MD
Chair, ACIP JEV Vaccines Workgroup

Dr. Cieslak offered gratitude to the technical advisors the workgroup was able to obtain from the outside including, Christina Greenaway (International Society of Tropical Medicine), Tony Marfin (Washington Department of Health), David Shlim (ASTMH), and Tom Solomon (University of Liverpool).

He explained that the JEV Vaccines Workgroup was charged with reviewing safety and immunogenicity data for the new inactivated Vero cell-derived JEV vaccine, tradename Ixiaro ®; updating and revising the 1993 ACIP recommendations for the use of JE vaccines among US travelers; monitoring the availability of JEV vaccines for US travelers and working to mitigate possible supply issues (BIKEN's production of JE-VAX ®); and addressing the availability of JEV vaccines for US children, with the new vaccine being labeled only for persons 17 years of age and above.

Revised Recommendations for the Use of Japanese Encephalitis Virus Vaccines

Marc Fischer, MD, MPH
Arboviral Diseases Branch
DVBID, NCZVED, CDC

Dr. Fischer reminded everyone that Japanese encephalitis virus (JEV) is a mosquito-borne flavivirus. JEV is the leading cause of encephalitis in Asia, with an estimated 35,000 to 50,000 annual cases. Of these, 20%-30% of patients die and 30%-50% of survivors have significant sequelae. There are no specific antiviral therapies, and treatment consists of supportive care. JEV is transmitted in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds. JEV is transmitted to humans through the bite of an infected mosquito, but less than 1% of infected people develop symptomatic disease. Humans are a dead-end host and do not develop a level or duration of viremia sufficient to infect mosquitoes.

Japanese encephalitis occurs primarily in rural agricultural areas, often associated with rice production and flood irrigation. The mosquitoes that transmit JEV feed primarily outdoors during the evening and night. In endemic countries, most adults have protective immunity and JE is

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primarily a disease of children. However, since travelers from non-endemic countries usually do not have JEV antibodies, travel-associated Japanese encephalitis can occur among persons of any age. In most temperate areas of Asia, JEV transmission is seasonal, and human disease usually peaks in summer and fall. In the subtropics and tropics, transmission patterns vary and human disease often peaks during the rainy season, but may occur year round.

From 1973 to 2008, there were 55 cases reported in the literature of travel-associated Japanese encephalitis among people from non-endemic countries, including the US. The median age of these cases was 34 years, patients ranged from 1 to 91 years of age, 53% of the patients were male, 34 of the travel-associated cases were tourists, 9 were expatriates living in Asia, and 6 were soldiers or military personnel. The type of travel was unknown for another 6 cases. Ten of the reported cases were fatal, and 24 of the survivors had sequelae. None of these patients had received JEV vaccine.

For 37 of the 55 travel-associated cases, more complete information was available regarding their itineraries and activities. Duration of travel for these cases ranged from 10 days to 34 years, and 65% of the cases were traveling for a month or longer. Of the 13 short-term travelers, 10 had a trip duration of 2 to 4 weeks, and 3 had traveled for 10 days to 2 weeks. Among these shorter-term travelers, 3 had known extensive rural exposures, and 8 stayed in resorts or coastal hotels with shorter trips into more rural areas. Two cases did not have any risk-related itinerary information available. No cases were reported among short-term travelers who visited only urban areas.

From 1943 to 1972, there were more than 300 cases of JE among U.S. military personnel. Between 1973 and 1992, 11 cases were reported among US citizens, including 5 among civilian travelers. Since December 1992, when a JEV vaccine was first licensed in the US, only 4 cases of Japanese encephalitis have been reported among US citizens, all among civilian travelers or expatriates. Three of these cases occurred among returning immigrants or travelers visiting family in Asia.

Estimating the incidence of Japanese encephalitis for travelers to Asia is difficult. Extrapolating from the rates of disease among unimmunized US military personnel or resident children in endemic areas, the risk of Japanese encephalitis for travelers with prolonged stays in rural areas with active JEV transmission may theoretically be as high as 10 to 200 cases per 1 million travelers per week. However, most travelers do not have this type of itinerary or risk, and between 1973 and 2008, there were only 15 cases of JE reported among US travelers to Asia. In 2004, there were an estimated 5.5 million entries of US travelers into Japanese encephalitis endemic countries. Using these figures, for all travelers to Asia, an overall risk of less than 1 case per 1 million trips would be estimated.

Based on the available data, the workgroup concluded that the overall risk of Japanese encephalitis for most travelers to Asia is very low, but that the risk varies based on destination, duration, season, and activities. The risk of Japanese encephalitis among expatriates and travelers who stay for prolonged periods in rural areas with active JEV transmission, are likely similar to that of the susceptible resident population. Travelers on brief trips may be at increased risk if they have outdoor or nighttime exposures in rural areas, especially during periods of active transmission. Short-term travelers, whose visits are restricted to major urban areas, are at minimal risk for Japanese encephalitis.

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Two JEV vaccines are currently licensed in the US. JE-VAX®, an inactivated mouse brain-derived vaccine, has been licensed since 1992 for use in travelers one or more years of age. In March 2009, the FDA approved IXIARO®, an inactivated Vero cell-derived vaccine, for use in travelers 17 years of age or older. The inactivated mouse brain-derived vaccine was first developed in the 1960s. It has been administered to millions of people worldwide and has been used effectively to control Japanese encephalitis disease in several Asian countries including Japan, Taiwan, South Korea, and Thailand. In December 1992, a formulation of this vaccine was first licensed in the US. The vaccine was manufactured by BIKEN in Osaka, Japan and is distributed in the US by sanofi pasteur. However, in 2006, BIKEN discontinued production of JE-VAX®, and remaining supplies are now limited.

JE-VAX® is a formalin inactivated vaccine derived from wild-type Nakayama-NIH JEV strain grown in mouse brains. The final preparation is lyophilized and contains gelatin as a stabilizer and thimerosal preservative. The primary immunization series consists of three doses administered subcutaneously on days 0, 7, and 30. Efficacy of the mouse brain-derived vaccine was demonstrated in a randomized, controlled trial conducted among 65,000 Thai children. Study participants were randomized to receive two doses of JEV vaccine or tetanus toxoid. After 2 years, the vaccine had an efficacy of 91% [Hoke 1988]. The current 3-dose primary immunization series for travelers was established based on immunogenicity studies performed in adults from non-endemic countries.

Mouse brain-derived JEV vaccine results in mild injection site reactions in about 20% of recipients. Mild systemic side effects such as fever, headache, or diarrhea have been reported in approximately 10% to 30% of vaccinees. This vaccine has also been associated with allergic hypersensitivity reactions and rare, but serious neurologic adverse events. Allergic hypersensitivity reactions, including generalized urticaria and angioedema of the face and oropharynx, have been reported primarily among adult travelers and military personnel. The reported frequency of allergic reactions range from 10 to 260 cases per 100,000 vaccinees, and these risks vary by country, year, case definition, surveillance method, and vaccine lot [Plesner 2003; Takahashi 2000; Berg 1997; CDC 1993]. The study with the highest incidence of allergic hypersensitivity reactions included active follow-up of over 14,000 US Marines in 1997 in which 38 allergic reactions were identified, including 27 patients with urticaria, angioedema, and / or wheezing, and 11 patients with generalized pruritis. Two patients were hospitalized for observation. Although most of these reactions occurred within the first 24 hours after the first dose, when they occurred following a subsequent dose, symptom onset was often delayed with a median of 4 days and a range of up to 2 weeks [Berg 1997].

Gelatin, which is used as a vaccine stabilizer, may be responsible for some of these allergic reactions. In one study among Japanese children who received mouse brain-derived JEV vaccine, 10 children who developed an immediate hypersensitivity reaction all had measurable immunoglobulin E (IgE) antibodies against gelatin. By contrast, only 1 of 28 children developed a delayed hypersensitivity reaction, and none of 15 controls who had no allergic reaction had evidence of anti-gelatin IgE antibodies [Sakaguchi 2001].

The incidence of neurologic events reported following receipt of mouse brain-derived JEV vaccine has ranged from 0.1 to 2.6 per 100,000 vaccinees [Takahashi 2000; Plesner 1998]. These neurologic events have included paresthesia, seizures, encephalopathy, gait disturbance, and Guillain-Barre syndrome. In addition, there have been case reports of children

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in Japan and Korea with acute disseminated encephalomyelitis (ADEM) following vaccination. In 2005, in response to these cases, Japan suspended routine immunization with mouse brain-derived JEV vaccine. In reviewing this decision, the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety determined that a causal link had not been demonstrated. The committee recommended that, although current use and policies should not be changed, the mouse brain-derived vaccine should be gradually replaced by new generation JEV vaccines [Matsukura 1980; Ohtaki 1992; Ohtaki 1995; Sohn 2000; Takahashi 2000; Matsui 2002; Ferguson 2007; Plesner 2000; Plesner 2003].

The recently licensed inactivated Vero cell-derived JEV vaccine is manufactured by Intercell Biomedical and distributed in the US by Novartis Vaccines. This vaccine is now available in the US, Europe, and Australia, and the manufacturer anticipates having adequate supplies to meet US civilian traveler needs. IXIARO® is a formalin inactivated vaccine derived from the attenuated SA 14-14-2 JEV strain propagated in Vero cells. The final liquid preparation contains aluminum hydroxide as an adjuvant. It does not contain gelatin or thimerosal. The primary immunization series consists of two doses administered intramuscularly on days 0 and 28. The vaccine is not licensed for use in children less than 17 years of age.

Due to the availability of several effective JEV vaccines in Asia, randomized, controlled efficacy trials to evaluate new vaccines would now be logistically difficult and potentially unethical. As a result, there are no efficacy data for the new Vero cell-derived JEV vaccine. Instead, the vaccine has been licensed based on its ability to induce JEV neutralizing antibodies as a surrogate for protection, and based on safety evaluations in almost 5,000 adults [Hombach 2005; Markoff 2000].

The pivotal non-inferiority study compared people randomized to receive two doses of the new Vero cell-derived vaccine to three doses of the existing mouse brain-derived vaccine. The study was performed among adults in the US, Austria, and Germany. The primary outcome measure was the proportion of vaccinees who developed JEV neutralizing antibodies based on a 50% plaque reduction neutralization test or PRNT50. The immunogenicity analysis was performed on 735 subjects who met all protocol criteria, including having no JEV neutralizing antibodies prior to vaccination. The safety analysis was performed on 863 subjects who had received at least one dose of either vaccine. Of the Vero cell-derived vaccine recipients, 98% developed a neutralizing antibody titer of 10 or greater, compared to 95% of the mouse brain-derived vaccine recipients, at 56 days after the first dose. This met the study criteria for non-inferiority. The geometric mean titers (GMTs) were significantly higher among recipients of the Vero cell-derived vaccine. However, it is important to note that this study used SA 14-14-2 as the target strain in the neutralizing antibody assay and GMTs were higher for the mouse brain-derived vaccine when the Nakayama JEV strain was used in the assay. In this study, severe pain or tenderness at the injection site was uncommon and occurred in less than 2 percent of recipients of either vaccine. However, severe redness or swelling at the injection site was significantly less common among recipients of the Vero cell-derived vaccine. The frequency of systemic adverse events was similar between the two groups [Tauber 2007].

The pivotal safety study compared 1,993 subjects who received two doses of the new Vero cell-derived JEV vaccine to 657 subjects who received two doses of a placebo adjuvant composed of phosphate buffered saline and aluminum hydroxide. Adverse events were monitored for 56 days following the first dose. The proportion of vaccinees who reported any adverse event, medically attended adverse events, serious adverse events, or an adverse event that resulted in termination from the study, were similar between the two groups [Tauber 2008].

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Among the 12 (0.6%) subjects in the Vero cell-derived vaccine group who terminated the study prematurely due to adverse events, 2 (0.1%) of the events were classified as severe, including one case of gastroenteritis and one rash. Of the adverse events leading to termination, 8 (0.4%) were considered possibly related to the study vaccine, including two subjects with headaches, and one subject each with influenza-like illness, injection site pain, nausea, fatigue, rash, and dermatitis. One case of generalized urticaria was reported in a patient at 8 days after she had received her 2nd dose of the Vero cell-derived vaccine. The urticaria was described as being of moderate intensity. It was treated with an antihistamine and resolved within 3 days. Angioedema was not observed. The event was assessed by the study investigator as being unlikely related to the vaccine and the subject completed the study.

Overall, the new inactivated Vero cell-derived JEV vaccine is a very promising vaccine for use in adult travelers, given its favorable immunogenicity and reactogenicity profile after a two dose primary series. In addition, because the vaccine does not contain gelatin or murine proteins, there are likely to be fewer vaccine-associated hypersensitivity or neurologic adverse events compared with the mouse brain-derived vaccine. However, because the new vaccine has been studied in less than 5,000 recipients, the possibility of these or other rare adverse events cannot be excluded. Post-licensure surveillance data will be important to further evaluate safety in a larger population.

The new Vero cell-derived JEV vaccine is currently approved for use in adults 17 years of age or older. As a result, the mouse brain-derived vaccine is the only JEV vaccine that is approved for use in children in the US. Although the mouse brain-derived vaccine is still approved for use in adults, sanofi pasteur will now restrict purchase of their remaining inventory of JE-VAX® for use in children 1 to 16 years of age. All remaining doses of JE-VAX® will be available through this pediatric stockpile. One pediatric clinical trial with IXIARO® has been completed and others are planned, but it will likely be several years before the vaccine is approved for use in children in the US.

Recommendations regarding the use of JEV vaccine for travelers must weigh the risks of travel-associated Japanese encephalitis, with the benefits and potential risks of JEV vaccine. The overall risk of Japanese encephalitis for most travelers to Asia is very low, but again varies based on destination, duration, season, and activities. When Japanese encephalitis does occur, it has a high morbidity and mortality, and there is no specific treatment. Safe and effective vaccines are available. However, the possibility of rare serious adverse events cannot be excluded. Given these considerations, the workgroup developed the following general recommendations for the prevention of JE among travelers:

1. Travelers to JE endemic countries should be advised of risks of JE disease and the importance of measures to reduce mosquito bites

2. JEV vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JEV transmission season

3. JEV vaccine should be considered for short-term travelers to endemic areas during the JEV transmission season if they will travel outside of an urban area <u>and</u> their activities will increase the risk of JEV exposure

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4. JEV vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JEV transmission season

With regard to recommendations for the prevention of JE among travelers, the following language was crafted:

> "Travelers to JE endemic countries should be advised of the risks of JE disease and the importance of personal protective measures to reduce the risk of mosquito bites. For some travelers who will be in a high risk setting based on location, duration, season, and activities, JEV vaccine may further reduce the risk of infection."
>
> "All travelers should take precautions to avoid mosquito bites to reduce the risk of JE and other vector-borne infectious diseases. These precautions include using insect repellent, permethrin-impregnated clothing, and bed nets, and staying in screened or air conditioned rooms. Additional information on protection against mosquitoes and other arthropods can be found at [CDC Yellow Book website]."

Recommendations for the use of JEV vaccine are as follows:

> "JEV vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JEV transmission season. This includes longer-term travelers, recurrent travelers, or expatriates who will be based in urban areas but are likely to visit endemic rural or agricultural areas during a high risk period of JEV transmission."
>
> "JEV vaccine should be considered for the following:
>
> - Short-term travelers (<1 month) to endemic areas during the JEV transmission season if they plan to travel outside of an urban area and have an increased risk of JEV exposure. Examples of higher risk activities or itineraries include: 1) Spending substantial time outdoors in rural or agricultural areas, especially during the evening or night; 2) Participating in extensive outdoor activities (e.g., camping, hiking, trekking, biking, fishing, hunting, or farming); and 3) Staying in accommodations without air conditioning, screens, or bed nets.
> - Travelers to an area with an ongoing JE outbreak.
> - Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel."
>
> "JEV vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JEV transmission season."

Dr. Fischer also presented the draft recommendations for laboratory workers, reporting that at least 22 laboratory-acquired JEV infections have been reported in the literature. JEV may be transmitted in a laboratory setting through needle sticks or theoretically through aerosol or mucosal exposure. Work with the wild-type JEV is restricted to laboratories with Biosafety Level 3 (BSL-3) containment and select agent registration. Some well-characterized attenuated JEV strains may be handled safely at BSL-2. Based on this information, the workgroup developed the following recommendations, which he noted differed slightly from the original handout:

> "JEV vaccine is recommended for laboratory personnel who work with live, wild-type JEV strains. Vaccinated, at-risk laboratory personnel should receive appropriate booster doses of JEV vaccine or be evaluated regularly for JEV-specific neutralizing antibodies to assure adequate titers."

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Discussion

Dr. Marcy inquired as to what had been the previous use annually of this vaccine, thinking about the 2500 to 4000 doses left in the stockpile and how long that was expected to last.

Dr. Fischer responded that this had varied over time and partially depended upon how much has gone to the military.

Dr. Hosbach (sanofi pasteur) replied that while it was difficult to predict how long the stockpile was anticipated to last, based on their estimates, it probably would last approximately 2 to 3 years. It was very difficult to calculate how many children were actually receiving the vaccine. In total, just over 100,000 doses were used annually, and about 80% to 90% of that went to the military. Thus, there was not a major marketplace for the use of this vaccine.

Dr. Marcy inquired as to whether Intercell planned to move along quickly to amass more data and whether the FDA would seek a fast track. He expressed concern that the vaccine supply would be depleted before the new one was available.

Dr. Katrin Dubischar-Kastner (Intercell) indicated that Intercell, the manufacturer and license holder of the vaccine, is progressing with its pediatric development plan. They are currently starting trials and expect them to begin in the 4th quarter of 2009. Pediatric licensure is expected within the next 2-3 years.

Dr. Fischer mentioned that the possibility had been discussed with FDA of setting up an investigational new drug (IND) that could be used in the event that the JE-VAX® supply was completely exhausted but no licensure had been issued on the new vaccine. That is the way this vaccine was administered in Europe for years. They did not have a licensed JE vaccine. They do believe that the supply should last for approximately 2 years. The number of children is small and the regimen is 3 doses.

In terms of global warming, Dr. Marcy wondered whether attention was being given to changes in patterns of the viruses. For example, there have been changes in the dengue season.

Dr. Fischer responded that there has definitely been a change in the geographic area that JEV covers over the past few decades. It is unclear how much of that is a surveillance artifact versus actual change. There has probably been change in agriculture practices, herd migration, and other things. There is no clear evidence of global warming or climate change playing a role in that. For vector-borne diseases, it is really very complex as to what global warming or climate change affects, because there will be changes in rainfall as well as warming. Therefore, it is very unclear for most vector-borne disease what the effect of climate change would be. With regard to season, it is less certain whether there have been changes. There has certainly been more recognition of classic outbreaks that occurred in Northern Asia where this disease was first recognized in the early 1900s, in which there are high peaks in very short periods of time (July through September) as is observed with West Nile Virus. There is certainly more recognition moving into South Asia and the Western Pacific that the disease occurs even more sporadically or year round. It is not clear whether that reflects a change over time or merely recognition of the disease.

Dr. Hosbach (sanofi pasteur) indicated that the doses stockpiled are due to expire in May 2011.

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Dr. Stanley Gall (ACOG) said he did not hear anything about use of this vaccine during pregnancy, although this is bound to occur. He wondered whether the assumption could be made that because it was non-live virus vaccine it would be safe during pregnancy.

Dr. Fischer responded that this would differ for the two vaccines. One vaccine is considered a category C, one a Category B. For the new vaccine, there have been some studies in rodents so the category is a little different. Basically, it is considered for both the vaccines to be a precaution; that is, because it is not a live vaccine, there is no known risk, but data are limited. Thus, the wording basically states that vaccination should be deferred unless the person has to travel to a high risk area and the risk of the disease outweigh the risks of the vaccination.

Dr. Meissner pointed out as a working group member that the group did discuss that the Vero cell-derived vaccine appears to be a significant improvement over the mouse brain-derived vaccine. Although it is still early, at least at this stage, it appear to have significant advantages. He thought that was a tribute to Intercell Biomedical for their production of this vaccine and Novartis for their plan distribute this vaccine. This vaccine does not have gelatin as a stabilizer, will not have nervous tissue proteins from the mouse brain, and appears to be more immunogenic. He thought that should be acknowledged. There have been only 4 cases of JEV in 15 years since the first set of recommendations were issued in 1993, which also weighed heavily on the working group deliberations.

Christine Hahn (CSTE) noted that this recommendation relied heavily upon knowing when JEV transmission season is. She wondered whether this appeared on the CDC travel site for quick reference.

Dr. Fischer responded that there is a table that has transmission seasons by country and areas that are endemic. The table is included in the current recommendations. The working group agreed that it could be updated more readily and changed to refer to the Yellow Book website, and would then be updated in the Yellow Book every other year. There is also a cautionary statement that there are limits to surveillance data, and that there are changes from year to year. A general idea is given of the seasons and the locations where JE occurs, but people must be careful in interpreting that data. Those caveats are included in the document.

An inquiry was posed regarding what the new vaccine product insert would say about revaccination for those who have continuing exposure over the years, and how often revaccination should occur.

Dr. Fischer responded that for the new vaccine, there are really no recommendations with regard to booster doses or revaccination. There are some data on the ration of neutralizing antibody, which cites two different studies, one which is published and one which has been presented at a meeting, in which Intercell is examining duration of neutralizing antibodies. One study shows as many as 83% of vaccinees having neutralizing antibodies at 12 months. The other study went out as far as 24 months and had a little less than 60% at 12 months, and 48% at 24 months. Currently, in both the package insert and the ACIP recommendations, there are basically no recommendations similar to what was done initially for meningococcal conjugate vaccine with regard to booster doses. It simply states that this will need to be determined.

Dr. Beck noted that at one point, the DoD had a back-up stock of JE-VAX®. He wondered whether that still existed and could serve as a potential back-up for the civilian population.

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COL Cieslak (DoD) responded that he believed that stock was sold back to the company in advance of the Beijing Olympics. The DoD basically relinquished that supply. What is currently being held for pediatrics is in part some of that stock that was sold back by DoD.

Dr. Hosbach (sanofi pasteur) expressed gratitude to the military, the cooperating agencies, and Dr. Gellen for helping arrange this. A couple of times sanofi pasteur was able to buy back material from the military to supply to the private sector. However, the military still has a stockpile of JE-VAX®, of which sanofi recently repurchased another 5,000 doses to keep going so until IXIARO® is licensed.

Regarding cost considerations, Dr. Chilton indicated that there was a statement in the committee's packages that were received prior to the meeting indicating that those who travel to rural areas or expatriates living in rural areas probably have roughly the same exposure to this disease as those who live in those areas, which is listed in that material at 0.1 to 2 cases per 100,000 persons per week in those areas. He wondered if that was correct.

Dr. Fischer responded that those data are extrapolated significantly from military population data primarily during the Korean Conflict and Vietnam War.

It seemed to Dr. Chilton that for those traveling to or living in one of these rural areas, preventing one case of JE would cost $5 to $100 million at the price quoted for this vaccine. That seemed high to make a recommendation as strong as the one pending a vote.

Dr. Fischer replied that two things needed to be taken into consideration. First, all of the cases reported have been in the context of vaccination. It is not clear exactly who is being vaccinated, but it is assumed that the vaccine is being somewhat appropriately targeted such that cases are being prevented. Second, the numbers presented were of cases reported in the literature. There are likely more cases that are not diagnosed and / or reported. He cautioned against making too many assumptions. While the disease is believed to be rare, he would not try to put a specific number on it. The working group did engage in discussions about cost, but this is a travel vaccine.

Dr. Sumaya pointed out that Recommendation #2 states that "JEV vaccine should be considered." He wondered whether there was a reason it did not say "recommended," particularly when one of the items is travelers to an area with an on-going JE outbreak.

Dr. Fischer responded that this was similar to the current recommendations, and they have the strongest evidence that these are the people at greatest risk. More thought really needs to be placed on the individual traveler and their itinerary.

Dr. Cieslak said he thought the incidents cited were 100,000 per year and not per week, and the week extrapolation was different. He thought it was as high as 1 per 5000 per week.

Dr. Fischer replied that they were per week for the highest risk populations.

Motion: Revised JE Vaccine Recommendations

Dr. Meissner moved to approve the revised recommendations as proposed. Dr. Sawyer seconded the motion. The motion passed with 12 affirmative, 1 negative, and 0 abstentions.

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Hepatitis Vaccines

Introduction

Dr. Mark Sawyer, Chair
Hepatitis Vaccines Work Group

Dr. Sawyer indicated that the terms of reference for the Hepatitis Vaccines Work Group were to:

- Determine the advisability and extent of hepatitis A vaccination recommendations for families adopting children from other countries
- Review data from recent hepatitis B outbreaks among diabetics in institutional care to determine whether vaccination is appropriate
- Review data related to long-term immunity of hepatitis B vaccine to determine if additional vaccine doses are necessary; if so, what dosage and schedule
- Review hepatitis A vaccine long-term immunity to see if updating recommendations is warranted

The first term of reference regarding hepatitis A recommendations was dealt with in the past. During this session, an update was presented on the work group's deliberations pertaining to the second term of reference regarding recent hepatitis B outbreaks among diabetics in institutional care to determine whether vaccination is appropriate for this population.

Hepatitis B among Residents of Long-Term Care Facilities

Nicola D. Thompson, PhD
Division of Viral Hepatitis
NCHHSTP, CDC

Dr. Thompson presented a summary of information the hepatitis vaccine work group has discussed in recent months with respect to the role of hepatitis B vaccine use among residents of long-term care facilities, specifically those with diabetes. While seemingly unrelated, these three issues had arisen which the work group was charged to address (e.g., hepatitis B virus, diabetes, and long-term care). During this session, she discussed hepatitis B virus transmission during delivery of health care, summarized hepatitis B virus infection outbreaks among people with diabetes, discussed diabetes epidemiology in the US, addressed long-term care, and raised possible prevention strategies for consideration.

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There has been a dramatic decline in the incidence of acute HBV infection in the US last few decades. Much of this decline can be attributed to the implementation of vaccine recommendations for infants and children, and targeted high risk groups, such as injection drug users, persons with high risk sexual behaviors, healthcare workers, and chronic hemodialysis patients. The decline observed has been much more striking in younger age groups when compared to older adults when incidence is stratified at 50 years of age. In 2007, about 4500 cases of acute HBV infection were reported, and the acute HBV infection fatality rate was 1.5%. It is important to note that due to under-reporting and the high proportion of asymptomatic acute infections, it is estimated the actual number of new cases in 2007 was around 43,000 [National Notifiable Diseases Surveillance System (NNDSS)].

There is an inverse relationship between the age at infection and the development of chronic HBV infection. The risk of developing chronic HBV is highest in those who are infected as infants and children, compared to healthy adults. [Shepard et al. Epidemiologic Reviews 2006;28:112-125]. However, older adults and immune suppressed individuals are also at high risk for developing chronic HBV infection Studies have shown that this risk may be as high as 59% in older adults [Kondo. Hepatology 1993;18:768-74], between 40% and 45% for hemodialysis patients [Hyams CID 1995;20:992-1000], and up to 22% for HIV-infected individuals [Alter MJ J Hepatol 2006; 44:S6–9].

The CDC estimates that between 800,000 and 1.4 million persons in the US have chronic HBV [CDC MMWR 2008;57 No. RR-8]. Other estimates suggest that it may be higher at around 3 million, and that immigration plays an important role in chronic HBV infection in the US, with estimates indicating that approximately 46,000 cases are imported each year [Welch et al. Estimating Prevalence of chronic hepatitis B in Foreign-born persons in the US. Abstract OP059. ISVHLD 2009; Mitchel et al. Increasing burden of imported chronic hepatitis B – US, 1973-2007. EIS Conference 2009]. Chronic carriers are central to the epidemiology of HBV, as they may be asymptomatically infected for many years and unknowingly provide a risk of transmission to susceptible persons. Chronic carriers are at increased risk of cirrhosis and liver cancer. It is thought that between 2000 and 4000 people die each year from HBV-related chronic liver disease [CDC MMWR 2008;57 No. RR-8].

The primary modes of HBV transmission are perinatal, sexual, and by percutaneous and permucosal exposures. This includes injection drug use, non-sexual household contact with HBV infected persons, and healthcare related transmission. While healthcare related transmission due to occupational exposures and through the receipt of blood and blood products has been decreasing, patient-to-patient HBV and hepatitis C (HCV) transmission during the delivery of healthcare has been increasingly recognized in the US [1:Thompson et al. Nonhospital health care–associated hepatitis B and C virus transmission: United States, 1998–2008. AIM 2009;150:33-39].

With respect to the number and cause of HBV and HCV outbreaks that have been reported since 1998 in the US, all of these outbreaks have involved patient-to-patient transmission during the delivery of healthcare due to poor infection control practices. Both hepatitis B and C outbreaks have occurred in a variety of settings, including endoscopy clinics, nuclear imaging clinics, pain remediation clinics, oncology clinics and physician offices. One area of particular concern is the multiple and continuing outbreaks of HBV infection among long-term care residents that have repeatedly been associated with poor practices during diabetes care,

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specifically during blood glucose monitoring [Thompson, Perz. JDST 2009;3:283-89; Thompson et al. AIM 2009;150:33-39].

While the prevalence of chronic HCV infection is higher in the US than chronic HBV infection, there are some important features of HBV that help facilitate its transmission; the high viral titer and high environmental stability. A virus can be present in tiny or invisible amounts of blood, and due to the environmental stability, dried blood on surfaces, equipment or devices can remain viable for at least seven days [Beltrami et al, Clin Microbio Reviews, 2000. MMWR 2001;50(No. RR-11); Bond et al. Lancet 1981; 8219:550-1. Shikata et al. J Infect Dis 1977;136:571–76; Shikata et al. J Infect Dis 1977;136:571–76; Kamilli et al. ICHE 2007;28:519-24]. Together these characteristics play an important role in healthcare-related HBV transmission and specifically during diabetes care when equipment used for finger stick procedures and monitoring blood glucose levels are shared among multiple persons. HBV transmission has been associated with blood contamination of the end and barrel of spring-loaded finger stick devices, with blood contamination of blood glucose testing meters, and with failures by staff to wear or change gloves or perform hand hygiene between performing finger-stick procedures.

Preventing this type of transmission relies on consistent adherence to standard infection control recommendations. In 1990, CDC and the FDA published recommendations clearly stating that spring loaded finger stick devices should be restricted for individual use. Later, guidance on this issue came from the American Association of Diabetes Educators. In 2005, CDC again reinforced the 1990 recommendations and made specific recommendations for prevention of blood borne pathogen transmission during diabetes care in long-term care settings. This issue is also addressed in the 2007 Healthcare Infection Control Practices Advisory Committee (HICPAC) Isolation Guidelines, which are applicable to all settings were healthcare is delivered. Just a few months ago, the FDA issued a health alert for the appropriate use of insulin pens in healthcare settings. This alert was issued after it was discovered that these devices, designed for individual use, were found to have been used on multiple patients in two US acute care hospitals.

In the US, the first recognized outbreak of hepatitis B associated with diabetes care was reported in 1990. Since then, and despite multiple comprehensive prevention recommendations, these outbreaks have continued to occur. A notable shift from acute care hospitals to the long-term setting appears to have occurred, first in nursing homes and then in assisting living facilities. In total, 19 outbreaks of HBV infection among diabetic persons have been reported since 1990, with 6 outbreaks occurring in the past 2 ½ years. Given that most newly infected adults will be asymptomatic and that the diagnosis of acute hepatitis B is often not suspected or missed in older adults, it is likely that these outbreaks under represent the true number that have occurred.

From combined data from 13 seroprevalence surveys conducted during investigations of these outbreaks, in which 1308 persons were tested for HBV infection, persons with diabetes had a high prevalence of both past and chronic infection compared to those without diabetes. In these outbreaks, acute HBV infections occurred predominantly among persons with diabetes, 30.5% compared to 0.9% among those without diabetes. Overall, the prevalence of ever being infected with HBV (including those with past, chronic, and acute infection among non-diabetics) was 5.6%, but was 42.9% among persons with diabetes. The median age of people with acute HBV infection from these outbreaks was 75 years with a wide range from 42 to 92 years. The vast majority with acute HBV infection (92%) had diabetes and were monitoring their blood glucose levels. A small number of secondary cases have been reported in non-diabetic

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roommates and family members of infected individuals, and among non-vaccinated staff members. About 1/3 of those with acute infection were symptomatic, and among those that were symptomatic, 37% were hospitalized. The acute HBV infection fatality rate was 5% among all people infected and was actually as high as 15% among those with symptomatic acute hepatitis B. Those who died from acute HBV infection had a median age of 85 years and ranged from 64 to 92 years [CDC. Unpublished Data 2009].

Among 29 people who were re-tested at least six months after their initial diagnosis of acute infection, 50% had developed chronic infection. As already noted, this is similar to rates that have been reported in the literature for older adults and immune suppressed individuals, such as hemodialysis patients, and is higher than that for HIV infected individuals [CDC Unpublished Data 2009; Kondo. Hepatology 1993;18:768-74; Hyams CID 1995;20:992-1000; Alter MJJ Hepatol 2006; 44:S6–9]. It has been well reported that the prevalence of diabetes has been and continues to increase rapidly in the US. Only about 5-10% of those with diabetes have Type 1, the vast majority have Type 2 diabetes. In 2006, just under 18 million people in the US had been diagnosed with diabetes [CDC available at: www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm].

This equates to about 5.8% of the total US population, but the prevalence is highest among people 65 years of age and older [Cowie et al., Diabetes Care 2009;32:287-94. CDC available at http://www.cdc.gov/diabetes/statistics/prev/national/tprevage.htm]. As the population continues to age, the number of people with diabetes will also continue to increase. By 2050 it is estimated that 29 million people will have diabetes, with most of them being older than 65 years of age and our colleagues in the division of diabetes translation tell us that this 29 million is an underestimate of what the actual burden will be [Boyle et al. Diabetes Care 2001:24:1936-40]. Daily blood glucose monitoring is a common practice among those with both Type 1 and Type 2 diabetes. Approximately 60% of all people with diabetes are estimated to self-monitor their blood glucose level at least once a day. This is in line with the Healthy People 2010 goal of 61% [CDC. Behavioral Risk Factor Surveillance System. MMWR 2007;56:1133-1137].

Long-term care provides both medical and non-medical care to people with chronic illnesses or disabilities. Long-term care is provided in many settings, but there are two main categories of residential long-term care and they have very different philosophies. Nursing homes provide care to people who cannot be cared for at home or in the community setting. They provide a wide range of personal care and health services that are medically oriented. Regulation and oversight of nursing homes occurs at the federal level. Assisted living is a group living arrangement that provides residents help with activities of daily living, such as eating, bathing, using the bathroom, and medication administration, this includes diabetes care. Social and recreational activities are usually provided and these facilities operate under a social model. There is no federal definition of assisted living and facility licensing and oversight occurs at the state level.

It is important to point out that the data for nursing homes is much more robust than it is for the assisted living facilities. The nursing home data largely comes from the National Nursing Home Survey conducted by CDC. The data from assisted living comes from a couple of different sources, some of which is from 2002, and some of which is more recent data from non representative samples. In both nursing homes and assisted living facilities, the majority of residents are female and the median age is between 84 and 85 years. In both settings, a substantial number (10-12% or around 270,000 persons) of residents are less than 65 years of age. Memory and mental health disorders are common among residents of long term care. In nursing homes, it is estimated that about 25% of residents have diabetes, and between 15 and

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20% in assisted living. Other common health conditions among residents include stroke and COPD or emphysema. About 2/3 of nursing home residents are considered to be in fair or poor health, compared to 50% of those in assisted living [National Nursing Home Survey, 2004, NCHS/CDC; US Dept of HHS Assistant Secretary for Planning and Evaluation Office of Disability, Aging and Long-Term Care Policy. November 2002; Overview of Assisted Living, 2006. NCAL].

In long-term care settings, there are relatively few professional, licensed medical staff: 32% of direct care staff in nursing homes and only 15% in assisted living. The duties of licensed nurses include resident assessment, medication reviews, care plan development, staff monitoring, wound care, vital sign readings, oxygen administration, blood glucose monitoring, and delivery of injections. In some states, these activities can be delegated to unlicensed, paraprofessional staff that comprises the majority of direct care staff in both of these settings. Few states have minimum staffing ratios for assisted living. Some require that a registered nurse (RN) be available 24 hours a day, but they do not have to be on site, or they only have to come in when medications are administered. Few states require paraprofessional staff, such as personal care aides, to be certified. Most paraprofessionals have no formal healthcare or medical training and learn while they are on the job [American Health Care Association. Estimates of Current Employment in the Long-Term Care Delivery System and Bureau of Labor Statistics; National Nursing Home Survey, 2004, NCHS/CDC; Overview of Assisted Living, 2006. NCAL].

Recruitment and retention of staff is recognized as a major challenge in long-term care settings. The average annual staff turnover rates range from 36-41% for registered nurses, 44-50% for licensed practical nurses, and between 45-66% for paraprofessional staff. Compared to other healthcare workers, long-term care staff earns the lowest salaries, receive the fewest benefits, are less likely to have employer sponsored health insurance, and have few advancement opportunities. In one recent HBV outbreak investigation, when the public health department staff returned to the facility 6 months after the initial investigation to conduct follow-up assessments, the new nursing director and staff were unaware that hepatitis B outbreak had even occurred. The impact of training and education initiatives is hampered in settings with such high staff turnover [Sikorska-Simmons. Gerontologist 2005;45:196-205; Zimmerman et al. J Am Geriatr Soc 2002;50:1987-95; 2007 American Healthcare Association Survey: Nursing Staff Vacancy and Turnover in Nursing Facilities; 2007 AAHSA National salary and benefit surveys]. In addition, high nursing turn over and low staffing rates have been associated with incident of infections in long term-care. In this setting, infections have been recognized as the leading cause of morbidity and mortality among residents. This increase in risk is due to the vulnerable resident population and the institution environment where residents share bedrooms and bathrooms and group activities are encouraged [Zimmerman et al. J Am Geriatr Soc 2002;50:1987-95; Richards. Infections in Residents of LTC Facilities: An Agenda for Research. Report of an Expert Panel. JAGS 2002;50:570-576].

Infection prevention and control programs have been poorly implemented in long-term care. Few resources or personnel are devoted to infection control activities, and there are no dedicated infection control staff. Staff charged with infection control duties often have many other duties and spend few hours on infection control issues. About half of the staff who are charged with infection control have no training in infection control themselves [Goldrick. Infection Control in skilled nursing LTC facilities: An Assessment. AJIC 1999;27:4-9]. There are few data on the effects of infection control interventions on resident outcomes and cost. This limits the uptake and implementation of infection control programs and dedication of resources to this issue [Richards. Infections in Residents of LTC Facilities: An Agenda for Research. Report of an Expert Panel. JAGS 2002;50:570-576].

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Two surveys have been conducted by CDC to assess routine diabetes care in non-outbreak situations. These surveys were used to assess the standard of diabetes care in these long term care facilities. Selected results from those surveys showed that, among facilities using spring loaded finger stick devices, between 16 and 24% of were sharing these among their diabetic residents despite there being recommendations in place since 1990. Among facilities sharing blood glucose testing meters among residents, 50-72% were not cleaning meters between each use. In both these surveys, the facilities were aware that the public health authorities had a planned visit to review diabetes care at their facility. In Virginia, the state health department had mailed educational packets and CDC safe diabetes care recommendations to each facility ahead of their visit. It is, therefore, likely that the prevalence of unsafe diabetes care practices may be higher than reported here [Virginia data: Patel et al. ICHE 2009;30; Florida data: CDC Unpublished Data 2008].

Currently, it is estimated there are about 2.5 million people residing in long-term care facilities in the US. Most of these residents are in nursing homes, although most growth in long-term care residency has occurred in the assisted living arena. This sector of long-term care has the least regulation and oversight, and the fewest medically trained staff [US Dept of HHS. Office of Disability, Aging and Long-Term Care Policy. November 2002; Overview of Assisted Living, 2006. NCAL and National Nursing Home Survey, 2004, NCHS/CDC]. As the US population is aging and living longer, there will be an increasing demand for long-term care services among adults with disabilities. It is expected that over the next 30 years, there will be a doubling of the number of people with moderate or severe disability [Johnson et al. Meeting the LTC needs of the Baby Boomers: How Changing Families will affect paid helpers and intuitions. 2007. The Urban Institute].

In summary, the reported incidence of acute HBV has been declining dramatically in the US; however, this decline has been much less dramatic among people greater than 50 years of age. Patient-to-patient HBV and HCV transmission due to poor infection control practices during the receipt of healthcare has been increasingly recognized in the US. This type of transmission has occurred in a variety of healthcare settings. However, persons receiving diabetes care in long-term care facilities have emerged as one risk group. In these settings, multiple people undergo daily and often multiple daily percutaneous exposures during blood glucose monitoring. Despite long-standing and comprehensive prevention recommendations, HBV infection outbreaks continue to be reported in long-term care. These outbreaks have shown that HBV is not an insignificant disease in this population of older adults with diabetes, with a high rate of acute HBV deaths and chronic infection being reported. Improving infection control, oversight, and regulation of long-term care is an increasing public health priority, although many challenges remain. Without change, the number of people placed at risk for infection will increase as the prevalence of diabetes and utilization of long-term care both increase.

CDC is addressing the prevention of hepatitis B among diabetics in three ways: 1) by improving the implementation and adherence to existing infection control recommendations; 2) by working with equipment manufacturers to develop technology and safety engineered devices to help prevent sharing of equipment, by developing and designing and marketing equipment for institutional use, and by developing equipment that reduces or eliminates blood borne pathogen transmission; and 3) by assessing the role of hepatitis B vaccine in prevention, which is the current charge of the Hepatitis Vaccines Workgroup.

Future workgroup meeting topics include examining the epidemiology of HBV infection, focusing on older adults without traditional risk factors; reviewing data on hepatitis B vaccine

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immunogenicity and safety by age, focusing again on older adults and people with diabetes; and assessing feasibility, programmatic issues, and cost-effectiveness.

Discussion

Dr. Judson found it amazing that 50% of the facilities surveyed were not following even the most basic or reasonable prevention techniques. He thought states regulated these facilities closely. His 92 and 94 year old parents live in such a facility and tell him that state inspectors come by to review practices, and everyone is very tense.

Dr. Thompson replied that most people who work with infection control in this area would agree that oversight and regulation is sorely missing in long-term care facilities, particularly assisted living facilities. While surveys are conducted, these may only be done once every three years and often they are assessing non-infection control issues.

Dr. Baker indicated that inspections are every three years in Texas, and facilities are notified in advance. Because facilities are forewarned, they look great on paper for one day.

Dr. Judson wondered whether facilities were directly violating the regulations that pertain to them or were simply undertrained with no one really in charge.

Dr. Thompson thought the latter was the case most of the time. While she did not know whether there specific regulations were in place for this issue, there are certainly recommendations from CDC. Unfortunately, there are 50 states with 50 different sets of regulations, oversight, and licensing. For example, in Pennsylvania, to work in an assisted living facility and perform blood glucose monitoring and administer insulin injections, you would only need to have to have a high school diploma and attend a four-hour training class. Under-training and under-staffing are definitely issues, and there are very few professional staff. There are infection control recommendations that some facilities follow, but this is certainly not happening in all of them.

Dr. Judson thought that from a public health standpoint, this situation ought to be fixable with the proper regulations and enforcement.

Dr. Thompson agreed. The working group plans to address infection control in terms of implementation of the existing recommendations, technology (e.g., safe devices), and vaccines.

Ken Schmader (AGS) noted that nursing homes are highly regulated by various federal and state organizations; however, infection control practices are not addressed amongst all the quality measures and regulations. Many issues need to be addressed (e.g., delirium, pressure sores, weight loss, depression, et cetera) within quality measures. Quality infection control can occur in the nursing home, for which there is evidence from the VA. The Department of Veterans Affairs is the largest single provider of nursing home care in the US, with over 130 nursing homes and 11,000 patients. The VA has put into practice infection control training practices, practitioners, programs, et cetera. There is very good evidence that this works. In fact, in the *American Journal of Infection Control* in 2008, there was an article published on that, which could serve as a model for the work group. Dr. Chesley Richards of CDC is one of the authors [Prevalence of nursing home-associated infections in the Department of Veterans Affairs nursing home care units; AJIC: American Journal of Infection Control. 36(3):173-179, April 2008].

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Dr. Thompson added that the Study on the Efficacy of Nosocomial Infection Control (SENIC) study was instrumental in showing that there is a cost benefit to implementing infection control, and that savings can be made by the facility. However, there is no such equivalent study or data for long-term care.

Alexis Elward (HICPAC) emphasized that infection control implementation is very resource-intensive and requires a considerable amount of education—repeatedly. There is a large proportion of paraprofessional staff, as high as 65%-85% in some of these facilities. This raises further challenges. With the lack of consistent regulatory oversight and dedicated resources, the problem is further compounded. Hepatitis B vaccination would only be one arm of a comprehensive program to address this issue.

Dr. Baker thought it would be beneficial to have some data pertaining to immunity. She agreed that infection control is extremely labor-intensive and education must be repeated regularly. Even certified nursing assistants who require more than four hours of training do not know anything about infection control and blood borne precautions. They are paid $8 an hour in most assisted living facilities with no benefits, so the minute there is a better place down the street, they move on. It is all about money.

Yellow Fever Vaccine

Introduction

Carol J. Baker, MD, Chair
ACIP Yellow Fever Work Group

Dr. Baker indicated that the Yellow Fever Work Group was charged to update and revise the 2002 recommendations based on new evidence. Many organizations were involved in the process of a rigorous review of the literature. The following Yellow Fever Work Group meetings were held, with the topic areas addressed shown for each:

- September 16, 2008
  - Introduction and background YF disease and vaccine
- November 10, 2008
  - Vaccine presentation, dose and booster
  - Simultaneous Administration of Other Vaccines
- December 9, 2008
  - General Safety
  - Requirements for vaccination before international travel
  - Upcoming changes to yellow fever risk areas

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- January 12, 2009
  - Hypersensitivity
  - Yellow fever vaccine-associated viscerotropic disease

- February 9, 2009
  - Thymic disease and use of vaccine
  - Yellow fever vaccine-associated neurotropic disease

- March 9, 2009
  - Travelers and individuals living in endemic areas
  - HIV
  - Elderly

- April 14, 2009
  - Pregnancy
  - Breastfeeding
  - Young children

- May 11, 2009
  - Cancer and cancer treatments
  - Immunomodulatory drugs
  - Additional topics

The resulting proposed revisions were reported to the full committee during this session for the purpose of information.

Proposed Updates to the ACIP Yellow Fever Vaccine Recommendations

J. Erin Staples, MD, PhD
CDC / CCID / NCZVED / DVBID

During this session, Dr. Staples reviewed yellow fever disease, the vaccine used to prevent it, and the proposed updates to the 2002 yellow fever recommendations the work group is considering.

Yellow fever disease is caused by yellow fever virus which is the prototypic flavivirus. It is transmitted to humans predominantly by Aedes mosquitoes, though other mosquitoes are involved in rural settings. However, in urban areas, Aedes aegypti mosquitoes can effectively spread the disease from human to human leading to large outbreaks of the disease. Yellow fever disease is endemic to 47 countries in equatorial Africa and South America. It can cause a range of disease in humans from mild illness to jaundice and hemorrhage. The WHO estimates there are approximately 200,000 cases and 30,000 deaths per year due to yellow fever; however, most cases go unrecognized by the current surveillance systems.

Yellow fever vaccine was developed in the 1930s. It is a live-attenuated viral vaccine produced in eggs (e.g., chicken embryos). From 1937-2008, over 500 million doses have been given to humans. Currently, one vaccine licensed for use in the US, YF-VAX®, produced by sanofi pasteur. It is derived from 17D-204 vaccine strain, so it is often referred to as a 17D vaccine.

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There are two primary reasons to vaccinate someone against yellow fever, which are to: 1) protect travelers and endemic populations against the disease; and 2) limit the introduction and spread of the disease into new areas. Many countries require proof of vaccination for all travelers. Yellow fever vaccine is the only vaccine exclusively covered under International Health Regulations, which were updated in 2005. Countries have the right to detain a traveler without proof of yellow fever vaccine for up to 6 days (e.g., the incubation period of the disease).

Multiple factors must be weighed when deciding whether to vaccinate someone against yellow fever (e.g., country requirements, risk of disease, and risk of vaccine adverse events). The risk of illness and death for yellow fever in an unvaccinated traveler traveling 2 weeks to endemic area in West Africa is 50 and 10 per 100,000 population, respectively. For South America, that risk is estimated to be about 10 times lower at 5 illnesses and 1 death per 100,000 population [Monath Clin Infect Dis. 2002;34:1369-1378]. Risk for vaccine adverse events must be taken into consideration as well. Risk for general adverse events is approximately 43 per 100,000 doses and for serious adverse events is approximately 4.7 per 100,000 doses [Based on US VAERS data 2000-2006; Lindsey et al. Vaccine. 2008; 26: 6077-6082].

The potential serious adverse events following yellow fever vaccination fall into three categories. The first is anaphylaxis. Individuals who are allergic to eggs, chicken proteins, and gelatin are at increased risk at a rate of 1.8 per 100,000 doses. Neurotropic disease / neurologic disease is a conglomerate of various presentations that are due to one of two mechanisms. The first is direct vaccine viral invasion of the central nervous system resulting in encephalitis or meningitis. The other is autoimmune-mediated phenomenon such as Guillain-Barré Syndrome (GBS) or acute disseminating encephalomyelitis. The rate for all neurologic disease following yellow fever vaccination is 0.8 per 100,000 doses. Another serious adverse event is viscerotropic disease in which the vaccine virus, as a live attenuated virus, proliferates and causes a disease similar to natural infection with multi-system organ failure. This occurs at a rate of 0.4 per 100,000 doses, with a case fatality of over 50%.

The Yellow Fever Work Group took two general approaches for revising the yellow fever recommendations that were published in 2002. The first was that the group wanted to provide more specific information when possible based on published literature, unpublished reports, or expert opinions. They also wanted to further clarify the risks of disease versus the vaccine to help better guide travel practitioners in advising their patients about whether to be vaccinated. The work group also wanted to align the yellow fever ACIP recommendation with other ACIP documents. For example, there are pregnancy and breastfeeding guiding principles, so that language would be used to help unify the way breastfeeding and pregnancy are put forth. When there is a lack of evidence for yellow fever vaccine specifically, the group plans to adhere to the general recommendations for live viral vaccines with respect to timing intervals and Immunocompromised individuals.

Anticipated revisions to the 2002 recommendations for the upcoming 2009 recommendations fall into broad categories, which are to: update the epidemiology of yellow fever disease, include information on International Health Regulations (2005), update vaccine safety data, add / improve wording for vaccine precautions and contraindications based on new data; and outline research priorities. In terms of the updated epidemiology of yellow fever disease, a new risk map was created in 2008 which harmonizes the WHO and CDC areas at risk:

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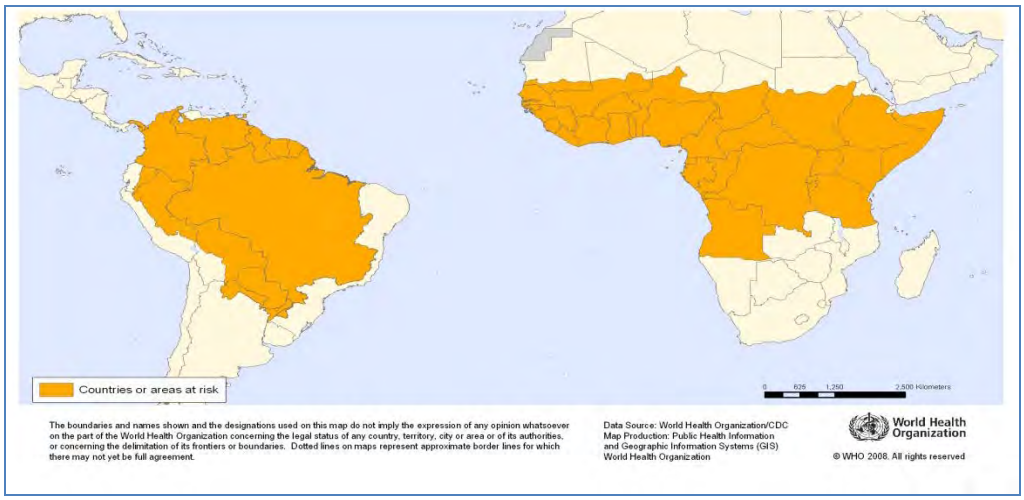

Disease activity has been increasing in the last couple of years in terms of the areas affected, specifically for South America where areas in which yellow fever disease has been dormant for the last 30 years now have disease activity. That includes Northern Argentina, Paraguay, the Eastern edge of the endemic area for Brazil, and Trinidad. In Africa, there has been an increase outside of their normal endemic area of West Africa in the central African countries.

In terms of vaccine safety data, the work group wants to update the incidence rates. This information will come from more recent VAERS data, which includes the serious adverse event rate of 4.7 for all comers. Specific age group incidents will also be highlighted, particularly for serious adverse events. For individuals 60-69 the rate will be 6.3 serious adverse events per 100,000 doses, and for those greater than 70 the rate goes up to 12.6 per 100,000 doses. More information will also be provided on serious adverse events. When the last recommendations were published in 2002, viscerotropic disease had just been recognized. There have been more cases, so those data will be summarized to present key clinical characteristics that are observed. The neurologic disease observed will also be characterized. Specific testing that can be conducted for vaccine adverse events will be described to assist in determining whether the event that is noted is potentially related to the vaccine. Potential treatments will as be discussed which would apply for events such as GBS. More information will also be provided on yellow fever vaccine precautions. For breastfeeding, updated information will be included on transmission and vaccine-associated adverse events. For those ≥ 60 years, the risk of the disease versus serious adverse event will be clarified. For HIV, risk will be further defined based on CD4 counts and anti-retroviral therapy.

In terms of contraindications, in 2004 thymic disease was recognized as a risk factor for viscerotropic disease. Language was subsequently added to package inserts. Thus, language needs to be added to the ACIP recommendations to clarify thymic conditions that will place someone at risk. Immunomodulatory drugs are a relatively new class of drugs that alter immune response. There are many different groups of immunomodulatory drugs, some of which include tumor necrosis factor-alpha (TNF-α) blockers, Interleukin1 (IL1) blockers, and monoclonal antibodies (Mab). Many of the package inserts contraindicate the use of live viral vaccines, so that language will be added to the 2009 yellow fever recommendations.

During the next couple of months, the work group plans to craft specific language for the revised yellow fever vaccine recommendations. It is anticipated that final recommendations will be

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presented for an ACIP vote in October 2009, with the final document expected to be submitted to the MMWR in November 2009.

Discussion

Dr. Temte inquired about the methodology for doing conducting assessments, noting that VAERS had been mentioned a couple of times. In his experience, many patients receiving yellow fever vaccines are typically receiving several other vaccines simultaneously. In addition, increasing numbers of patients in older age groups are travelling internationally. Thus, it seems that it would be extremely difficult to determine adverse events caused by yellow fever vaccine versus other vaccines, and / or the potential synergistic effects of yellow fever vaccine co-administered with other vaccines.

Dr. Staples responded that in the VAERS analysis, the work group examined whether other travel vaccines were co-administered. For the cases specifically classified as the most serious adverse events being considered (e.g., viscerotropic disease and neurotropic disease), many of the cases had diagnostic testing to confirm that yellow fever vaccine was the source of their adverse event. This issue can be further considered.

Dr. Baker added that the statement will include information about how to test to confirm whether there is an association with yellow fever vaccine.

In terms of safety, Dr. Neuzil pointed out that this vaccine is frequently given in other countries as part of campaigns. They may be able to acquire additional safety data from some of these sources. She also inquired as to whether any other vaccines are available or in development.

Dr. Staples responded that as far as she knew, there were no other vaccines available or in development. There are other routes of administration, and there have been some preliminary studies examining inactivation of the current vaccine. Until recently, when viscerotropic disease was discovered to have been a risk of the vaccine, it was considered to be very safe and effective. It is still a fairly safe and effective vaccine, particularly for endemic areas.

Dr. Katz (IDSA) asked what was known about boosters and what the International Health Regulations state says about them.

Dr. Staples responded that the International Health Regulations, as well as the WHO, state that boosters should be given every 10 years. Most of the serious adverse events observed have been reported after primary vaccination, so it is not believed that boosters increase the risk of serious adverse events. There are some data to suggest that immunity lasts longer, but when the WHO conducted a comprehensive review about the booster interval, they still thought that 10 years was a reasonable timeframe for this vaccine.

Ms. Stinchfield (NAPNAP) inquired as to whether it was correct that special certification was required to serve as a yellow fever vaccine clinic, and if so what the rationale was for that requirement.

Dr. Staples responded that a certificate is regulated through CDC's Division of Migration and Global Quarantine (DMGQ). However, much of the regulation also requires state health department involvement. This was linked to the International Health Regulations, which prior to the 2005 recommendations, emphasized yellow fever disease as one of the immediately notifiable diseases considered important. However, the specific regulations for yellow fever

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vaccine and proof of yellow fever vaccine have been sustained in the 2005 regulations. She believed that it was the International Health Regulations and the requirements for proof of vaccination that supported detainment for lack of proof of vaccination.

Public Comments Day 1

No public comments were offered during the first day of the meeting.

June 25, 2009

Unfinished Business

Call to Order

Dr. Dale Morse
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP, CDC

Dr. Dale Morse welcomed the group to the second day of the meeting. He turned the floor over to Dr. Larry Pickering to address unfinished business.

Dr. Pickering offered a few comments about Dr. Morse on the occasion of his final meeting serving as an ACIP member and Chair of ACIP. He reflected on the time and energy that Dr. Morse had spent on ACIP and with CDC, and enumerated Dr. Morse's many accomplishments as Chair of ACIP. Dr. Pickering expressed appreciation to Dr. Morse for his many contributions to the committee, which include the following ACIP recommendations made during his chairmanship:

CDC. Prevention of Rotavirus Gastroenteritis Among Infants and Children; recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2009;58 (No. RR-2)
Recommended Adult Immunization Schedule—United States, 2009. MMWR 2009;57
Recommended Immunization Schedules for Persons Aged 0 Through 18 years --- United States, 2009. MMWR 2009;57
CDC. Prevention and Control of Influenza; recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2008;57 (No. RR-7)
CDC. Prevention of Herpes Zoster; recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2008;57 (No. RR-5)
CDC. Prevention of Pertussis, Tetanus, and Diphtheria Among Pregnant and Postpartum Women and Their Infants; recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2008;57 (No. RR-4)
CDC. Human Rabies Prevention - United States, 2008; recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2008;57 (No. RR-3)

Dr. Morse thanked Dr. Pickering and those present, offering a wrap-up of his time with ACIP. He noted the rapid growth that ACIP saw during Jon Abramson's leadership from 2005 to 2007,

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including: 1) voting to recommend rotavirus vaccine for children and the HPV vaccine for young females; 2) recommending a second dose of the varicella vaccine; 3) zoster vaccine for adults; 4) conjugated meningococcal vaccine for adolescents and college students; 5) Tdap vaccine for adolescents and adults; 6) expanded adult recommendations for hepatitis B vaccine and expanded recommendations for hepatitis A vaccine for all children over 12 months; and 7) expansion of use of influenza vaccine to include children age 24 through 59 months.

Dr. Morse then turned to 2007 to 2009, when ACIP entered a maintenance phase. This phase did not bring less work for the committee, however. Vaccine guidelines were updated for children, adolescents, and adults; anthrax; meningococcal; HAV for prophylaxis; HAV for foreign adoptee contacts; pneumococcal; combination vaccines; and second dose of rotavirus. Further, ACIP has prepared for October 2009 votes on PCV 13, bivalent HPV for females, quadrivalent HPV for males, and novel H1N1 influenza. He noted that 12 votes were pending for this June meeting: rabies, polio, JE, MMR, influenza antivirals, meningococcal, MMRV safety, and combination vaccines.

Dr. Morse noted the important progress toward universal flu immunization, with expansion of recommendations for children through 18 years of age. While flu recommendations for adults have not yet been completed, he anticipated that these recommendations could be achieved in the near future. He pointed out that a change in leadership is a good time to assess where the committee has been, where it is currently, and where it is going. It is also a good time for the committee members to share in their combined accomplishments and to recognize the individual contributions of their colleagues. In particular, he recognized the efforts of Jean Smith, Antonette Hill, Larry Pickering, and all ACIP staff. Further, Dr. Morse acknowledged the importance of science in ACIP's work. He cited David Axelrod, former New York Commissioner of Health who said, "We must remain devoted to the canons of science that are so much part of the practice of medicine and the practice of the allied arts. To do otherwise would be to build public policy on quicksand." Knowledge without application is useless. ACIP must also remember the faces behind the numbers and the people who are served by their work, as Dr. Jules Richmond, Former Surgeon General, said: "statistics are people with their tears wiped dry. As Xenophon in *Cryopaedia*, 400 BC said, "As there are persons who mend torn garments, so there are physicians who heal the sick; but your duty is far nobler and one befitting a just person – namely to keep people in health." Collectively, they have been able to accomplish more than they could individually. The cause of keeping people healthy is noble, and Dr. Morse thanked ACIP for allowing him to be part of the process.

General Recommendations on Immunization

Dr. Andrew Kroger
CDC.CCID/NCIRD/ISD

Dr. Morse asked Dr. Andrew Kroger to present revised language for the General Recommendations on Immunization for the committee to consider. Dr. Kroger reminded the group of Option Two from the previous day's discussion, which stated:

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> "The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines if licensed and indicated for the patient's age, but depends on the vaccination status of the patient, provider preference, patient preference, the potential for adverse events, and vaccine availability."

Discussion regarding this option led to a consensus that it was the best of those offered, but the language needed streamlining. The term "licensed" is redundant, and concern was expressed about describing vaccines as recommended for a specific age. There was an affirmative vote by ACIP for this option. The General Recommendations Working Group of ACIP met and discussed how best to incorporate feedback from the general group into the recommendation. Their deliberations resulted in the following clarification:

> "The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment*, patient preference, and the potential for adverse events," with a footnote to state: "*Provider assessment should include storage costs, number of injections, vaccine availability, vaccination status, likelihood of improved coverage, and likelihood of patient return visits."

Discussion:

Dr. Englund felt that storage cost was not the most important thing for practitioners to consider, so she suggested that the order of the items in the superscript list be revised. She commended the working group on this clarification.

Dr. Neuzil said that the potential for adverse events is part of the provider assessment, and she wondered about the rationale for putting that element in the first part of the statement rather than in the second part.

Dr. Kroger replied that from a public health point of view, the potential for adverse events is important to add because vaccine safety stakeholders play an important role along with providers and patients and this issue will be revisited in future decisions about combination vaccines.

Dr. Temte added that in current practice situations, the largest barrier to immunization is concern over adverse events. Placing it in the first statement highlights its significance and the degree to which ACIP considers it to be an important issue.

Dr. Sumaya said that the working group debated whether to include the issue in the body of the recommendation or in its annotation. Because the issue will be critical in monitoring, they concluded that it should be in the body of the recommendation.

Dr. Baker asked for clarification about where the annotated text would be placed. Dr. Kroger answered that in recent history of *MMWR* publications, this information has gone at the bottom of the page.

Dr. Stinchfield noted that storage and cost are two different issues, so they should be separated by a comma. She agreed with rearranging the order of the items.

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Dr. Ehresmann commented that some of the issues fall under "patient preference," and she wondered whether providers consider patient preference in their assessment. The phrasing could state, "considerations should include provider assessment and the potential for adverse events" and note patient preference as part of the assessment.

Dr. Judson agreed that patient preference is a subset of the provider assessment.

Dr. Englund disagreed, stating that physician offices do not carry every vaccine combination, so the language should remain as written.

Dr. Cieslak said that the general recommendation stated too much. He suggested "the use of combination vaccines generally is preferred," leaving physicians to consider what they usually consider.

Motion: General Recommendations on Immunization

Dr. Chilton made a motion to approve the recommendation of the work group to accept the newly-written clarification for Option Two as written, with the exception of moving "storage" and "cost" to the end of the statement and to separate them with a comma. Dr. Judson seconded the motion. The motion carried with 14 affirmative votes, 0 abstentions, and 1 negative vote.

Agency Updates

Centers for Disease Control and Prevention

Dr. Anne Schuchat presented updates on CDC's work in international use of vaccine. The WHO recently recommended global use of rotavirus vaccine. CDC is part of a consortium working to provide scientific and technical support to introducing both rotavirus and pneumococcal conjugate vaccines around the world. CDC is also completing the Hib Initiative, a four-year Global Alliance for Vaccines and Immunization (GAVI)-supported initiative, with the mandate to promote evidence-informed decisions in resource-poor countries about the use of Hib vaccine. More than 90% of the birth cohort in developing countries is now living in countries that have decided to use this vaccine. This initiative has the potential to reduce global deaths substantially. The last part of CDC's major global effort regarding vaccines is the Measles Initiative. Last January, CDC announced a 74% reduction in worldwide measles deaths since 2000. The work that ACIP does on these vaccines has a direct link to these global efforts.

Center for Medicare and Medicaid Services (CMS)

Dr. Linda Murphy reported that in February 2009, the Children's Health Insurance Program Reauthorization Act (CHIPRA) and the American Reauthorization and Recovery Act (ARRA) were approved. As a result, many programs and changes are anticipated. Grants under CHIPRA will be announced in July 2009, and the funds will be awarded by September 30, 2009. These grants are aimed at schools and a range of local and religious groups, which are not typical outreach groups. The groups include coalitions and other agencies that will reach rural and tribal children that state and federal entities may not be able to reach. Six million children are uninsured, and grants are available to reach out to them to enroll them in CHIP or Medicaid.

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Once the children are reached, the states must be able to take the new enrollments. When the grants are posted on www.grants.gov, applicants will have 30 days to submit grant proposals. CMS is focusing on outreach and enrollment, quality, and information technology as they work to improve healthcare to Medicaid- and CHIP-eligible children.

CMS is always seeking to improve in the area of pandemic planning. They are considering ways to be flexible with Medicaid, given the H1N1 situation. As it stands, Medicaid works well in an epidemic situation. CMS will work with each individual state when new plans are written.

The Vaccines for Children (VFC) rates were put on hold in the absence of a Secretary of Health and Human Services (HHS) or a Director of Medicaid. Now that Cindy Mann has been named the Director of Medicaid and Kathleen Sibelius as Secretary of HHS, they are able to rewrite and update the *Federal Register* notice for VFC, with more developments on the horizon.

Department of Defense (DoD)

Dr. Wayne Hatchey explained that DoD is focusing on influenza. A mandatory influenza immunization requirement is in place for active duty service members. They began mandatory immunization for healthcare workers providing direct patient care last year. This year, services must report compliance with the program. DoD is preparing for two simultaneous (or overlapping) influenza immunization programs with seasonal influenza and novel H1N1. They are collaborating with CDC and FDA to track vaccine effectiveness through the Armed Forces Health Surveillance Center (AFHSC), as well as vaccine safety through the Military Vaccine Agency (MVA). DoD is developing an immunization strategy that is based on variable disease virulence. The strategy will be adjusted by target groups, based on the epidemiology of novel H1N1.

Department of Veterans Affairs (DVA)

Dr. Linda Kinsinger reported that on April 25, 2009, the DVA activated an operations center to coordinate communications to and from the field. They instituted case reporting for the VA based on CDC policies. Reporting occurred daily at first, and then occurred weekly as of mid-May. Based on evolving CDC recommendations, and with input from VA subject matter experts, DVA issued seven clinical advisories to the field. They held a series of five VA-wide teleconferences over a three-week period to allow the field to ask questions, and they have participated in a number of inter-agency working groups and policy committees.

Food and Drug Administration (FDA)

Dr. Norman Baylor noted that most of FDA's activity updates involved H1N1 work; therefore, he presented an update later in the meeting agenda.

Heath Resources and Services Administration (HRSA)

Dr. Geoffrey Evans updated the group on the autism hearing. Decisions were made regarding the Theory One combination of MMR vaccine and thimerosal. Theory Three was also decided upon, as there was no new evidence for the MMR vaccine-only theory. Decisions for three cases are in, and are under appeal. The first-level appeal decisions should be in later in the year. Theory Two, the thimerosal-only decision, is awaiting the end of briefing. He expressed hoped that the briefing would end in the next few months, with decisions later in the year. The Institute of Medicine (IOM) contract project to review vaccines and adverse events, which

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started in September 2008, held an organizational meeting in April and a Biologic Mechanisms Workshop in Washington the previous day. The committee is adding varicella vaccine, influenza vaccines, HPV, and hepatitis B. If additional funding is obtained, then four additional vaccines will be added.

Indian Health Services (IHS)

Ms. Amy Groom reported that IHS instituted influenza-like illness surveillance using its electronic health records system. The system receives daily feeds from approximately 300 facilities, and compile the data weekly for their sites and administrative areas. The trends of influenza-like illness in Indian Country mirror national trends. They are, however, investigating a cluster of severe H1N1 disease resulting in hospitalizations in a group of Indians in Arizona. IHS will determine whether this is an unusually high hospitalization rate or a result of widespread transmission in the area.

National Institutes of Health (NIH)

Dr. George Curlin stated that influenza research advances in seasonal influenza as well as in novel H1N1. He assured them that seasonal influenza has not been forgotten, despite concerns regarding H1N1. Enrollment has begun in a study of influenza vaccines for pregnant women, and basic research also continues.

National Vaccine Advisory Committee (NVAC)

Dr. Gus Birkhead presented an update on NVAC's recent accomplishments: 1) input into draft National Vaccine Plan; 2) RAND study of the effectiveness of NVAC; 3) completion; 4) Adult Vaccination Report release in June 2009; 5) Vaccine Safety Working Group Report on the CDC ISO Scientific Agenda in June 2009; and 6) NVAC's role in the H1N1 vaccination program.

The National Vaccine Plan is being updated for the first time since 1994. The IOM and NVAC have both been involved. Over 450 public comments have been received, and five public sessions have been conducted by IOM. NVAC has provided comments directly to IOM. NVAC held three public engagement sessions in St. Louise, Missouri; Syracuse, New York; and Columbus, Ohio. A public stakeholders' meeting was held in Washington, DC. These sessions examined population values pertaining to vaccinations. The final report is due in November. Additional information is available at: http://www.hhs.gov/nvpo/vacc_plan/.

Dr. Birkhead described the RAND Corporation's study of the effectiveness of NVAC. A draft report of the study was presented during ACIP's last meeting. The report consisted of a literature review, reviewing past recommendations to NVAC, and interviews with key stakeholders. The report concluded that NVAC has a broad mission and there may be confusion in the minds of the general public and of healthcare professionals regarding the mission of each of the HHS advisory committees relating to vaccines. There are at least four other agencies in addition to NVAC. Further, the report states that NVPO is under-resourced to fully support its broad mission. The study highlighted gaps in representation on the group, including public members, economists, communication experts, and others. The report's recommendations focus on these areas and on engaging in more active follow-up and seeking feedback from the Assistant Secretary of Health (ASH).

The Adult Vaccine Working Group completed the first part of its charge to review federal agency activities relating to adult immunizations. The working group created the following

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recommendations: 1) Better assess immunization coverage; 2) Conduct health services research; 3) Emphasize adult immunization with grantees; 4) Update immunization guidance; 5) Health care worker immunization; 6) Secure funding support, in particular including all ACIP vaccines in Medicare Part B; 7) Develop incentives; 8) Conduct outreach and promotional campaigns; and 9) Improve safety monitoring.

Regarding the fourth recommendation, it was noted that many federal programs do not operate on the current ACIP guidelines, so the group recommended that all federal agencies dealing with adult immunization examine their internal program guidance. The report will go to the ASH and will be posted soon. The working group is moving to its second charge, which is to broadly consider vaccine financing in the public and private sectors.

In June 2009, NVAC's Immunization Safety Working Group issued a report on its review of the CDC Immunization Safety Office Scientific Agenda. The report contains advice on the content of the research agenda, adding draft topics and providing a framework for prioritizing research topics. The report also details possible barriers to implementing the research agenda and suggestions for addressing them. It was adopted during the June 2009 meeting, and a draft is available on the NVAC website. The process of reviewing the agenda was extensive, and included community meetings and keystone and stakeholder meetings.

The Vaccine Safety Working Group's second charge is to review the current federal vaccine safety system. Over the next year, they will review the current federal vaccine safety system. Further, the working group will develop a White Paper describing the infrastructure needs for a federal vaccine safety system, which are to: 1) fully characterize the safety profile of vaccines in a timely manner; 2) reduce adverse events whenever possible; and 3) maintain and improve public confidence in vaccine safety. The membership of the working group has expanded. Its three chairs are Andy Pavia, Marie McCormick, and Tawny Buck. Three new members have been added to the group: Vicky Debold, PhD, RN, Health Administration and Policy Department at George Mason University, VRBPAC Public Representative; Robert Beck, JD; ACIP Member Public Representative; and Bill Raub, PhD, Former Deputy Director of the National Institutes of Health and Science Advisor to the Secretary, Department of Health and Human Services.

Current plans for NVAC include a kick-off working group meeting on July 15 – 16, 2009, in Washington, DC. The meeting will include presentations and discussion on five panels: 1) Principles and policy alternatives for a robust vaccine safety system; 2) Identifying innovative ways of overcoming gaps in vaccine safety science infrastructure; 3) The ideal system to meet the needs of the public, public health, and healthcare professionals for confidence in vaccine safety; 4) Lessons from other safety arenas; and 5) Enhancing the adoption and implementation of the NVAC white paper.

Dr. Birkhead also described NVAC's role in the response to novel H1N1 influenza. The June 2, 2009 NVAC meeting included informational presentations from a number of advisory committees and partner organizations. He emphasized that NVAC's role in the response includes maintaining partner input. NVAC will focus on the implantation of a vaccination program; ensuring stakeholder input; maintaining coordination among vaccine advisory committees; and contributing to vaccine safety and post-marketing. They plan to hold two public teleconferences and to submit recommendations to the ASH. A subgroup of the Safety Working Group will work with CDC and ISO concerning surveillance and vaccine safety issues.

NVAC made a series of recommendations to the new ASH regarding response to novel H1N1. The recommendations include accelerating the urgency of the response. While response has

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begun, state and local planning must begin before it is too late. Further, resources are needed at the state and local levels, where health departments have lost 10,000 staff in the past year and expect similar losses this year. State and local health departments will bear the brunt of H1N1 response, and pandemic response will be occurring simultaneously with response to seasonal influenza. Further, pandemic influenza funding for state and local entities was terminated in 2008, and other preparedness funding has declined. NVAC's recommendations noted that while the $350 million in supplemental funding was helpful, at a cost per dose of $15, the vaccination program will cost $9 billion dollars. Finally, vaccine safety monitoring is a critical piece of the response effort.

National Vaccine Program Office (NVPO)

Dr. Bruce Gellin noted that Dr. Howard Koh had been confirmed as the ASH. Before he came to HHS, he was the Harvey Feinberg Professor of the Practice of Public Health.

Haemophilus Influenzae b (Hib) Vaccine

Introduction: Overview of Session

Abigail Shefer, MD
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Shefer reported that a nationwide shortage of Hib vaccine began in December 2007 when several lots of the vaccine produced by Merck were recalled voluntarily and production was temporarily suspended. To address the limited supply of Hib vaccine, CDC recommended that the Hib booster dose at 12 to 15 months be temporarily deferred for healthy children. Since then, there has been enhanced surveillance for Hib disease to identify any increase in incidence of cases. Using sentinel site registry data in select states, there has been some indication that the third dose of the primary series may have declined due to programmatic issues as well as a mismatch between local supply and demand, she said. Some information on both of these issues has been presented at past ACIP meetings. The shortage has been on-going for approximately 1.5 years.

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Glaxo-Smith Kline (GSK) Monovalent Hib Vaccine

Remon Abu-Elyazeed MD, MPH, PhD
Head, Pediatric Vaccines
Clinical and Medical Affairs, North America
GlaxoSmithKline

Dr. Abu-Elazeed thanked ACIP for the opportunity to present clinical data highlights of GSK's Hib conjugant vaccine. GSK has been working closely with CDC and FDA to make HIBERIX®, its Hib vaccine, available in the US as quickly as possible to help alleviate the Hib vaccine shortage that has become a public health concern.

HIBERIX® is reconstituted at the time of use before intramuscular administration. Each 0.5mL single dose contains 10 micrograms of purified capsular polysaccharide conjugated to approximately 25 micrograms of inactivated tetanus toxoid. It contains no thimerosal and is latex-free. HIBERIX® was first licensed in Germany in 1996 and is currently licensed in 98 countries. From its launch until November 2008, approximately 55 million doses of HIBERIX® have been distributed worldwide. A Biologic License Application (BLA) was submitted to the FDA on March 17, 2009, and it is being reviewed under accelerated approval. License of HIBERIX® in the US will provide an additional source of vaccine to the US market for booster dose. The proposed indication under review by the FDA is active immunization as a booster dose for the prevention of invasive disease caused by Hib in children ages 15 months through 4 years of age, and prior to their first birthday.

The clinical package to support approval of HIBERIX® contains data from nine studies. Seven studies provide core data when HIBERIX® was administered as a booster dose. These include 1008 subjects. Two additional studies focus on administration of HIBERIX® as a primary vaccination series. These studies provide supportive safety data and include 1396 subjects. The studies were chosen in consultation with FDA as the most relevant to evaluation of HIBERIX® use in the US.

In all of the trials, HIBERIX® was administered to children between 11 and 25 months. All seven studies support the safety of HIBERIX®. Six studies support immunogenicity, and three of them study administration of HIBERIX® as a booster in children who received primary vaccinations with HIBERIX® according to a 2-4-6 month schedule, or according to a 3-4-5 month schedule. Four studies provided data on the interchangeability when a booster dose of HIBERIX® was administered to children previously vaccinated with another vaccine. These four studies provided safety and immunogenicity data of HIBERIX® following priming with other Hib vaccines that are licensed in the US.

Polyribosyl ribitol phosphate (PRP) immune responses after a booster dose of HIBERIX® following priming in infancy with HIBERIX® were studied in children aged 14 to 23 months. They received HIBERIX® co-administered with a combination DTaP-HBV or DTaP-IPV vaccine. In a series of studies after booster vaccination with

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HIBERIX®, 100% of the subjects achieved seroprotection at both 0.15 microgram per mL and at 1 microgram per mL cutoffs. In all three studies, HIBERIX® elicited a marked increase in GMCs from pre- to post-vaccination. In three additional studies, children were primed in infancy with either HIBERIX®, ActHIB®, HibTITER®, or PedvaxHIB®. After a booster vaccination with HIBERIX®, 100% of the subjects achieved protection at the 0.15 microgram per mL cutoff. Further, between 96.4% and 100% of subjects achieved anti-PRP antibodies concentration greater than or equal to 1 microgram per mL. In all three studies, HIBERIX® elicited a marked increase in GMCs from pre- to post-booster vaccination.

Regarding the immunogenicity of co-administered vaccines, in one study a booster dose of HIBERIX® was co-administered with DTaP and OPV. In the second study, a booster dose of HIBERIX® was co-administered with DTaP-HBV-IPV. The studies are not meant to be comparative, but both measure immunogenicity with co-administered vaccines. All subjects in both studies achieved seroprotective antibody levels against diphtheria, tetanus, and polio. At least 95% of the subjects demonstrated pertussis vaccine response. The group who received the Hepatitis B vaccine achieved seroprotective antibody levels against Hepatitis B, demonstrating that HIBERIX® does not interfere with immune response to concomitantly administered vaccines.
In terms of safety, solicited local and general adverse events were reported in all seven studies within four days after the booster dose was administered. Two representative studies include Study DTaP-HepB-IPV 010 and Study DTaP-IPV 026. In one study, children 12 to 25 months of age received HIBERIX® and a combined DTaP-HepB-IPV vaccine. This study included 371 subjects. The second study included 65 children aged 15 to 19 months of age who received HIBERIX® and DTaP. In both studies, HIBERIX® was administered concomitantly at a separate site. Relatively few local and general adverse events were reported, and there were very few cases of Grade 3 symptoms.

Three serious adverse events were reported in 1008 subjects in the seven booster studies. All subjects recovered with no sequelae. No deaths were reported in any of the seven clinical studies. It was concluded that the safety of HIBERIX® was clinically acceptable. From the launch of HIBERIX® in 1996 until 2008, approximately 55 million doses have been distributed worldwide. Evaluation of post-marketing adverse events reports since the product launch have not revealed safety concerns, and HIBERIX® has not been withdrawn in any country due to safety concerns or regulatory issues.

Regarding immunogenicity, a booster dose of HIBERIX® provides strong immune response in children previously primed with Hib vaccine, regardless of the priming vaccine or the priming schedule. HIBERIX® is immunogenic when administered following primary vaccination with another US-licensed Hib conjugate vaccine. Further, HIBERIX® is immunogenic when co-administered with other commonly-used pediatric vaccines.

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Dr. Abu-Elazeed reiterated that the BLA was submitted on March 17, 2009 and is awaiting accelerated approval. As a post-license commitment, GSK plans to conduct a confirmatory trial for the booster dose in US infants, with HIBERIX® given at months 2-4-6 and 15 to 18 months as scheduled. This trial will include co-administration with commonly-used pediatric vaccines.

Discussion

Dr. Ehresmann asked about the timeframe for an accelerated FDA review. Dr. Abu-Elazeed replied that the maximum time is six months from the submission date.

Dr. Baylor added that there is no specific time for accelerated review. Priority review timeframes are six months, where the criteria for accelerated approval allow for vaccine approval on a surrogate, which in this case is immunogenicity. A confirmatory study is required post-licensure. FDA's goal is to complete this process as soon as possible.

Hib Surveillance

Michael L. Jackson, PhD, MPH
Meningitis and Vaccine Preventable Diseases Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Jackson reported on Hib surveillance during the Hib vaccine shortage. In October 2008, when Merck announced that they would not be able to return to market until mid-2009, CDC began enhanced surveillance for Hib. They worked to raise awareness among clinicians and laboratorians of the on-going vaccine shortage, the need for testing of suspected *H. influenzae* cases, and for reporting to local health departments. CDC disseminated messages through a number of venues, including an *MMWR* report; notices through organizations such as PIDS and NACCHO and the Epi-X system; and presentations at national meetings.

Since November 2008, CDC has actively followed up with state health departments on all reported cases of invasive *H. influenzae* in children less than five years of age. This follow-up is to make sure that CDC has the best available information on serotype, vaccination history, and disease outcome. For this evaluation, the focus is on invasive Hib, defined as isolation of Hib from a normally sterile site such as blood or cerebrospinal fluid.

Using enhanced surveillance data, CDC began testing for an increase in Hib incidence. The pre-shortage baseline was defined as the years 2000-2007, as these were years during which the incidence of Hib in the US was relatively stable. Fairly good surveillance data are available for that timeframe. Using the 2000-2007 data, the expected number of annual cases of Hib during the baseline period were calculated, with 95% confidence intervals. Starting from January 2009, each month the number of Hib cases reported in children less than five years for the past twelve months is compared with the upper confidence limit of the expected cases from baseline. This analysis tests whether the cases have exceeded the expected counts. These analyses were conducted for the US as a whole and for each state or jurisdiction individually.

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For the US as a whole, the expected cases of Hib for each calendar month, with confidence limits, were also calculated. They then compare the monthly number of reported Hib cases with the upper confidence limit of the expected monthly cases. This calculation is repeated for Hib plus untyped *H. influenzae*. The analysis of Hib plus untyped *H. influenzae* is needed to account for possible differences in the proportion of cases that were serotyped during the shortage compared to the baseline period.

Another question of interest is whether the population at risk for Hib has changed as a result of the Hib vaccine shortage. In particular, it is important to learn whether there have been shifts in the age distribution or the vaccination history of Hib cases among children less than five years of age. To address this, CDC compared Hib cases occurring since November 2008, when the active follow-up started, with Hib cases reported through the ABC system from 1995 through 2007, prior to the vaccine shortage.

For the twelve month period of May 2008 through April 2009, a total of 43 cases of invasive Hib in children less than five years were reported to CDC. For comparison, the annual average during the baseline period was 31.4 cases per year. Although somewhat higher than average, this difference was not statistically significant.

Hib cases reported in each state or jurisdiction from May 2008 through April 2009 in children less than five were compared with the state-specific annual averages. Overall, 32 states or jurisdictions reported as many or fewer cases than average during baseline. Twenty states or jurisdictions reported more cases than average during baseline. Despite media reports of clusters of Hib in a few places, none of the increases were statistically significant. Hib case counts for the US as a whole exceeded the historical limits during February of 2009, but not in the subsequent months. Dr. Jackson reminded the group that the period from November 2008 through April 2009 represented a timeframe during which CDC worked to enhance Hib surveillance, so some of this increase may be a surveillance artifact. The combined counts of Hib and untyped *H. influenzae* have remained within the historical limits during the shortage.

Age and vaccination histories for Hib cases during the vaccine shortage were compared with cases from the pre-shortage era for whom age and vaccination history are available. During the shortage, cases tended to be younger and were more commonly un- or under-vaccinated than pre-shortage cases. However, the differences were not statistically significant.

Dr. Jackson concluded that CDC has not observed a sustained, statistically significant increase in Hib cases in children less than five years of age either for the US as a whole or for any individual state, despite enhanced surveillance efforts. In addition, there has been no apparent change in the population at risk for invasive Hib. Hib cases in children less than 5 years of age during the shortage are not significantly different from cases prior to the shortage in terms of age distribution or vaccination history. There has not been a substantial impact on invasive Hib in children less than five years of age in the US during the Hib vaccine shortage. CDC will continue to monitor Hib incidence as the booster dose is reinstated and as new Hib vaccines are introduced.

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Discussion

Dr. Schuchat found the data to be reassuring. When the shortage began, they discussed a "cushion of protection," given the herd effect of the vaccine. She expressed her hope that people would not interpret these data to mean that the shortage has not been a concern or that additional cases are not possible. They have learned from other countries with similar difficulties that problems can emerge over time. They are probably in the "cushion of protection" and a long delay for booster doses would present a problem.

Dr. Pickering asked for clarification on the untyped cases and how typing rates might be improved, as well as what the demographic differences were between untyped cases and Hib cases.

Dr. Jackson replied that the enhanced surveillance efforts have included contacting the states to verify serotype information. They have better serotype information available now than they did prior to the shortage. An average of 40% of cases were untyped before the shortage, and now about 12% of cases are untyped. He did not have information regarding distribution of age among untyped influenza cases since the start of the shortage, though he noted that these were a small proportion of the Hib cases.

Dr. Ehresmann confirmed that these cases are untyped, not untypable. Dr. Jackson agreed.

Vaccine Supply

Jeanne Santoli, MD
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Santoli presented information regarding the anticipated 2009 supply to support reinstatement of the Hib booster dose.

Sanofi pasteur will supply at least 18 million doses of Hib-containing vaccine, including both monovalent and combination product, to the US market during 2009. The increased supply will be available beginning in July 2009. This volume will support return to the fourth dose and to begin catch-up efforts.

GSK has applied for licensure of their monovalent Hib vaccine, HIBERIX®. They have the capacity to produce more than 4 million doses for the US during 2009. The regulatory review response is anticipated no later than mid-September, and the indication sought is for the booster dose.

Merck is working with FDA toward the following goals: 1) a limited supply of PedvaxHIB® to be available in the fourth quarter of 2009; and 2) full availability of PedvaxHIB® is expected in the first quarter of 2010. The return of COMVAX®, the combination with hepatitis B and PedvaxHIB® will be dependent upon the supply situation for both the Hib and hepatitis B vaccine components.

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Hib Vaccine Implementation Plan

Abigail Shefer, MD
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Shefer presented plans for the implementation of the Hib booster dose. The currently available Hib-containing vaccines include monovalent Hib (ActHib®) and DTaP-IPV/Hib (Pentacel®). Both are manufactured by sanofi pasteur. An increased number of doses of both vaccines will be available starting July 1, 2009. The increased number of doses will be sufficient to reinstate the booster dose of Hib vaccine to be administered on time at 12 to 15 months for all children who completed the primary three-dose series. However, there will only be enough supply for limited catch-up at this time.

Limited catch-up means that older children whose booster dose was deferred should receive a dose of Hib vaccine at their next routinely scheduled visit or medical encounter. Supply constraints do not permit mass recall of all children whose booster dose was deferred. This means that CDC does not recommend that practices institute an active notification process to contact all children with deferred booster doses at this time. Rather, CDC recommends that practices target children presenting for their next scheduled appointment or who have a medical encounter for any reason.

The current availability of Hib vaccine means that providers will be able to order some additional doses of Hib vaccine each month based on previous purchasing patterns or on practice birth cohort and estimates of additional needs. This applies to both private and public vaccine supplies. Practices need to develop a tailored plan that best suits their office environment, taking into account such elements as staffing, responsibilities, and clinic setup. The plan will likely include a review of electronic or paper records or registries or IIS prior to a physician encounter; screening children during scheduled visits; and discussing and sharing immunization schedules with parents.

Most of the challenges at the practice level are related to the use of combination products and the goal of minimizing extra immunization. This might lead to a mismatch between patient vaccination needs and the available stock of different vaccine formulations available in a local provider's office. For example, practices using Pentacel® for Hib vaccination need to ensure that adequate supplies of monovalent Hepatitis B vaccine are available to complete the Hepatitis B vaccine series. Further, children who have already received four doses of DTaP should be prioritized to receive monovalent Hib vaccine.

In collaboration with several partners, CDC has prepared a number of educational materials about reinstating the booster dose and limited catch-up. The June 26, 2009 *MMWR* will include an article on the topic. Q & As for providers and patients are in the clearance process and may be ready for posting in early July 2009. Additionally, a one-page provider letter will be placed in all McKesson vaccine shipments and will alert providers to the reinstatement of the booster dose and limited catch-up. Another resource is an algorithm table on "Protecting Infants against Hepatitis B Virus Infection When Using Pentacel® Vaccine during the Hib Vaccine Shortage." It outlines the issues and thinking that a practice needs to undergo when considering Hepatitis B

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and Hib-containing vaccines. It is posted on the CDC website: http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm.

Plans for monitoring the situation are under discussion. They will continue to monitor Hib vaccine use through the registry sentinel sites. These registries are located in eight states throughout the country that have higher-quality data and are able to provide more timely data. This information will give CDC an idea of provider compliance with the recommendation. They are also considering conducting a provider survey to assess knowledge and practices related to administration of the booster and catch-up. The survey can be targeted through the registry sentinel sites, which will allow validation of actual vaccine delivery. A national survey of pediatricians and family physicians is also possible. The monitoring plans will depend on several factors, including vaccine supply and any new Hib-containing vaccines that come to market and affect that supply.

Discussion

Dr. Morse complimented all of the individuals who worked to manage the shortage. A tremendous amount of work took place, from surveillance to allocation and education. Professional agencies and manufacturers worked to help increase supply.

Dr. Ehresmann clarified that the booster will be reinstated as of July 1, 2009. Dr. Shefer confirmed that the recommendation will be to reinstate the booster dose on time for children 12 – 15 months old, with limited catch-up for children during a regular visit or other encounter.

Dr. Ehresmann shared comments from a listserv of state grantees, who expressed concern regarding vaccine supply and concerns pertaining to the reinstatement of the booster dose. She was encouraged to hear about the GSK product.

Dr. Leonard Friedland (GSK) said that all manufacturers need to adequately plan for vaccine supply. He asked about sanofi pasteur's distribution plans for July between monovalent Hib and combination Hib vaccines as they reintroduce additional supply. This information will help them at GSK understand their supply constraints.

Dr. Phil Hosbach (sanofi pasteur) replied that while he could not share that information in this forum, they have shared detailed information with CDC so they have a month-by-month supply for Pentacel® and Hib. They are pleased to have kept supply in place for at least three doses for the last year and one half. They have been able to adjust their supplies to provide a fourth dose.

Dr. Shefer said that AAP and AFP will communicate with their members about the reinstatement of the booster dose in various ways.

An inquiry was posed regarding why HIBERIX® is indicated for 15 months and why it could not be given at 12 months.

Dr. Schuchat replied that GSK would need to submit infant information.

Dr. Abu-Elazeed said that the clinical package submitted for approval of HIBERIX® as a booster dose includes children less than 15 months, but the numbers are not sufficient to expand the indication for less than 15 months.

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Dr. Pickering requested further information about plans to expand HIBERIX® in the future.

Dr. Abu-Elazeed answered that GSK has committed to a post-approval study. The primary series will be administered at two, four, and six months with a booster at 15 to 18 months.

Nancy Messonnier (NCIRD) said that the indication for Hib, the ACIP recommendations, and the Red Book start at 12 months for the booster dose. However, sanofi pasteur's vaccine is not licensed for 12 to 15 months. The only vaccine with this licensure is produced by Merck. Because sanofi's vaccine is not licensed for 12 to 15 months, GSK's vaccine, which is based on a comparison with sanofi's, will have the same indication as Sanofi's—only 15 months. Physicians are likely to administer it anyway.

Dr. Friedland (GSK) added that GSK is in late development with a combination HiB-meningococcal-CY vaccine for infants. The fourth dose in that schedule will be at 12 months. They look forward to presenting data on that vaccine during the October 2009 ACIP meeting.

Claire Hannon (Association of Immunization Managers) echoed concerns that grantees have about the supply of Hib. She has heard from programs that are waiting for supplies to maintain the 3-dose series. The supply for July has only recently been sent, and it is difficult for grantees to know where they will be in the middle of July. They are happy to get additional vaccine in July and glad to have details about monovalent and combination products, but not knowing how much will be in the future is difficult. Some providers use a combination of a different type, so they need monovalent and need information about the future.

Dr. Santoli said that they have given grantees quarterly information about their allocation, recognizing the need for them to plan ahead. They were not able to give that information the first time because of a need to understand reactions to the first allocations. They adopted a different approach to be more equitable across states. She agreed that grantees need as much information as possible in advance.

Tom McCubbins (Merck) announced that Merck has restarted its Hib process. The data are very promising, and they should have supply available in the fourth quarter of 2009. They anticipate a return to full supply in 2010.

Dr. Mark Netoskie (AHIP) said that AHIP supports these recommendations. A survey of their member organizations indicated that they would not require changes to their current vaccine policies.

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Vaccine Supply

Dr. Jeanne Santoli
CDC/CCID/NCIRD/ISD

Dr. Santoli offered updates on the supply of vaccine for pediatric and adult hepatitis B, hepatitis A, and MMR-V.

In February 2009, CDC analyzed available pediatric supply data from both United States manufacturers of pediatric hepatitis B to assess sufficiency over the remainder of 2009. This assessment would help them understand the situation and how to proceed. In conjunction with the Vaccine Supply Stakeholder Group, which includes representatives from AAP, AAFP, ASTHO, NACCHO, AIM, FDA, and ACIP, CDC determined that there was no need to adjust routine pediatric vaccine recommendations. Following that analysis, in March 2009, CDC and its partners communicated broadly to encourage providers to continue routine ordering practices and to avoid placing larger-than-normal orders or stockpiling. Some delays had occurred in January and February, which could have caused ordering behavior to change and therefore create a situation that they hoped to avoid. Both manufacturers and CDC's 64 immunization grantees are currently managing provider orders to support judicious vaccine ordering. This endeavor takes a great deal of work, but the process is critical to moving forward without issuing interim recommendations for this vaccine.

The analysis showed that the summer months of June, July, and August were anticipated to have the tightest vaccine supply. At this point, both manufacturers are supplying vaccine to the United States market. GSK will supply additional product to the United States beginning in September 2009 to assure sufficient supply. Merck expects supplies to be limited during the remainder of 2009, although supplies are still forthcoming, and they do not expect to return to full supply until 2010.

She then addressed adult hepatitis B vaccine. Merck is not currently distributing its adult or dialysis hepatitis B vaccines. These products will not be available for the remainder of 2009, but will return to full supply in 2010. Fortunately, the supply of GSK's adult hepatitis B vaccine and adult hepatitis A/hepatitis B combination vaccine is sufficient to meet national demand at this time. The supply will meet increased demand that comes from CDC's High Risk Adult Hepatitis B Initiative.

Regarding adult hepatitis A vaccines, Merck is not currently distributing this product currently and does not anticipate doing so during 2009. Merck will provide additional information regarding the availability of adult hepatitis A vaccines when it becomes available. GSK's production and supply of adult hepatitis A vaccines and adult hepatitis A/hepatitis B combination vaccine are currently in good supply to meet national demand, said Dr. Santoli.

MMR-V vaccine has not been, and will not be, available during the remainder of 2009. Merck expects MMR-V to return to the United States market with full availability in the first half of 2010.

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Finally, she addressed monovalent vaccines for measles, mumps, or rubella. Merck is not distributing these products at this time. They plan to resume production of these monovalent vaccines in the future, based on available resources and capacity. However, Merck does not expect that these vaccines will be available for at least two years. They are making customers who inquire aware of that longer time frame.

Discussion

Mr. John T. McCubbins (Merck) thanked his colleagues at GSK and sanofi for helping with the shortage issues that Merck has experienced. They understand the shortages' significance to public health. He offered apologies to ACIP, public health providers, and patients for Merck's difficulties. They have a two-fold plan to resolve their issues. An acute plan will address issues with specific vaccines that are in short supply, and long-term infrastructure issues will be addressed so that when temporary issues arise, they are not translated into supply issues. Progress has been made on that front. For example, Merck has produced 25% more varicella-containing product in the first five months of 2009 than they have produced in any previous year. They have restarted Pedvax, and the supply should be available at the end of 2009 and the beginning of 2010. Merck has been producing its hepatitis B product, and they expect full supply in 2010. Additionally, they are investing in expanding infrastructure and in building new facilities in Ireland and North Carolina. They anticipate licensure for the North Carolina facility in 2010, which will improve the supply situation. They are investing in the future to ensure that they will get where they want to be and not have a recurrence of this situation. Merck is in the vaccine business for the long haul, and they commit to greater transparency on their supply situation, including progress and setbacks. He understood that the only appropriate apology was to put these vaccine products back on the market, and Merck is committed to that effort.

Dr. Sawyer asked for comments from Merck regarding the rationale for returning to production of monovalent measles, mumps, and rubella, given that there are no recommendations from ACIP to use those vaccines.

Mr. McCubbins replied that the monovalent M, M, and R have been given a lower priority than the combination product. This prioritization is due to a capacity issue and the belief that better coverage is achieved with the combination product. Merck will return to monovalents, but not for at least two years.

Margie McGlynn (President, Merck Vaccines) responded that Merck has heard mixed feedback from the marketplace. There is no clear, good answer regarding production of monovalent M, M, and R. They feel that if providers are interested in using the monovalent vaccines, it is their obligation not to make that decision on behalf of the providers. They understand the on-going public health debate and the feelings of physicians who believe in using monovalents because of fears of problems with co-administration of combination vaccines. The concerns are not valid, but could affect penetration rates and utilization rates of the vaccine. They also appreciate that some providers and patients want monovalent products. For these reasons, Merck decided not to make the choice. At the same time, MMR has priority to immunize the greatest possible number of children on a global basis. They welcome additional input. She stressed that this decision was one of her most difficult as President of Merck Vaccines.

Dr. Birkhead stated his belief that Merck had made a mistake by proceeding with monovalents.

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Dr. Temte said that the Wisconsin Council on Immunization Practices (WCIP) has heard that various hospitals and health systems have been using the pediatric hepatitis B vaccine off-label, giving two doses to adult employees for cost savings. He asked about broad communication efforts to avoid this practice.

Dr. Santoli answered that CDC is in the process of clearing a set of hepatitis B Q & As about supply challenges on the pediatric and adult sides. This Q & As will state clearly that to make the best use of pediatric vaccine supply during a time when supply is limited, that supply should not be used to vaccinate adults. She agreed that the cost incentive may cause people not to heed that guidance.

Dr. Sumaya asked about communication or agreement between the pharmaceutical companies that supply the vaccines and the information that reaches providers via a number of advisory groups that make decisions and plans. He wondered whether the pharmaceutical companies have strategic plans for the next few years, and whether CDC has a sense of time frames and the availability of vaccines.

Mr. Phil Hosbach (sanofi pasteur) replied that they in close contact with CDC and the ACIP working groups as they work on vaccine development. They also work with NVAC and share information about their plans for vaccine development to target infectious diseases in the US and around the world. Information is shared at this working-group level.

Dr. Santoli added that when there is an issue or a challenge, the Vaccine Supply Stakeholders Group shares proprietary information as part of their discussions. They use this information to make decisions and recommendations. The involved organizations share a great deal of information that is not always made public. For example, the information used to make the decision about pediatric hepatitis B was based on month-by-month supply projections from each of the manufacturers, plus stockpile data.

Dr. Stan Grogg (AOA) expressed concern about Merck's decision to produce monovalents, and his concern about delays in immunizations.

Dr. Schuchat reminded the group that pediatric vaccine shortages are addressed with a pediatric vaccine stockpile, which is part of the VFC program. There is a six-month supply of pediatric vaccines. With all of the new vaccines and combination vaccines, and with some formulations going out of production, the stockpile is undergoing re-evaluation and assessment. It has helped in some shortage situations and fallen short in others.

Dr. Christine Hahn (CSTE) recalled a discussion about combination vaccines in which it was concluded that MMR is not a combination vaccine because the individual antigens are not available. The vaccine recommendations were used to support combination vaccines, but the newly-approved statement is softer and includes patient preference as a prominent consideration. She felt that this statement could be interpreted as support for moving to monovalents for MMR. This interpretation seems to be in conflict with the committee's sentiments.

Ms. Stinchfield (NAPNAP) echoed concern for single-antigen vaccines for measles, mumps, and rubella. Science should drive ACIP's decisions, and it seems that producing these vaccines is not a good use of resources or efforts when the call for them comes from a small minority of parents and providers who will give in to the "too many, too soon" or "too young" arguments.

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Science disproves those assertions. To make single-antigen vaccines available goes against science and toward public opinion, which is sometimes erroneous.

Dr. McGlynn (President, Merck) indicated that there is a two-year time period between now and a point at which Merck would be able to reintroduce these vaccines. She welcomed and encouraged clear and specific ACIP recommendations. The physician community places orders for vaccines, and these calls influence Merck's decision. Clearly, the physician community is most influenced not by Merck's statements as a manufacturer, but by clear and strong recommendations from ACIP and other stakeholder groups. She expressed hope that they could work together to assure that the right outcome takes place.

Dr. Schuchat suggested that since an upcoming session of the meeting would focus on MMRV, they should delay their discussions about formulations until that session.

Dr. Birkhead said that ACIP has issued clear guidance on the MMR and monovalent issue. He pointed out that ACIP "holds the strings" to the VFC program, and he was not sure that monovalents would automatically be included in the program when they became available, or whether it would require an ACIP vote to include them.

Dr. Lance Rodewald noted that monovalents were previously available from Merck, but were never in the VFC program.

Dr. Temte said that before the measles vaccine, the rate of febrile seizure with measles was 70 per 10,000 people. The rate with the monovalent measles vaccine is about 9 seizures per 10,000. The rate with MMR is 3 to 4 per 10,000. The perception that the measles vaccine by itself is safer than measles mixed with mumps and rubella is not supported by data. He suggested that they take a proactive approach to keep this information in front of physicians and the public.

Ms. Hannon (AIM) was grateful that manufacturers share information with CDC and the Stakeholders Group, which includes an AIM representative. This information cannot be shared further than those groups, however. Some grantees were informed about the hepatitis B vaccine situation either by providers or by McKesson's announcement that the product was on back order. Even given the numerous legal issues, it is possible to make significant improvements in planning if more information about supply is available. Grantees are sometimes the last to find out even though they are engaged with CDC, and CDC makes decisions with information from manufacturers.

In light of the request from Dr. McGlynn, Dr. Ehresmann suggested that ACIP make a strong statement in opposition of Merck's approach to producing monovalents, based on the current status of the science and ACIP statements. She suggested that a future meeting could generate a formal resolution to express the committee's concern.

Dr. Keyseling (SHE) pointed out a limited use of monovalent vaccines during epidemic situations of mumps or measles for healthcare personnel and community coverage. If a limited supply of monovalent vaccine were controlled by the government and available for release, then it could be a cost-effective method for handling epidemics.

Dr. Schuchat said that one of the uses of the stockpile is for outbreak response, but CDC's recommendation for outbreak response in the US is MMR.

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Mr. Hosbach (sanofi pasteur) recalled discussions from the previous day regarding policy decisions and their influence and impact on manufacturers. Many manufacturers were surprised at the direction of the committee regarding combination vaccines, as the manufacturers were not involved with the Combination Working Group. Knowing that the committee no longer prefers a type of vaccine will change manufacturers' plans. Manufacturers try to share their development plans. A policy change has a significant impact on what they have done previously and their future directions. Manufacturers should not drive policy, but should be part of the process. If manufacturers participate, then they can help committees make well-informed decisions and understand complete impacts. Further, the public is also included in decision-making processes. ACIP is concerned about maintaining public involvement, and the manufacturers are also seeking guidance and information from providers and the public. He asked that manufacturers stay involved as much as possible.

Jane Quinn (GSK) supported Mr. Hosbach's comments and elaborated on the collaborative efforts and willingness of manufacturers to work closely with CDC and all stakeholders. Issues of global planning capacity and supply constraints on particular antigens, as well as combination vaccine planning versus monovalent use, are important for all to consider. GSK has produced monovalent vaccines on a number of occasions, but they realize the breadth and interconnectedness of vaccine supply planning, especially around infant immunization schedules and combination vaccines. The process is difficult, and they take as many inputs into account as possible. They wish to remain open with CDC and all stakeholders in this effort. Vaccines must be brought forward in appropriate volumes and are readily available to all who need them. GSK is supportive of continued collaboration and supports Merck's comments regarding transparency, especially in public health crises.

Dr. Katz (IDSA) said that the Measles Partnership, which administers the measles vaccine throughout resource-poor nations, uses monovalent measles vaccine. Some countries have now been able to switch to measles-rubella. MMR is not necessarily the international product. The Serum Institute in India, which makes most of the vaccine used for the Measles Partnership, makes monovalent measles vaccine. International use of monovalent vaccine does not mean that the US should change its preferences, but serves to point out that from the manufacturers' point of view, different markets demand different products.

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Measles-Mumps-Rubella-Varicella Vaccine Safety

Introduction

Jonathan Temte, MD, PhD
University of Wisconsin
ACIP, Working Group Chair

Dr. Temte opened the MMRV Vaccine Safety Working Group session, first offering background information pertaining to the group's process. They have worked on MMRV vaccine safety issues for approximately 16 months. In February 2008, preliminary data were presented to ACIP suggesting an increased risk for febrile seizures following the first dose of MMRV vaccine among children aged 12 through 23 months in the first to second week after vaccination. Therefore, ACIP recommended removing the preference for the combination MMRV vaccine over separate administration of MMR and varicella vaccines and forming and ACIP MMRV Vaccine Safety Working Group [*Morbidity and Mortality Weekly Report* (MMWR), March 2008].

The group's first term of reference was risk assessment being lead by the CDC Immunization Safety Office (ISO). The group was charged with a careful review of post-licensure studies and suggesting any additional analyses that might be needed to fill data gaps. Further, the group was to review encephalitis cases following the MMRV vaccine, and to communicate vaccine safety findings in a clear and transparent manner. The second term of reference concerned risk management and the formulation of policy options for ACIP's consideration, taking into account both the benefit of vaccination and risks of vaccine adverse events. Additionally, the group was charged to identify and reconcile potential inconsistencies in previous ACIP statements related to measles, mumps, rubella, varicella vaccination, and febrile seizure prevention.

In June 2008, the work group presented the terms of reference and other process information to ACIP. In October 2008, they presented results from the Vaccine Safety Datalink MMRV Febrile Seizure Study and heard final results from the Merck-sponsored febrile seizure study. October's report also included work group's interim synthesis of risk for febrile seizures after MMRV. In February 2009, ACIP heard preliminary results from a physician survey regarding opinions for MMRV vaccine use and was presented the elements of the policy framework that would be assessed to formulate options for MMRV vaccine use. Dr. Temte stressed that the group's overall procedure had been intensive. They have had the benefit of great expertise of the work group members, as well as input from various other federal, state and local organizations and programs. They have also benefited from two unpublished studies providing detailed information on MMRV vaccine safety. Physician and mother opinion surveys and studies and the ethics consultation had an important impact on their work. An abundance of data has filtered through the work group in over 50 hours of teleconference meetings.

He reminded everyone of the social context in which they are dealing with discussing febrile seizure as a vaccine adverse event. Over the last few years, there has been a substantial increase in the number of vaccines recommended for usual use. Because of the effectiveness of vaccines, we are now in a situation in which many parents express more concern and fear of a vaccine and its potential adverse events than of the disease the vaccine has been so successful in preventing. Public trust in the safety and efficacy of vaccines is key at this point to

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the on-going success of immunization programs. Also, communication and influence from multiple media sources is rapid (e.g., internet). These sources of information may or may not be factual. In conclusion, Dr. Temte reminded everyone that the recommended schedule in the US in 2009 is for the first dose of measles, mumps, and rubella for persons aged 12 through 15 months of age followed by a second dose at 4 to 6 years of age. The same schedule applies for varicella vaccine. MMRV vaccine is approved for use among healthy children aged 12 months through 12 years [http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm].

Parental Perceptions of MMRV Vaccine

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Health Communication Specialist
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Mr. Janssen provided preliminary results of a qualitative study conducted with mothers and pediatricians regarding the MMRV vaccine. The objective of the study was to explore perceptions regarding the risks and benefits of the MMRV vaccine with pediatricians and with mothers. In addition, the study tested draft communication materials regarding the MMRV vaccine with mothers.

Regarding the methodology of the pediatrician survey, data collection included in-depth, thirty-minute interviews conducted one-on-one with 21 pediatricians. The interviews addressed dose one and dose two of the MMRV vaccination. The pediatricians were provided with an MMRV product profile. Studies were conducted in a commercial market-research facility in New York City and Kirkland, a suburb of Seattle, Washington, from May 9 - 15, 2009. They encouraged a diverse panel of respondents from the pediatric community, all of whom were board-certified. Of the panelists, 6 were male and 15 were female; 14 were White, 4 were African-American, and 3 were Asian. The pediatricians surveyed spend 70% of practice time in direct patient care and self-reported giving at least 5 MMR vaccines per month.

Pediatrician perceptions of MMRV vaccine were generally favorable. Common comments included the following:

"We loved having it."
"I have no reservations about ProQuad."
"I miss it. I wish it would come back."
"I'm definitely in the ProQuad pack."

A few pediatricians expressed reservations, such as the following:

"I'm not that comfortable with it, really."
"I don't like it that much."

Pediatricians were asked to rank the significance of the MMRV vaccine to their armamentarium on a scale of 1 to 7, with 1 representing no significant contribution to the practice and 7 representing a highly significant addition to the practice. Most of the 17 pediatricians interviewed were very favorable toward the MMRV vaccine, with 9 respondents rating the vaccine's significance at a 7, and 5 at a 6.

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When provided with data regarding the rates of fever and febrile seizures following MMRV vaccine, several pediatricians remarked on the data, but were not alarmed by them. Some of their remarks were as follows:

"I don't think [fevers, febrile seizures] are numerous or serious enough to not use [ProQuad]."
"It makes sense. If you have more fevers, you'll have more seizures."
"…of significance to the patient, not clinically…I'd still use it."

Pediatricians considered that for parents fever and febrile seizures are important and distressful events. Some of the comments were as follows:

Fever
"Fever is worrisome [for parents] and it's across the board."

Febrile Seizure
"The kids are fine and it takes the parents years to recover."
"It's really not a big deal. I talk the parents down."
"Really scary for the parents; really harmless for the child."
"It's a very, very scary thing for parents to observe."
"That's what freaks them out. Then they get fever phobia."
"[Parental trauma] – that's the big one."

Regarding acceptance of the MMRV vaccine, most pediatricians reported that they would stock the MMRV vaccine as well as MMR and varicella vaccines. The top four factors rated as "very important" in influencing the decision to use MMRV vaccine were: 1) ACIP and AAP recommendations; 2) the potential for the MMRV vaccine to improve coverage for varicella vaccine; 3) parental preference for fewer injections at a visit; and 4) parental concerns for risk of febrile seizure. Another factor considered for decision-making was pediatricians' support for flexibility to be able to meet the needs of their patients.

The interview included this question: "What do you think ACIP should recommend for dose 1 MMRV at ages 12 to 15 months?" Of the 21 responding pediatricians, 11 said that they wanted provider choice between the MMRV vaccine and separate MMR and varicella vaccines, 5 stated a preference for separate MMR and varicella vaccines with an option to permit the use of MMRV, and 5 stated a preference for the MMRV vaccine. Some of their comments were

"We want families to have choices."
"There are families that want to unbundle vaccines and some who want to bundle. It would be nice to have a choice."
"It makes our lives a little bit easier."
"I just want to keep it simple. MMRV for both would simplify our conversation."

The interview also asked pediatricians' opinions regarding ACIP recommendations for dose 2 of MMRV vaccine at ages 4 to 6 years. Again, 11 pediatricians recommended provider choice between the MMRV vaccine and separate MMR and varicella vaccines, 10 had a preference for the MMRV vaccine for the second dose, and none supported separate MMR and varicella vaccines for dose two. Some of their comments were:

"It's a much bigger deal with 5-year olds."
"I think it's more distressing with older kids."
"Four-to-six year olds really, really, really don't like shots"

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In summary, among the 21 pediatricians interviewed in two cities, approximately 50% stated a preference for provider choice between the MMRV vaccine and the separate MMR and varicella vaccines for both doses. Consistent with other studies, pediatricians reported less concern for fever and febrile seizures, but they also perceived that parents were likely to have greater fever and seizure concerns.

With respect to the methodology utilized in the Mother study, data were collected by means of a series of "mini focus groups" in Kirkland, Washington and New York City. The sessions included up to six participants per group, lasted about one hour and were moderated by a professional moderator who provided the mothers with background material about the MMRV vaccine and febrile seizures. The study assessed the mothers' views about combination vaccines in general and about dose one of the MMRV vaccine for children aged 12 through 15 months. The participants all had children aged 7 months to 3 years of age. Their children had neither experienced seizures nor had a condition which compromised the child's immune system and thus their ability to receive certain vaccinations. The participants also expected their child to receive all or most of the recommended childhood vaccinations. A total of 16 focus groups were conducted with 82 respondents. The median age was 31 years, with a range of 20 through 46 years. Of the 82 participants, 63 had at least one college degree. Respondents were White (n=58), African-American (n=10), Hispanic (n=6), Asian (n=5), and mixed race (n=3).

When asked about combination vaccines in general, the mothers produced a modest list of advantages, a longer list of disadvantages, and an even longer list of questions. The list of advantages included the chance for fewer shots and less pain and trauma; protection against several diseases at once; fewer doctor trips; and potentially lower costs for vaccination. The list of disadvantages associated with combination vaccines included an inability to pinpoint a source of allergic reaction; the potential for increased side effects; the concern that the combination shot may be too great a challenge for the child's immune system; and less parental choice regarding how children receive vaccines. The mothers' questions focused on the side effects of the combination vaccines, whether the combination is as effective as separate vaccines, and how combination vaccines fit into the immunization schedule, including the catch-up schedule.

The degree of acceptance of the MMRV vaccine varied substantially among the mothers. After reviewing information about the MMRV vaccine, mothers were asked if their physician recommended MMRV for dose 1 for their child aged 12 to 15 months, to rank their acceptance of that recommendation on a scale of 1 to 7. Of the respondents, 18 gave a rank of 1, or "no way / no how" and 18 gave a rank of 7, or acceptance without reservations.

Comments of mothers who were acceptors of the MMRV vaccine centered on their trust of their pediatrician. They also liked the idea of giving one less shot. The non-acceptors of the MMRV vaccine determined that the risks were not worth the benefit of the combination vaccine, and there was a great deal of concern regarding seizures among this group.

Mothers were generally less concerned about fever than they were about seizures, although some respondents did express strong concern about fever. Their assessment of the importance of the difference between the separate and combination vaccines varied. Some mothers spontaneously reported that fever and seizures could be prevented by using Tylenol™. The mothers' perception of post-vaccination fever in general appeared to be affected by their experience. One mother commented, *"That just comes with the territory, but you still worry."* Regarding seizures, there was general agreement among the mothers that seeing their child

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have a febrile seizure would be a harrowing experience. For some, information on the rates of febrile seizure was of significant concern; for others it was not. A number of the mothers responded that they did not know what a febrile seizure was. After receiving information on the rates of seizure and the MMRV vaccine, some mothers responded that the numbers were not alarming.

In summary, the Mothers study was conducted with a small sample of mothers who reported that they have their children vaccinated. They generally expressed a high degree of trust in their pediatricians. Mothers can differ in their conclusions regarding the data about MMRV vaccine and the rates of fever and febrile seizures and, thus, in their acceptance of MMRV vaccine. After reviewing and discussing risks and benefits of MMRV and separate MMR and varicella vaccines, almost one-third of the mothers reported that they would be resistant to having their child receive the MMRV vaccine; about one-quarter of the mothers were neutral, and about 40% of them would accept it.

Discussion

Dr. Neuzil thought that it might be helpful to put these surveys into perspective with the perception survey reviewed at the February 2009 meeting. That survey included 300 pediatricians and family practitioners. The physician interviews and mothers' focus groups have very small numbers, and there could be different types of biases.

Dr. Temte answered that two different methodologies were used. The first survey was a randomized sampling of family physicians and pediatricians to have a general overview. Focus groups and interviews are not intended to be representative, but rather to determine common themes that occur across clinicians. In this case, they involved a multi-modal approach. Some themes were fairly consistent. They were not necessarily looking for percentages, but at themes that could be followed up with questions. Taken as a whole, the comments were consistent.

Mr. Janssen said that an advantage of a qualitative study is the ability to explore in more depth and to learn what is behind decisions. The combination of both methods is helpful in the decision-making process.

Dr. Dixie Snyder noted that the group of mothers had no major concerns about vaccines, as they planned to have their children vaccinated. A large proportion of the mothers were concerned when they received information about fever and febrile seizures after the MMRV vaccine. All studies have limitations or biases, but it is striking that this group of respondents were vaccine-friendly, yet expressed these concerns.

Dr. Baker echoed Dr. Snyder's comment, adding that the "vaccine acceptable" group is not concerned about safety and is generally "pro-vaccination." She asked about the methodology behind the selection of cities for the study.

Mr. Janssen replied that the Seattle area population has numerous questions about the safety and use of vaccines. Mothers in this area were recruited via their play groups and asked a series of questions about vaccines. The New York City area has more concerns with disease because of the crowded nature of the city, so mothers there are likely to have opinions regarding vaccines. In contrast, focus groups in the center of the country showed that parents tend to follow physician recommendations. They chose areas in which they were likely to receive a range of responses. He has conducted studies like these for 10 years and was struck

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by the number of questions and concerns raised, even among groups of vaccine acceptors. They trust their physicians, but many are going to other sources for information about vaccines that they then discuss with their physicians.

Dr. Baker commented on the finding that many parents do not know what a febrile seizure is, or that there is a risk for one with any vaccines. When counseling their patients, practitioners need to be aware of these gaps in knowledge and of reluctance on the part of parents.

Dr. Temte observed the New York City focus groups and noted the following: 1) fevers were of concern to parents; 2) in general, parents were not aware of febrile seizures until they heard a description of them, and the description alarmed them; and 3) almost all of the focus groups mentioned a risk of thimerosal exposure with MMR, even though that does not exist. The amount of misinformation is immense, making it even more important to ensure that patients receive clear information.

Dr. Sumaya agreed with the utility of the methodology that assesses perceptions. At the same time, these studies need to be supplemented by studies with multiple providers and populations with broader demographic characteristics.

Evaluation of MMRV and Febrile Seizures: Updated VSD Analyses with Chart Review Results

Nicola Klein, MD, PhD
Northern California Kaiser Permanente
and the Vaccine Safety Datalink MMRV Team

Dr. Klein reported on the updated VSD analyses with chart review results from the Vaccine Safety Datalink (VSD) / MMRV Rapid Cycle Analysis (RCA) study evaluating MMRV and febrile seizures. The VSD is comprised of 8 HMOs: Group Health Cooperative, Kaiser Permanente Colorado, Kaiser Permanente Northwest, Harvard Pilgrim Health Care, Health Partners, Northern California Kaiser Permanente, Marshfield Clinic and Southern California Kaiser Permanente. Data are available on more than 8 million members.

Over the last few years, following the licensure of new vaccines, the VSD has undertaken RCA studies for each new vaccine. RCA utilizes data which are updated weekly on all vaccines and all outcomes. Analyses on outcomes specific for each vaccine are conducted every week. Each RCA study has a lead principal investigator from one of the VSD sites. Dr. Klein is the principal investigator at Northern California Kaiser Permanente, which is the lead site for the MMRV RCA Study.

Dr. Klein reviewed the MMRV seizure results, which were presented at the February 2008 ACIP meeting. The study monitored for seizures, among other outcomes, after the first dose of MMRV for patients presented in the emergency room and inpatient settings during post-vaccine days 0 to 42 among 12 through 23 month olds. A signal for seizures was detected in the 42-day period following MMRV compared with historical rates in MMR recipients. Upon further evaluation, the study found significant clustering of seizures on days 7 through 10 after both MMRV (N= 43,353) and MMR + varicella (V; N= 314,599) vaccines using temporal scan statistics. VSD reviewed charts to confirm febrile seizures during the seven to ten days after vaccination for both MMRV (N=45) and MMR + V (N=132) through 2007. Based on those

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reviews, the study calculated an odds ratio of 2.3 (95% CI 1.6, 3.2), which translates to one additional febrile seizure for every 1,923 MMRV doses administered instead of MMR + V.

Following this presentation, ACIP voted to change the recommendations from a preference for MMRV to no preference for MMRV or MMR + V. In addition, an MMRV Work Group was formed. One of the terms of reference of the Work Group was to evaluate additional data that would be helpful. A few questions remained after the preliminary work: 1) chart confirmation of febrile seizures outside the 7- to 10-day risk period; 2) the risk for seizures after MMRV versus MMR + V in different time windows: 0 to 42 days, 0 to 30 days, 5 to 12 days, and 13 to 30 days to directly compare with the Merck-sponsored Phase 4 study in a post-hoc analysis; and 3) to conduct further investigations of risk for seizures in 4- to 6-year-olds, particularly evaluating for excess risk.

To address these questions, the investigators took advantage of the fact that the VSD had a supply of MMRV through most of 2008, so they utilized those data to conduct additional studies. The investigators considered seizures among 12 through 23 month olds after the first dose of vaccine administered during 2000 – 2008. There was a strong peak and clustering between days 7 and 10 for MMRV, MMR + V, and MMR alone. Further, there are no obvious clustering or peaks outside this window. Temporal scan statistics show that for MMRV, MMR + V, and MMR, there is significant clustering between 8 and 10 days, 7 and 10 days, and 7 and 11 days, respectively, depending on the vaccine. No clustering was identified for varicella alone.

The investigators also considered the question of detecting outpatient visits for fever. They collected data on outpatient fever visits among 12 through 23 month olds after the first dose of vaccine from 2000 – 2008. The results were similar to the seizure conclusions in that there was a peak in days 7 through 10. Temporal scan statistics of fever showed remarkable clustering between days 7 and 10 for all three measles-containing vaccines. Again, no significant clustering was identified for varicella alone.

Using these data, the investigators evaluated chart confirmation of febrile seizures outside the 7- through 10-day risk period. In consultation with the VSD investigators and the ACIP MMRV Working Group, a chart review plan was devised to include all seizures 0 to 42 days after MMRV, all seizures 7 to 10 days after MMR + V, and a sample of seizures at 0 to 6 and 11 to 42 days after MMR + V. That sample was equivalent to the number of MMRV seizures during days 0 to 6 and 11 to 42.

A total of 491 charts were sampled, and 451 were reviewed. The review confirmed that an acute seizure of any type had occurred in 94% of the charts (n=424). One of the study questions concerned whether there is a differential confirmation between MMRV versus MMR + V. There was no difference in confirmation rate between MMRV and MMR + V, with 94% of the charts being confirmed as an acute seizure of any type for both vaccines (n=424). Further, 87% of the total charts reviewed were febrile seizures (n=392), and there was no difference between the MMRV and MMR + V groups. Another question concerned whether there was a differential confirmation rate between cases that occurred within the 7- to 10-day risk period or outside it. Of the cases, 90% were confirmed in the 7- to 10-day window as febrile seizures, versus 83% outside the 7-10 day risk window and these two confirmation rates are significantly different from each other. More importantly, there is no differential in terms of the confirmation rate in the MMRV versus MMR + V groups either during the 7-10 day window or outside this risk period. However, because there was a difference between the confirmation rates of the two windows, when the sampling scheme was applied to a regression analysis, 90% was applied to any case in the window (7-10 days), and 83% to cases outside the window. In the chart review findings

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among febrile seizure cases in 12 through 23 month olds, no difference was detected between whether it was a first seizure event between MMRV versus MMR + V, or whether there was a positive family history for seizures between recipients of MMRV versus MMR + V. Given that data pertaining to family history were missing from nearly half the charts, the results should be interpreted with caution.

The study next sought to evaluate the risk for seizures after MMRV versus MMR + V in the time windows of 0 - 42 days, 0 - 30 days, 5 - 12 days, and 13 - 30 days to directly compare with the Merck-sponsored Phase 4 study. When the study compared the risk of seizures 7 to 10 days after MMRV compared to MMR + V, the automated data showed a relative risk of 1.98 with confidence intervals of 1.43 and 2.73. These results were similar to Dr. Klein's presentation to ACIP in February 2008. Chart-confirmed febrile seizures are similar, with approximately a two-fold increase in relative risk (RR=2.04). These data translate to risk difference of 4.3 per 10,000 doses; that is, for every 2,300 MMRV doses given rather than MMR + V, one more febrile seizure will occur 7 to 10 days after vaccination. A similar analysis for seizures 0 – 42 days after MMRV showed an increased relative risk of 1.42 in the automated data, with confidence intervals of 1.11 and 1.81. The chart-confirmed febrile seizure case data were very similar, with a relative risk of 1.46 and confidence intervals of 1.11 and 1.92. The risk difference for this window was 6.2 per 10,000 doses.

The data from 2000 – 2008 include mostly historical data for controls. While the investigators controlled for confounders as best they could, there are issues associated with using historical controls. Therefore, a case-centered logistic regression analysis was conducted. This analysis is a variation of the self-controlled case series method. Given that a seizure occurred, this analysis compares MMRV to MMR + V and determines whether the patient was more likely to have received the vaccine 7 to 10 days before the seizure, or during the control window of 43 – 180 days before the seizure. This analysis showed an increased odds ratio for febrile seizures of 1.92 and significant confidence intervals of 1.39 and 2.66 for the MMRV compared with MMR + V for the 7-10 day postvaccination period. When the analysis was conducted for the window of 0 – 42 days, there was an increased odds ratio of 1.3 and confidence intervals of 1.03 and 1.65. Thus, the previous analyses were confirmed, and there is increased risk for febrile seizures in these windows. Using regular regressions, post-vaccination risk was considered for days 5 through 12; 13 – 30; and 0 – 30 days. Using chart-confirmed cases only, increased relative risk was found for having a febrile seizure during the 5 – 12 and 0 – 30 day periods. However, no difference in risk of febrile seizures in the MMRV versus MMR + V group was detected in the 13 – 30 day window. The automated data results were very similar to the chart-confirmed data.

Further investigations were also conducted on risk for seizures in 4 - 6 year olds, particularly evaluating for excess risk. In this group, there were 4 seizures during days 7 – 10 after the MMRV vaccine. Zero occurred during that time for MMR + V. There is no significant difference between the 4 versus zero split. Further, only 1 of the 4 cases was diagnosed as a febrile seizure. In evaluating risk for 4 – 6 year olds, the investigators adopted a conservative approach. Instead of evaluating excess risk as before, in this case they evaluated for absolute risk. When evaluating absolute risk for MMRV for one case out of approximately 85,000 doses given, the upper limit of the confidence interval was one per 15,194. At most, therefore, for every 15,000 MMRV doses given, 1 febrile seizure will occur 7 to 10 days after vaccination, even if all of the risk is due to the MMRV vaccine. Similar calculations for MMR + V show one febrile seizure per approximately 17,000 doses.

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In summary, among 12 - 23 month olds after the first vaccine dose, fever and seizure are elevated 7 - 10 days after all measles-containing vaccines. MMRV increases fever and seizure about twice as much as does MMR + V. Analyses of chart-reviewed febrile seizures confirmed a two-fold increase risk of febrile seizures on days 7 - 10 following MMRV as compared to MMR + V. The increased risk for seizures observed during other time windows is due to the risk during the 7 - 10 day window. Among 12 - 23 month olds after the first vaccine dose, for every 2,300 MMRV doses given instead of MMR + V, one additional febrile seizure will occur 7 - 10 days after vaccination. Among 4 - 6 year olds, no evidence of elevated seizure risk was found during the six weeks after MMRV. For the 7 - 10 days after vaccination, an absolute risk greater than 1 febrile seizure per 15,000 doses of MMRV can be ruled out. Among 12 – 23 month olds after vaccination, there is a sharp peak for seizures between days 7 and 10 for MMRV. The graph demonstrates that the increased risk for seizures detected during the longer windows is due solely to the increased risk in the 7- to 10-day window.

Synthesis of Evidence for Febrile Seizure Risk after MMRV Vaccination

Karen Broder, MD
CDC / CCID /NCPDCID / DHQP / ISO

Dr. Broder presented the final synthesis of the evidence for febrile seizure risk after MMRV vaccination on behalf of the MMRV Vaccine Safety Work Group. She reminded everyone that an interim synthesis was presented in October 2008. The framework for her presentation included a review of the evidence framework used to assess risk for febrile seizures after MMRV vaccine; risk assessment for Doses 1 and 2 of MMRV; the clinical importance of febrile seizures assessment; and a discussion of other terms of reference, including an encephalitis case review, additional analyses, and communication of findings.

In October, the work group presented an evidence framework that they developed to assess the risk for febrile seizures after MMRV. The framework was based on frameworks used by IOM, WHO, and the draft ACIP evidence-based work group guidance. The framework contains three lines of evidence, and all lines were evaluated for Doses 1 and 2. The first line is population-based risk, or epidemiologic risk. The second is biologic plausibility, which in this case is the plausibility of having a febrile seizure after MMRV vaccination. The last line is clinical importance of the adverse event, which the group divided into two assessments: 1) the medical importance of febrile seizures, and 2) the psychosocial importance of febrile seizures as an adverse event.

The analysis used quality of evidence grading definitions from the draft evidence-based work group guidance. One modification has been made since the October 2008 presentation in that evidence ratings no longer include the impact of further research. They are specific to the nature of the evidence. Four levels were used: high, moderate, low, and very low.

The approach to evaluating the evidence across all lines included a thorough review of two unpublished post-licensure studies of febrile seizure risk after MMRV: VSD (principal investigator: N. Klein), and a Merck-sponsored study (principal investigator: S. Jacobsen). In addition to these studies, the group reviewed literature and other data sources, including unpublished data. They consulted with numerous experts and held multiple discussions. Two work group surveys assessed and graded the quality of evidence for MMRV and febrile seizure risk. As noted, the group presented its first assessment in October 2008.

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With respect to the synthesis of the Dose 1 MMRV risk assessment, Dr. Broder summarized the data available in October 2008 from the VSD and Merck-sponsored studies. Both studies considered rates of confirmed febrile seizures after MMRV and compared them with rates after MMR and varicella vaccines administered in separate injections at the same visit (MMR + V) in children aged 12 through 23 months. Both studies found an increased risk for febrile seizures in the 1 to 2 weeks after vaccination with MMRV compared to MMR + V. No chart review data were available in the VSD study outside the 7- to 10-day period at the time. The results in the Merck-sponsored study were final. In the Merck-sponsored study, no difference in risk was noted in the 0 – 30 days after MMRV compared to MMR + V. A non-statistically significant decrease in febrile seizure risk was observed after MMRV compared to MMR + V in the 13 – 30 day window after vaccination, with a relative risk of 0.6.

Since October 2008, the VSD has provided data from the expanded chart review study of children aged 12 through 23 months receiving Dose 1 of MMRV compared with MMR + V. They enrolled more children, employed additional methods, and reviewed charts in time periods outside the 7- to 10-day window. The work group assessed the evidence for the early and late risk windows after MMRV compared with MMR+V to determine whether there is a decreased risk for febrile seizures after MMRV compared with MMR+V in the 13 to 30 days after vaccination that might compensate for the increased risk observed after MMRV in the 5 to 12 day period. Both studies compared rates of confirmed febrile seizures after dose 1 MMRV with rates after separate injections of dose 1 MMR + V in children aged 12 to 23 months. Both studies used a largely historical comparison cohort for the MMR + V cases. The VSD study included about 83,000 MMRV and about 376,000 MMR + V subjects. The Merck-sponsored study included about 31,000 subjects in each vaccination group.

The primary interval of interest in the VSD study was 7 to 10 days after vaccination on the basis of the temporal scan analysis. The primary interval of interest in the Merck-sponsored study was 5 to 12 days after vaccination, on the basis of pre-licensure data for fever. With the exception of one additional analysis in the 7 to 10 day period, which was not statistically significant, the Merck-sponsored data have remained unchanged since October 2008. Similar to the October 2008 data, the updated VSD study continues to show about a two-fold increase in risk for febrile seizures in the 7 to 10 days after MMRV vaccination compared with MMR + V. The VSD results in the later window showed a significant increased risk for febrile seizures during the 6 weeks after vaccination and observed no decreased risk in 13 to 30 days after vaccination for MMRV compared with MMR + V.

In terms of the previous experience regarding biological plausibility, the increased risk for febrile seizures in the 1 to 2 weeks after MMRV vaccination compared with MMR + V vaccination is biologically plausible. A study in the VSD of approximately 137,000 children under age 7 years showed that vaccination with MMR is associated with an increased risk for febrile seizure during the 8 to 14 days after vaccination. About one additional febrile seizure occurs per 3000 to 4000 children vaccinated [Barlow, Davis et al. NEJM, 2001]. A population-based study of about 35,000 children aged 12 through 23 months who were vaccinated with varicella vaccine identified no increased risk for febrile seizures during the month after vaccination, after controlling for co-administration of MMR vaccine. Pre-licensure trial rates of vaccine-related fever and measles-like rash were higher in children aged 12 through 23 months receiving Dose 1 MMRV than those receiving Dose 1 MMR + V, in the 6 weeks after vaccination [Black S et al. NEJM, Pediatric Infectious Diseases Journal, 1999]. In the trials, 22% of MMRV recipients had fever, compared with 15% of MMR + V recipients. The fever was clustered in the 5 to 12 days after vaccination. Among subjects who had fever after vaccination, the proportion who had

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fever during the 5 to 12 days was 45% for MMRV and 36% for MMR + V. Among subjects who had measles-like rash after vaccination, the proportion who had this rash during the 5–12 days was 82% for MMRV and 81% for MMR + V [Source: Package insert 2-2008 and unpublished data from Merck on 10-20-08]. Rates of outpatient fever visits after different patterns of MMR and varicella vaccine administration show that the medically-diagnosed fevers in all of the MMR-containing groups are clustered in the 7 to 10 days after vaccination, and MMRV rates are higher than MMR + V rates [N. Klein, ACIP presentation, June 25, 2009; excludes KPSC site].

The work group used the evidence scores to grade population-based risk and biological plausibility. The survey of the work group addressed two questions: 1) the quality of evidence supporting an increased risk for febrile seizures after MMRV versus MMR + V in the 1 to 2 weeks after vaccination; and 2) the quality of evidence supporting whether there is a decreased risk for seizures after MMRV compared with MMR + V in the 13 to 30 days after vaccination. The work group felt that the quality of evidence was high for the increased risk after MMRV in the early window, and that the quality of evidence was low to support the notion of a compensatory risk of MMRV compared with MMR + V.

In summary, two post-licensure studies assessed rates of febrile seizures in children aged 12 through 23 months who received Dose 1 MMRV vaccine and compared these rates with children who received separate Dose 1 injections of MMR and varicella vaccines at the same visit. The studies used different methods and populations of children. Despite using different methods and populations, the two studies showed remarkable consistency during the 1 to 2 weeks after vaccination.

On the basis of this review, the work group made two conclusions regarding the evidence for febrile seizure risk after Dose 1. First, among children aged 12 through 23 months, during the 1 to 2 weeks after vaccination (5 to 12 or 7 to 10 days, depending on the study) compared with separate Dose 1 injections of MMR and varicella vaccines administered at the same visit (MMR + V), the evidence supports a causal relationship between receipt of Dose 1 MMRV vaccine and an increased risk for febrile seizures; the magnitude of the risk is about two-fold. After vaccination, 7 to 9 febrile seizures occur per 10,000 children vaccinated with MMRV and 3 to 4 febrile seizures occur per 10,000 children vaccinated with MMR + V. After Dose 1 MMRV vaccine, 1 additional febrile seizure is expected to occur per approximately 2,300 to 2,600 children vaccinated, compared with MMR + V.

Additionally, among children aged 12 through 23 months, after considering multiple lines of evidence, the MMRV Work Group concluded that the body of evidence suggests that during the 6 weeks after vaccination (0 to 30 or 0 to 42 days, depending on the study), an increased risk for febrile seizures after Dose 1 MMRV compared with MMR + V is only present during the 1 to 2 weeks after vaccination (7 to 10 or 5 to 12 days, depending on study). The risk of febrile seizures occurring during other periods after vaccination is similar between Dose 1 MMRV and MMR + V. Therefore, the risk of febrile seizures occurring during the 1 to 2 weeks after Dose 1 MMRV compared with MMR + V is not offset by a decline in risk after MMRV in the later period after vaccination.

Regarding Dose 2 MMRV vaccine, the pre-licensure safety experience during Days 0 to 42 after vaccination, showed lower fever rates in children aged 15–26 months receiving dose 2 MMRV compared with dose 1 MMRV (N=1035) [ProQuad® Package Insert, February 2008]. There were similar fever rates in children aged 4–6 years receiving dose 2 MMRV (N=397) compared with MMR and varicella vaccines (N=193) (children received dose 1 MMR and varicella at least once month earlier) [Reisinger et al. Pediatrics, 2006]. Fever $\geq$102º F or warm to touch was

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10% in the MMRV group versus 9% in the MMR+V group. No febrile seizures were reported in pre-licensure study subjects receiving Dose 2 MMRV vaccine [Personal communication with Dr. Kuter, Merck on 10-20-08].

In terms of the summary of evidence for febrile seizure risk after Dose 2 MMRV vaccination, among children aged 4 to 6 years, epidemiologic and clinical data suggest adverse event experiences, including fever, are similar after vaccination with MMRV or separate injections of MMR and varicella vaccine administered at the same visit. Febrile seizures are much less common in the age range when Dose 2 MMRV is recommended (age 4 to 6 years) than when Dose 1 MMRV is recommended (age 12 to 15 months). Post-licensure studies were not designed to assess risk for febrile seizures after Dose 2 MMRV; however, in light of findings from the Dose 1 studies regarding febrile seizure risk in the early window, the MMRV Work Group assessed the evidence for febrile seizure risk in children aged 4 to 6 years. Information about Dose 2 MMRV febrile seizure risk was inferred from data on febrile seizure rates in 4 to 6 year olds.

Regarding the summary results from VSD and Merck-sponsored studies for confirmed febrile seizures in children aged 4 to 6 years after MMRV versus MMR + V vaccines, in the VSD study, there was one febrile seizure in the MMRV group of almost 85,000 subjects, and no febrile seizures in the MMR + V group of about 65,000. The VSD study did a calculation showing that given these observations, at most, one febrile seizure will occur after vaccination per approximately 15,000 doses of MMRV and 17,000 doses of MMR + V in children aged 4 to 6 years. The Merck-sponsored study identified no febrile seizures in the 5 to 12 days after MMRV or MMR + V in approximately 50,000 subjects [Sources: 2008-09 ACIP presentations; personal communication N. Klein 6/22/09; Personal communication with Merck-sponsored study investigators on 12-16-08].

In conclusion, regarding the risk of febrile seizure after Dose 2 vaccination, among children aged 4 to 6 years, the available data do not suggest that children who receive Dose 2 MMRV have an increased risk for febrile seizures after vaccination compared with those who receive separate MMR and varicella vaccine injections at the same visit; however, less information is available regarding the risk for febrile seizures after Dose 2 MMRV at ages 4 to 6 years than Dose 1 MMRV at ages 12 to 23 months.

Clinical importance of febrile seizures. Febrile seizures are defined in the medical literature as seizures that occur in febrile children who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures [AAP. Pediatrics. 2008; Johnston M. Nelson Textbook of Pediatrics. 2007]. They can occur in any setting of fever. They usually occur at ages 6 to 60 months, with a peak age of 14 to 18 months. This peak overlaps with the age of recommendation for the first dose of MMRV. Febrile seizures affect about 2% to 5% of young children in the US [AAP. Pediatrics. 2008; Baulac. The Lancet Neurology. 2004]. Other countries provide similar estimates. Febrile seizures generally have an excellent prognosis. More than 90% of children who have a febrile seizure will not develop epilepsy; however, certain factors and genetic predisposition can increase the risk for future development of epilepsy after a febrile seizure. One third of children with a first febrile seizure will have recurrent febrile seizures [Baulac. The Lancet Neurology. 2004].

The first conclusion of the Work group regarding the medical importance of febrile seizures is that children who have a first febrile seizure for any reason are likely to seek medical attention, which commonly includes a visit to the emergency department. The evidence from two population-based studies suggests that children who have a febrile seizure shortly after MMR

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vaccination are not more likely than children who have febrile seizures for other reasons to have future epilepsy or neurodevelopmental disorders [Barlow, NEJM 2001 and Vestergaard, JAMA 2004]. The evidence from one study in Denmark suggests that children who have a febrile seizure after Dose 1 MMR vaccination may have a higher risk for having another febrile seizure than children who had a febrile seizure for other reasons. The magnitude of this risk is likely small, estimated by this study at about a 19% increased risk. Although data on sequelae of febrile seizures after MMRV vaccine are not available, experts believe it is likely that the findings described above for MMR vaccine would be applicable to MMRV. The medical assessment is the same for Doses 1 and 2 of MMRV, except that febrile seizures in the 4 to 6 year age group occur less frequently than in the 12 to 15 month age group. Experts believe that the risk for recurrent febrile seizures would be lower for a child aged 4 to 6 years who has a febrile seizure after Dose 2 MMRV than a child aged 12 to 23 months who had a febrile seizure after Dose 1 MMRV [Vestergaard, JAMA 2004].

The second conclusion, pertaining to the psychosocial importance of febrile seizure, a national survey of physicians, which was presented to ACIP in February 2008, as well as interviews and focus groups of physicians and mothers, suggest consistently that parents and caregivers generally consider febrile seizures to be a more severe adverse event than is perceived by physicians [ACIP Presentations, Kempe 2/09 and Janssen 6/09]. Multiple studies across various cultures show that when a child experiences a febrile seizure, it may have a negative effect on the family, including adverse mental and physical health consequences in the parents and caregivers [Literature review presented to the WG by Dr. Skillen on 2/11/09].

One of the work group's terms of reference was a clinical review of the encephalitis cases identified in the VSD study and the Merck-sponsored general safety study. The VSD study assessed for outcomes other than seizures, and encephalitis and meningitis were among those outcomes. The VSD study detected 2 cases of possible encephalitis after MMRV using ICD-9 codes. These cases were presented by Dr. Klein in February 2008. Both cases were in children who also had febrile seizures 7 to 10 days after vaccination. When the cases were presented to ACIP, some clinicians raised questions about whether they were true encephalitis cases. The Merck-sponsored study detected 1 possible case of encephalitis after MMRV vaccine. This child did not have a febrile seizure. The work group then coordinated an expert review by two independent pediatric neurologists. They applied the Brighton Collaboration case definition [Sejvar, Vaccine 2007]for encephalitis to these three cases. Remarkably, both neurologists had the same assessment: 1 of the VSD cases met the criteria for encephalitis, and the other 2 cases were ruled out.

The work group was also charged to consider additional analyses that should be conducted regarding MMRV and febrile seizure risk. Over the last year, many of these analyses were completed, either by the VSD Study, focus groups, or special data requests. The work group believes that routine adverse event monitoring, which is done for all recommended vaccines, should continue when MMRV returns to the market. Further, an area of potential research might include studies regarding health outcomes in MMRV recipients who have febrile seizures shortly after vaccination. The work group also worked under the terms of reference to communicate its findings regarding risk assessment in a clear and transparent manner. To this end, materials are under development by CDC communication experts to communicate the risk of febrile seizures after MMRV vaccine, as well as the benefits of MMRV vaccine in a clear and transparent manner. Additionally, the Vaccine Information Statement (VIS) will be updated to reflect updated data.

Discussion after Drs. Klein and Broder's presentations

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Dr. Judson congratulated all those involved in the exhaustive investigation, complimenting their thorough approach to a large problem. He felt that the work made causal relationships clear, and he was glad that they were in a position to achieve closure on the subject.

Dr. Marcy concurred and added a perspective from the point of view of a pediatrician. The average pediatrician has approximately 1500 patients in his or her cohort. If 10% of them are changing every year, if there is 1 seizure per 2300 injections, then it will be 15 years before one additional seizure is observed. During this time, if 4% of patients have febrile seizures due to viral infections, the pediatrician will have seen 92 first febrile seizures, and a total of 120 if a third of those patients have a second seizure. Therefore, they are comparing 120 seizures over 15 years in a pediatric practice with 1 in 15 years. To him, that was a “small price to pay” when considering the probable increase in compliance. Parents frequently do not return for a varicella shot for many months, creating an increased period of risk. The minority opinion in the MMRV Work Group regarded the risks and benefits of vaccine and raised the point, “First, do no harm.” If one seizure every 15 years is used in that principle, then no vaccines would be administered, as every vaccine has adverse events. While the MMRV vaccine may result in additional office and / or emergency room visits due to febrile seizures, most emergency rooms can handle that volume. Public trust in vaccines is only a problem when there is a lack of transparency. If parents are not informed of the possibilities, then public trust will be lost. But if parents know the risks up front, and if they have the option to decline, the approach is reasonable, and the public trust will not be an issue. He believed that vaccine coverage would suffer and children would be put at risk for periods of time if MMRV was not used and if parents were not given the option to use it as much as possible.

Dr. Amy Middleman wondered about the existence of data regarding the difference in fever rates in those older than 6 years of age, since the vaccine is indicated for use up to age 12.

Dr. Broder answered that there are no safety data available beyond ages 4 to 6, but in the area of biological plausibility, similar adverse events were seen in 4- to 6-year-olds receiving the second dose as MMRV or as separate MMR and varicella vaccines. From a biological standpoint, it is fair to extrapolate that this would apply to older children. They do not have data to support this idea, however.

Dr. Klein said that they did consider fever in 4- to 6-year-olds, and those seem to be background seizure visits. There are 20-fold fewer overall visits than for children aged 12 to 23 months.

Dr. Harry Keyserling inquired about data on injection site risk. By giving a second injection, are there local site reactions, such as a localized infection at the injection site. Data were presented on thousands of doses, and he wondered whether infection is an issue.

Dr. Klein replied that they did not specifically look at injection sites, as they were monitoring for 6 outcomes following the RCA study. Injection site is not typically used in RCA studies for a variety of reasons. They tend to focus on outcomes that would not be evaluated in pre-licensure studies, but rather on outcomes that are more serious or rare.

Using the model by which the pathogenesis of varicella was developed, Dr. Mercy said after the injection is given there is a local, minor infection and a primary viremia. Then, the virus is disseminated throughout the body, and there is a secondary viremia, when the fever occurs. For this reason, he did not feel that the injection site was important. Rather, the secondary

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viremia is important, if the model for attenuated virus immunization is the same as natural varicella.

Dr. Judson asked whether the question concerned bacterial infection.

Dr. Harry Keyserling clarified that if there is an infection in 1 out of 10,000 injections, or one out of 100,000 injections, then the risk of a local infection is compared to the risk of excess febrile seizures. But if data support that giving 100,000 injections does not cause an increased local problem, then the information would be useful.

Dr. Dixie Snider responded that bacterial infections after vaccinations are relatively uncommon. Clearly, injection safety is an important issue, particularly in developing countries. He wondered about data on frequency of injection site infections, although Chesley Richards indicated that they did not have those data.

Barbara Kuter (Merck) addressed some of the conclusions based on the pre-licensure safety data that was collected in Merck's clinical trials. Regarding fever in the pre-licensure studies, she noted that in a study in which children were vaccinated with 2 doses of MMRV (first at 12 months and second at 15 months), the rates of fever were considerably lower with the second dose at a rate of 23% with the first dose, versus 8% with the second dose. In addition, Merck conducted studies in 4- to 6-year-olds. In these studies, children were either given MMR + V or MMRV. The fever rates were identical between the two groups. Further, there were no serious injection site reactions related to the MMRV vaccine. In fact, overall rates of injection site complaints were lower with MMRV than they were with MMR + V, with the exception of the rate of injection site rash, which was 1% higher for MMRV than for MMR + V.

Dr. Ehresmann commented that while she agreed with Dr. Mercy's comments, in Minnesota, with a birth cohort of 67,000 children, 30 febrile seizures would be expected per year. Even though the increase might not be significant to an individual practice, it may have a bigger impact on a population basis.

Dr. Joe Bocchini (APA) asked Dr. Klein whether the chart review, which indicated that 16% and 22% of two groups had a first febrile seizure, implied that this was the only group for which data were available, or whether a significant percentage had a prior febrile seizure.

Dr. Klein said that of all the reviewed charts, 16% for MMRV had a prior febrile seizure, and 22% for MMR + V had one. Data were available in 85% of the charts. The children were aged 12 through 23 months. The study did not exclude someone who had a febrile seizure from the study unless the second seizure did not occur within 42 days of the event. In that case, they were excluded when they were identified from automated data.

Dr. Bocchini followed up, asking if the patients had a febrile seizure prior to that period, what percentage included in the study may have had a febrile seizure that was their second or third. Dr. Klein clarified that they were excluded if their seizure occurred within 42 days.

Dr. Patricia Whitley-Williams asked for verification that the population studies reflected the heterogeneity of the US population.

Dr. Klein replied that VSD covers a large geographical area. This study included patients from Kaiser Permanente's Center in northern California. This population is representative of the

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underlying population of California, which is quite diverse. However, it is slightly under-representative of the very poor and of the very rich.

Policy Options for Use of MMRV Vaccine

Mona Marin, MD
CDC / CCID / NCIRD / DVD

Dr. Marin described the MMRV Vaccine Safety Work Group assessment of the elements of the policy framework and presented the work group's proposed policy options for MMRV vaccine use. The elements of the policy framework were presented to ACIP in February 2009 and include vaccine safety; efficacy / effectiveness and immunogenicity; burden of disease to prevent (i.e., measles, mumps, rubella, and varicella); program implementation; equity in access to vaccines and use of public funds; and social context.

The work group offered the following assessment of these elements for Dose 1 at ages 12 to 15 months, which is the age at which Dose 1 vaccine is routinely recommended. Regarding vaccine safety, Dr. Marin reiterated Dr. Broder's summary and emphasized that the safety summary describes an increased risk for febrile seizures during the first to second weeks (5 to 12 or 7 to 10 days, depending on the study) after Dose 1 MMRV vaccine compared with Dose 1 MMR and varicella vaccines administered at the same visit (MMR + V); one additional febrile seizure is expected to occur per approximately 2,300 to 2,600 children vaccinated with Dose 1 MMRV, compared with MMR + V. During the 4 to 6 weeks after vaccination, an increased risk for febrile seizures after Dose 1 MMRV compared with MMR+V is only present during the 1 to 2 weeks after vaccination [Adapted from presentation by Dr. Karen Broder, CDC. ACIP meeting, June 25, 2009].

Regarding the efficacy / effectiveness and immunogenicity, MMRV was licensed on the basis of non-inferior immunogenicity of the antigenic components compared with simultaneous administration of MMR and varicella vaccines, based on the results of four randomized, controlled clinical trials [FDA, ProQuad clinical review, available at http://www.fda.gov/cber/review/proquadR.pdf]. Efficacy was inferred on the basis of non-inferior immunogenicity. Effectiveness of MMRV was not evaluated in clinical studies. Based on this evidence, the work group assessment was that the quality of evidence for non-inferiority was high and that MMRV and MMR + V had equal immunogenicity. Equal effectiveness was assumed.

Dr. Marin reminded the committee that the burden of disease prevented is a function of vaccine effectiveness and vaccine coverage. The current burden of disease in the US for measles, rubella, and mumps is eliminated or very low [1-3]. The burden of varicella is low, with the 10-year vaccination program having had an important impact of approximately 90% reduction in disease incidence during 1995-2005[3]. There are still an estimated 400,000 varicella cases per year. These disease levels were achieved in the absence of MMRV. The current low levels of disease are due to high population immunity achieved through high vaccine coverage. The coverage of MMR vaccine among 19 to 35-month-olds has been between 90% and 93% since 1996[5]. All states had second dose measles-containing vaccine school entry requirements in 2005 – 2006. These requirements are an important tool for ensuring high vaccination rates. Coverage of varicella vaccine among 19 to 35 month-olds reached 90% in 2007. Forty-six states had one dose school entry requirements in 2008[7] [1. Katz SL and Hinman AR. J Infect Dis, 2004; 2. Reef SE and Cochi SL. J Infect Dis, 2006; 3. Barsky A et al. IDSA abstract, 2008;

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4. Guris D et al. J Infect Dis, 2008; 5. NIS, www.cdc.gov/vaccines/stats-surv/default.htm#nis; 6. http://www.cdc.gov/vaccines/vac-gen/laws/downloads/izlaws05-06.pdf; 7. CDC, unpublished data (courtesy of Jessica Leung, MPH)].

For burden of disease to prevent, the work group concluded that MMRV as a first dose likely has a similar impact to that of MMR + V for prevention of measles, mumps, rubella, and varicella. MMRV may lead to more children vaccinated against varicella at age 12 months rather than 15 to 18 months. An important burden of disease for varicella is not seen among children aged 12 to 18 months. The quality of evidence for this conclusion was expert opinion and the benefit of MMRV and MMR + V for preventing measles, mumps, rubella, and varicella for the first dose was assessed as equal.

Regarding program implementation, the work group discussed differences in storage conditions. MMR is stored in the refrigerator, where varicella and MMRV must be stored frozen. Further, many discussions focused on the impact of the number of injections, given that 9 or 10 vaccinations are recommended either routinely at age 12 to 15 months or for ages that overlap ages 12 to 15 months[1]. The work group also discussed the known parent and provider preference for fewer injections per visit [2-4]. The group examined the current experience with vaccine administration using data from two immunization information systems[5]. These data showed that the majority of children receive Dose 1 MMR and varicella vaccines at age 12 months. A minority receive them at 15 – 18 months. Among children who receive varicella vaccine, about 84% receive the first dose at 12 months, and the percentage increases to 97% by 18 months. The Immunization Information Systems also showed that one-third to one-half of children received four or more injections at one visit at ages 12 to 14 months [1.http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm; 2. Meyerhoff A. Clinical Pediatrics, 2004; 3. Lieu TA et al. Vaccine, 2000; 4. Freed GL et at. Pediatrics, 2006; 5. Source: Immunization information Systems, MI and OR sentinel sites].

Information was available from the 2006 – 2007 National Immunization Survey[1]. Regarding timeliness of vaccination among 24 to 35 month-olds, 20% of children fell behind in their vaccinations during the interval from the 6-month to the 15-month vaccines schedule, 67% of children were not fully vaccinated by age 16 months, including about 28% who did not receive MMR. The work group discussed multiple factors that could lead to delayed vaccination or under-vaccination. The group also discussed the potential impact of combination vaccines. There was expert opinion agreement that combination vaccines may offer benefit in terms of overall coverage or timeliness, but the literature is limited to quantitate the benefit[2-4] [1. Luman ET et al. Am J Prev Med, 2009; 2. Marshall GS et al. Pediatr Infect Dis J, 2007; 3. Happe LE et al. Pediatr Infect Dis J, 2009; 4. Allred NJ et al. PAS abstract, 2009].

In their consideration of program implementation, the work group discussed additional information from focus groups with mothers which indicated that mothers had questions and concerns related to safety of vaccines[1]. If MMRV were recommended by their physician, 41% of mothers would accept and 31% would refuse. Several different studies on physician use and opinions of MMRV vaccine were considered as well. These studies found good uptake when MMRV was available. Physicians interviewed reported no differences in experience using MMRV compared with MMR[1]. Regarding intended use of MMRV given post-licensure safety data, one study found that 9% of family physicians and 21% of pediatricians would give MMRV to a healthy 12- to 15-month-old, where 20% to 24% would let parents decide[2]. Another study indicated that about half of prior users and about 20% of non-prior users expect their patients aged 12 to 15 months to receive Dose 1 MMRV[3] [1. A. Janssen, CDC. ACIP meeting June 25,

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2009; 2. Dr. A. Kempe, Univ of Colorado. ACIP meeting February 26, 2009; 3. J. Kramer, Merck & Co. Presentation to the WG, May, 2009].

Examining all of this evidence, the work group considered the general preference among parents and providers for fewer injections at one visit and that it is likely that vaccination against measles, mumps, rubella, and varicella at ages 12 to 15 months would be preferred as one injection instead of two, assuming that the safety profile is similar. MMRV potentially can have a favorable impact on the on-time administration of other vaccines recommended for ages 12 to 15 months. However, for some parents and providers, the benefit of the reduced number of injections is outweighed by the increase in febrile seizure rate after MMRV.

Based on expert opinion, the work group concluded that there was insufficient evidence to assess the difference in benefit between MMRV and MMR+V in terms of program implementation. Available data from the National Immunization Survey suggest that in terms of coverage for Dose 1, there was no difference for measles, mumps rubella and varicella vaccines coverage by age 19 months with the use of MMRV. This is likely due to the already-high coverage rates prior to MMRV introduction [Zhen Z, CDC, communication to the WG, May, 2009. Source: NIS Q307-Q208]. A minority of work group members expressed concerns that use of MMR + V could adversely affect the overall vaccine coverage rates and incidence for other vaccine-preventable diseases. Also, the impact of the recommendation on acceptance by parents is unknown.

Regarding access to vaccines and the use of public funds, ACIP has issued recommendations for MMR, MMRV, and varicella vaccine use. These vaccines should be covered similarly by insurance companies. There are VFC resolutions, and the price of the vaccines per dose is similar [Available at http://www.cdc.gov/vaccines/programs /vfc/cdc-vac-price-list.htm. However, MMR + V includes two administration dose fees as opposed to one. MMRV and varicella are stored frozen, so there is no difference in availability due to storage requirements. The work group concluded that there is high quality of evidence for no difference in access and use of public funds between MMRV and MMR + V.

Besides the social context in general presented by Dr. Temte in the introduction, the work group consulted with CDC and academic ethicists regarding possible ethical aspects associated with the MMRV vaccine recommendations. The key question explored was whether the increased protection for the population offsets any increased risk for the individual. Considering the ethical principles of risk / benefit analysis, parental and provider preferences, and justice and fairness considerations, the ethics group recommended an approach that makes safety the default, therefore favoring a preference for separate MMR and varicella vaccines for Dose 1. The choice to use MMRV vaccine should be made available if the physician and parents decide it is the best option. Additionally, if future data show that a preference for separate vaccines has a larger-than-expected impact on coverage, then the option should be reconsidered.

In terms of the policy options for Dose 1, of the four options discussed by the work group and presented to ACIP in February 2009, three policy options received support from at least one group member. The work group proposes for a vote two of those options: 1) preference for separate MMR and varicella vaccines over MMRV vaccine; and 2) no preference for MMRV vaccine over separate MMR and varicella vaccines (current interim recommendation) [CDC. Update: Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine. MMWR. 57(10);258-260]. The third option was: MMRV not recommended for ages one to two years; always use separate MMR and varicella vaccines, and was supported by one work group member.

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With respect to the work group's assessment of the elements of the policy framework for Dose 2 at ages 4 to 6 years, regarding vaccine safety the conclusion presented by Dr. Karen Broder indicated that there was no increased risk after Dose 2 MMRV vaccine for children 4 to 6 years.

For efficacy / effectiveness and immunogenicity, as mentioned, MMRV was licensed on the basis of non-inferior immunogenicity of the antigenic components. The geometric mean titer (GMT) was the primary end point to demonstrate similar antibody responses. For measles, mumps and rubella the GMT fold rises were comparable between MMRV and MMR + V groups [Reisinger KS et al. Pediatr Infect Dis J, 2006]. However, for varicella, the GMT fold rise was higher after MMRV than MMR + V (difference statistically significant) but there were no tests done to show superiority. Therefore, the work group concluded that the evidence supports that MMRV and MMR + V are at least equal in terms of immunogenicity and effectiveness. Some experts felt that because GMT is higher after Dose 2 MMRV compared with Dose 2 MMR + V or varicella vaccine, the effectiveness may be higher after MMRV, but there are no data on possible superior protection against varicella provided by MMRV. The quality of evidence for non-inferiority was high, and the benefit of MMRV and MMR + V was equal in terms of immunogenicity. Equal effectiveness was assumed.

The burden of disease prevented was considered similar to that for Dose 1 at ages 12 to 15 months, with several differences in coverage for varicella. The second dose for varicella was recently recommended in 2006, compared with 1989 for MMR. In 2008, only 12 states had school entry requirements for two doses of varicella vaccine, compared with all states for measles-containing vaccine [CDC, unpublished data (courtesy of Jessica Leung, MPH)]. There are currently no good ways of measuring coverage for the second dose of varicella, so estimates are relied upon based on the number of states that have school-entry requirements. The work group concluded that MMRV as a second dose has the potential to have a greater impact on the control of varicella disease than MMR + V through increasing second-dose varicella coverage until states implement school entry requirements. There will likely be similar impact to that of MMR + V for prevention of measles, mumps, and rubella. The quality of evidence for this conclusion is expert opinion. For the difference in benefit between MMRV and MMR + V, the Working Group concluded that MMRV is potentially more beneficial for varicella than MMR + V.

Regarding program implementation, storage conditions for Dose 2 are similar to those discussed for Dose 1. In terms of the number of injections, 5 vaccines are routinely recommended at ages 4 to 6 years[1]. Anecdotal reports indicate that it is more difficult to administer multiple injections at one visit to children aged four to six years. Data from two immunization information systems indicates that the routine age for Dose 2 MMR vaccine is four years, and 37% to 48% of children aged 4 to 6 years received 4 to 5 injections at one visit[2]. One physician opinion study on the use of MMRV showed that 20 percent of family physicians and 38% of pediatricians would give MMRV to a healthy 4- to 6-year-old, and 21% to 25% would let parents decide[3]. Another study found that two-thirds of prior users and one-third of non-prior users expect their patients aged 4 to 6 years to receive Dose 2 as MMRV[4] [1. http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm; 2. Source: Immunization information Systems, MI and OR sentinel sites; 3. Dr. A. Kempe, Univ of Colorado. ACIP meeting February 26, 2009; 4. J. Kramer, Merck & Co. Presentation to the WG, May, 2009].

The work group reached a conclusion regarding program implementation that it is likely that vaccination against measles, mumps, rubella, and varicella at ages 4 to 6 years is preferred as one injection (MMRV) instead of two (MMR + V) by both parents and providers, provided that

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the safety profile is similar. A potential benefit for MMRV is a more rapid increase of coverage for Dose 2 varicella vaccine and improved coverage for other vaccines recommended at this age. The quality of evidence for this conclusion is expert opinion, and in terms of difference in benefit, it was concluded that MMRV is more beneficial than MMR + V.

Regarding equity in access to vaccines, use of public funds, and social context, the evidence and assessment for Dose 2 are similar to those for Dose 1 at age 12 to 15 months. The ethics consult did not address recommendations for Dose 2.

In terms of the policy options for Dose 2, after the previous day ACIP meeting when a vote occurred on the general recommendations for combination vaccines, the MMRV Work Group held a conference call. The group proposes to defer the recommendation for Dose 2 MMRV at ages 4 to 6 years to the ACIP General Recommendations for combination vaccines with the same language adopted by the committee.

In terms of evidence for Dose 1 and Dose 2 of MMRV vaccine at ages other than routinely recommended, no safety data are available for Dose 1 MMRV among children aged older than 23 months[1]. It should be noted that febrile seizures usually occur at ages 6 to 60 months, with the peak age being 14 to 18 months. Some data are available regarding the MMR experience: a study in Denmark showed a decreased risk for febrile seizures with increasing age at vaccination within the age group 15 to 23 months[1]. For Dose 2 MMRV at ages less than 4 years, data are available for ages 15 to 26 months. There is a lower incidence of fever and measles- and varicella-like rash than post-Dose 1[2,3]. In clinical trials, among approximately 2,700 subjects, two febrile seizures occurred (of which one in a setting of roseola) after Dose 2 when Dose 2 was administered 3 months and 6 – 9 months after Dose 1[4]. The immune response after dose 2 is primarily anamnestic response, of measles-containing vaccine recipients 95% have antibodies after Dose 1 administered at age 12 months. Immunogenicity was not inferior when the second dose was administered at ages younger than 4 years[2,3]. No safety or immunogenicity data are available for Dose 1 or Dose 2 MMRV at ages 7 to 12 years. However, febrile seizures occur almost exclusively among children aged 6 to 60 months [1. Vestergaard M et al. JAMA, 2004; 2. Shinefield H et al. Pediatr Infect Dis J, 2005; 3. Shinefield H et al. Pediatr Infect Dis J, 2005; 4. Merck & Co. Presentation to the WG, December, 2008].

With this evidence and in light of the recent ACIP General Recommendations on combination vaccines, the work group proposes that the Dose 1 recommendation apply to children aged 12 to 47 months. Supporting evidence for using 47 months, or 3 years, as the cutoff age: 1) the two post-licensure studies found an increased risk for febrile seizures 5 to 12 days after Dose 1 MMRV compared with MMR + V among children aged 12 - 23 months, 2) In the absence of safety data, the group recommended adopting an approach that favored safety during the period of risk for febrile seizures, and 3) The first febrile seizure is uncommon after age four, with 94% of seizures occurring in children aged younger than 4 years in a population-based study in Finland [Sillanpaa M et al. Population based study of febrile seizures in Finland. J Pediatr Neurology, 2008]. Further, the work group proposes that for Dose 1 at other ages besides 12 - 47 months and Dose 2 at any age up to MMRV's license of 12 years, the recommendation should be that from the ACIP General Recommendations on combination vaccines.

Regarding other MMRV vaccine-related guidance from the work group, studies suggest that children who have a personal or family history of febrile seizures or family history of epilepsy are at increased risk for febrile seizures compared with children who do not have such histories (see table in the slide presentation). The MMRV (ProQuad®) package insert lists individual or family

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history of convulsions as a warning. The work group therefore proposes that ACIP includes a personal or family history of seizures as a precaution for MMRV vaccine use. "Family" is defined as a first-degree relative. The ACIP General Recommendation document's definition of "precaution" was presented in the footnote ["A precaution is a condition in a recipient that might increase the risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce immunity (e.g., administering measles vaccine to a person with passive immunity to measles from a blood transfusion). A person might experience a more severe reaction to the vaccine than would have otherwise been expected; however, the risk for this happening is less than expected with a contraindication. In general, vaccinations should be deferred when a precaution is present. However, a vaccination might be indicated in the presence of a precaution because the benefit of protection from the vaccine outweighs the risk for an adverse reaction." ACIP General Recommendations on Immunization. *MMWR* 2006;55(No. RR-15)].

One of the work group's terms of reference was to reconcile the guidance for use of antipyretics for prevention of febrile seizures. In its 2008 guidance for long-term management of the child with simple febrile seizure, the American Academy of Pediatrics (AAP) states that no studies have demonstrated that antipyretics, in the absence of anticonvulsants, reduce the risk of simple febrile seizures [American Academy of Pediatrics. Clinical practice guideline for the long-term management of the child with simple febrile seizure. Pediatrics, 2008]. Although antipyretics may improve the comfort of the child, they will not prevent febrile seizures. Based on a literature review presented to the work group, there is insufficient evidence to recommend either ibuprofen or acetaminophen prophylaxis to prevent simple febrile seizures [Dr. R. Baumann, Univ of Kentucky. Literature review, presentation to the WG, December, 2008]. The work group therefore proposes to adopt the AAP guidance regarding use of antipyretics to prevent febrile seizures to the MMR and MMRV situations. The proposed wording is as follows:

> "MMR or MMRV vaccines may cause fever after vaccination. Most fevers after a measles-containing vaccine occur during the five to 12 days after vaccination. Parents and caregivers should be counseled about the possibility of fever after a measles-containing vaccine and educated on timing and measures to control it. Studies have not demonstrated that antipyretics (e.g., acetaminophen or ibuprofen) prevent febrile seizures. Guidance on diagnosis and management of febrile seizures has been published elsewhere."

The new language is proposed because the language regarding the use of antipyretics to prevent febrile seizure in the 1998 MMR statement is vague. It says that antipyretics may prevent febrile seizures, but notes that preventing febrile seizure is difficult due to the sudden onset of fever.

Dr. Marin then presented options for ACIP to consider for a vote. She began with a summary for Dose 1 at routine ages 12 to 15 months. To protect against measles, mumps, rubella, and varicella, two vaccine options are available: MMRV vaccine or MMR and varicella vaccines. The two options are considered equivalent in terms of disease protection. Use of MMRV vaccine results in one fewer injection compared with use of separate MMR and varicella vaccines and may improve the on-time coverage for the vaccines recommended at ages 12 to 15 months. Use of MMRV vaccine results in a higher risk for fever and febrile seizures 5 to 12 days after the first dose when administered during the second year of life compared with use of separate MMR and varicella vaccines at the same visit. There is about one extra febrile seizure for every 2,300 - 2,600 MMRV doses. The risk for febrile seizures after MMRV can be reduced, but not eliminated, by administering separate injections of MMR and varicella vaccines.

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Children who have febrile seizures generally have an excellent prognosis; however, febrile seizures often require a medical visit to the emergency room for the child and are distressing to parents and caregivers.

Therefore, the work group's first option proposed to the ACIP for a vote, which was supported by the large majority of the group, was as follows:

> "For the first dose of measles, mumps, rubella, and varicella vaccines at ages 12 to 15 months, separate MMR and varicella vaccines are preferred to MMRV vaccine. However, providers may choose to administer MMRV vaccine after discussing the benefits and risks of each option with the parents or caregivers."

The pros of this option include: 1) it considers evidence-based criteria for decision-making, including vaccine safety; 2) in the setting of language barriers, sets the default for the alternative with the lower risk for febrile seizure; and 3) leaves open the possibility of administering MMRV in situations in which its use provides a benefit. The cons of this option include: 1) it might negatively affect the on-time coverage for other vaccines recommended for ages 12 to 15 months and the control of the respective diseases; and 2) it might lead to more complex recommendations.

Dr. Marin then presented the work group's second policy option, which was supported by a sizeable minority of the group:

> "For the first dose of measles, mumps, rubella, and varicella vaccines at ages 12 to 15 months either MMRV vaccine or separate MMR and varicella vaccines can be used. The benefits and risks of both vaccination options should be discussed with the parents or caregivers."

The pros of this option are: 1) it allows physicians and parents to make a decision that best suits the child's individual situation; 2) it could result in simpler, more streamlined recommendations for all age groups, depending on the option chosen for Dose 2; and 3) it might be perceived favorably by the category of providers who prefer to be given the facts and let them make the decision. The cons of this option are: 1) it might mean more time for providers to counsel the parents about the options, weigh the evidence, and make a decision; 2) in practice, the choice could stop at the provider level, and not all children or parents would have access to the two options; and 3) it could potentially be perceived as a less pro-active role taken by the public health community for a vaccine safety issue.

Discussion

Dr. Chilton offered his comments as a practicing pediatrician in private practice in a state where there is universal purchase. He was in favor of recommending separate MMR and varicella vaccines for 5 reasons: The cost of inventory was one of his reasons. If he had to maintain an inventory of both MMRV and MMR + V, without knowing which one would be picked by patients, then he would prefer to have only one available. Second, if both vaccine options were available, then extra time would be needed to counsel parents about the available vaccines and the relative risks and benefits of both. Third, if he were to give the MMRV vaccine, his office would receive one fewer administration fee. He would be giving more counseling for less money. Fourth, he felt that there is an over-emphasis on the number of vaccines given. He did not feel that babies cried more when given four vaccines as opposed to three vaccines, and he hoped that they would downplay this aspect, given that they administer three or more vaccines

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at each visit at two, four, and six months. Fifth, taking his personal experience into account, he said that with each child that has a febrile seizure in his practice, he spends a fair amount of time counseling the family about the fact that febrile seizures are not important. He then schedules another visit for a week later, knowing that the family is worried at their initial conversation and the family will have more questions in the week following the seizure. Finally, he commented that his daughter has a child who has had three febrile seizures. Each time, his daughter calls him from the emergency room. Even when parents have a pediatrician in the family, febrile seizures are important. He recognized that the additional risk of febrile seizure may not add excessively to his overall "quotient," but he hoped to avoid any febrile seizures that he could. He added that the work group had done a great deal of epidemiological work on this problem, and he hoped that they would consider doing similar work on another problem, that of whether the availability of measles, mumps, and rubella as monovalent vaccines actually increases or will decrease the amount of vaccine uptake. They have time to consider this question before they issue a statement opposing the reappearance of these monovalent vaccines.

Dr. Temte thanked Dr. Marin and Dr. Broder for their work, as well as CDC, VSD, and Merck. There is a great deal of very good evidence, which was carefully reviewed by the work group. Their votes came out of this careful consideration. In essence, there is one clear signal that the MMRV first dose at young ages has a higher rate of febrile seizures. The evidence does not inform regarding differences in coverage rates depending on the two options. Until February 2008, ACIP expressed a clear preference for MMRV. Yet in actual practice, physicians still had the ability to choose between two options. They chose the separate vaccines at a high rate of 30% to 40% despite ACIP's preference. Therefore, expressing a preference did not close off other options.

Dr. Ehresmann expressed her personal preference for Option 1, based on the epidemiological data. For MN that would mean 30 extra febrile seizures per year. She also pointed out the "con" for Option 2, a potential perception as a less proactive role taken by the public health community. With all of the parental concern about vaccine safety, she felt that they should take a strong stance.

Dr. Marcy responded to Dr. Chilton's observation about febrile seizures. Parents perceive vulnerability. He estimated that, based on the patient population of a pediatrician and the rate of febrile seizures after MMRV and MMR + V, a pediatrician would see one more seizure every 15 years and reiterated that that is not many. Further, 30 extra seizures in a state is not many for an entire state. He would have liked more data to make a decision, but they have to consider the frequency of seizures, not only the fact that they occur. He did not know what the VIS would say, but presumed that it would be modified to include the finding of the increased risk for febrile seizures after MMRV. This will make it easier to present the situation to patients. He favored Option 2.

Dr. Marin replied that the VIS is going to present the increased risk information and include the rates of febrile seizure after MMR and MMRV.

Dr. Sawyer identified himself as a member of the work group and one of the "significant minority" who favored Option 2. His concern stemmed from data from the physician and parent interviews and focus groups. A significant minority of physicians and parents feel that the combined MMRV vaccine is a valuable option. Option 1 may effectively take that choice away, even though the language said that the choice was still there. If the ACIP statement clearly preferred separate vaccines, only a small number of pediatricians would choose the

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combination vaccine due to concerns regarding liability issues. They should weigh that possibility carefully. Further, there is a lack of clear evidence that a separate vaccination recommendation will lead to decreased coverage or decreased disease prevention; however, these decreases would be certain. There is a potential for 8 or 9 injections at a 12- to 15-month-old visit. Data from the Immunization Information Systems show that less than half of children will receive more than 4 doses at a single visit. It is inevitable that multiple visits and therefore failed visits and failed immunizations will occur. He feared that a separate recommendation would ultimately lead to decreased coverage. Regarding storage issues, he noted that the physician focus group participants did not indicate concern about stocking both vaccines.

Dr. Judson agreed with Drs. Sawyer and Marcy, clarifying that his focus was on the absolute risk of an adverse event, which is not terribly consequential in the overall perspective of febrile seizures. He recognized the effects of seizures, but he supported the minority opinion.

Dr. Meissner was a member of the work group who favored Option 2. He commented that there is an increased risk of 3 to 4 per 10,000 for febrile seizures for MMR + V. The conversation regarding seizure possibility will take place with parents if MMRV is administered, when the rate increases to 7 to 9 per 10,000, but it still needs to take place for MMR + V. Secondly, regarding storage, the recommendation for Dose 2 is unknown. If there is a preference for MMRV for Dose 2, then there will be a need for 3 different vaccines. Regarding the idea of ensuring that the recommendation is perceived as proactive, he did not feel that an ACIP recommendation should be based on concern of what the anti-vaccine group might say. The decision should be based on what is best for the child. He then offered a theoretical advantage for administering MMRV. MMRV may lead to more children vaccinated against varicella at age 12 months, rather than waiting until 15 to 18 months. The varicella vaccine has been available for approximately 15 years, and females who were vaccinated are entering their childbearing years and will likely have lower titers, and the antibodies that they will pass to their babies will be lower. If there is a later administration of the varicella vaccine, then there may be a longer window of vulnerability to varicella among children of these women. While the consideration is theoretical, it may become an issue as the years go by.

Dr. Marin responded that they do not see an important burden of varicella among young children or varicella outbreaks in preschool children. The virus tends to circulate among school-age children, so they do not see a burden of disease now in the younger children. Dr. Meissner agreed, reiterating that this situation may change as these women begin to have children.

Dr. Englund agreed with her fellow pediatricians, who in her experience do a good job of explaining the risks and benefits of the vaccines. The explanation process is part of the standard of care, and she felt that Option 1 took away choice; whereas, Option 2 preserved choice. Further, she was concerned about clinical significance versus statistical significance.

Dr. Morse recognized compelling arguments existed on both sides. ACIP's charge is to make science-based decisions, and the science shows an increased risk. Science alone is not the determining factor, though, and there are a number of other benefits to combination vaccines, as mentioned in the session that discussed the general recommendations on combination vaccines voted that morning. Other considerations, such as safety, are paramount.

With regard to storage, Dr. Judson indicated that for several decades, he was responsible for the Denver Public Health Immunization Program and Clinic. They found problems within clinics and other administration areas in the area of storage. For live virus vaccines, there is a greater

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chance that something will go wrong with a refrigerator door or in a general refrigerator where the temperatures get too warm or too cold than there is for a vaccine that is stored in the freezer. A number of early reports of measles and rubella vaccine failures were associated with potential failures with vaccine holding temperatures in refrigerators.

Dr. Joseph Bocchini reported on discussions at AAP concerning this issue. They addressed the issue most recently in April 2009 to keep up-to-date with ACIP and to provide input. AAP had a similar debate with strong opinions on both sides. Overall, there was favor for what would be considered Option 1.

Dr. David Kimberlin was the AAP liaison to the work group. Throughout their yearlong deliberations, the work group heard from numerous public health physicians regarding provider choice of either MMRV or MMR + V, Option 2, versus a recommended preference for separate MMR and varicella vaccines, phrased as Option 1. In addition, he had spoken with practicing pediatricians about the issue of provider choice versus a recommended preference. Overwhelmingly, the physicians strongly requested that provider choice be allowed for Dose 1. They want to make the decisions that they and the parents think are best for each child. This is consistent with the majority of the 21 pediatricians, and Mr. Alan Janssen's presentation, which requested that choice be allowed. Speaking for himself, Dr. Kimberlin added that the main issue for ACIP is whether a concern over a 0.05% increased chance of febrile seizures, which have no lasting medical consequence, is great enough to justify ACIP inserting itself into the physician-parent communication process in a way that limits the physician's options as a Dose 1 preference for MMR + V, as Option 1 would do. An option with provider choice for MMRV or MMR + V would allow physicians the flexibility that they request. Additionally, stating a preference for MMR + V for Option 1 put them on a slippery slope, especially when they heard of plans to make available monovalent measles, mumps and rubella vaccines.

Dr. Temte said that physicians and care providers see febrile seizures retrospectively; that is, they see them after the fact and after the child has recovered. Parents see the seizures prospectively and perceive the seizures as their children are perhaps dying. This common theme emerged from numerous cross-cultural studies. The parents see the children "doing something very scary." It does not affect them only for a day, week, or month—they may see the effects for years. Secondly, the focus groups made it apparent that the lay public does not understand what a febrile seizure is. When it is stated that a febrile seizure is a vaccine-induced neurologic event that is not significant, he felt that the approach from a committee standpoint was questionable. Third, there was a clear difference in fever between MMRV and MMR +V in the first dose. The parent focus groups showed high concern on this issue, which could set off a chain of medical events for the child.

Dr. Beck commented on the strong arguments on both sides, and he expressed his appreciation to the work group for using the draft document of the ACIP Evidence–based recommendation work group and for the evidence base. He felt that in the real world, the choice has to focus on the best interest of the child. At this age, the best interest of the child is only spoken through the parents. Therefore, the parental thoughts and feelings are important, including the factors that contribute to their decisions and to the physicians that help them make decisions. He admitted that the focus group was very small, but it was also very telling in how the physicians had similar concerns to the parents when faced with the issue of a child who might experience a seizure, albeit an event that is not medically life-threatening. In the mind of the parent, the event was serious. His experience in working with parents in the autism community and beyond, with a range of those who may be misinformed and those who are well-informed, shows a parallel. It is important that ACIP take into consideration the real concerns of parents, as the parental

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concerns are in the best interest of the child. He was persuaded by the economic issues created by stocking more than one vaccine and by other similar issues; however, he set these issues aside to focus on the best option for the child. The choice element seemed to address the interests of the child better than the "non-choice" element.

Dr. Schuchat expressed her appreciation of the discussion and the perspectives of practitioners and state public health programs. She added that CDC has conducted research in vaccine hesitancy with parents, learning about the issues on parents' minds. Repeatedly they hear that an adverse event is real to a parent, while a vaccine-preventable disease is theoretical. She reminded them that they are talking about a real 1 in 2000 risk of a febrile seizure from a vaccine. That parent is also thinking about the risk of measles, mumps, rubella, or varicella for their child. The 1 in 2000 may not seem like a lot for a practice, but it may be more than the child's risk for one of the conditions, as they have reduced rates.

Dr. Morse added that Susan Lett called in to express her support for Option 1.

Dr. Doug Campos-Outcalt added his support for Option 1, which preserved choice. AAFP members are increasingly moving toward evidence-based medicine and asking evidence-based medicine questions. He could defend an ACIP decision based on expert opinion when no other evidence existed, but he would have difficulty explaining an expert-opinion-based decision by ACIP that countered high-level evidence that there was distinct harm from a vaccine. There are adverse reactions at significant rates, and evidence against it is hypothetical or based on expert opinion. If they use evidence-based methodologies, then they should follow where it led.

Motion: Dose 1 at Ages 12 – 15 Months (Option 2)

Dr. Baker moved to accept Dose 1 at Ages 12 – 15 Months (Option 2) as stated. Dr. Meissner seconded the motion. The motion carried with 10 affirmative votes, 0 abstentions, and 5 negative votes.

Dr. Marin then presented policy options regarding Dose 2 at routine ages 4 to 6 years. She reminded the group that to protect against measles, mumps, rubella, and varicella, two vaccine options were available: MMRV vaccine, or separate MMR and varicella vaccines. The two options were considered equivalent in terms of disease protection. Use of MMRV vaccine results in one fewer injection compared with the use of separate MMR and varicella vaccines and has the potential to improve the coverage for Dose 2 varicella vaccine as well as for other vaccines recommended at this age. Available data do not suggest an increase in risk for fever or febrile seizure after the second dose MMRV vaccine at ages four to six years compared with second dose administered as separate MMR and varicella vaccines at the same visit.

The work group offered one proposed option. For the second dose of measles, mumps, rubella, and varicella vaccines at ages 4 to 6 years, the recommendation was deferred to the ACIP General Recommendations on combination vaccines (June 2009). The pros of this approach are: 1) currently no safety concerns; 2) the recommendation is simpler and harmonized with the General Recommendations on combination vaccines; 3) the option results in one fewer injection, which can reduce pain and pain anxiety and will likely be better accepted by patients, parents and providers; and 4) it could lead to a more rapid increase of coverage for Dose 2 varicella vaccine in the current context of incomplete school entry requirements. The con of this option is that it could create difficulties for providers ensuring their clinics have adequate supplies of all three vaccines.

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The policy option was worded to reflect the ACIP General Recommendations: For the second dose,

> "The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment, patient preference, and the potential for adverse events."
>
> A footnote, agreed upon that morning by ACIP, would read:
>
> "Provider assessment should include number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, cost, and storage considerations."

Motion: Dose Two at Ages 4 to 6 Years

Dr. Baker moved to approve the option for Dose 2 at Ages 4 to 6 years as stated. Dr. Chilton seconded the motion. The motion carried unanimously with 14 votes in the affirmative, 0 abstentions, and 0 negative votes.

Dr. Marin then presented the work group recommendations for Dose 1 and 2 at ages other than those routinely recommended. For Dose 1 at ages 12 to 47 months (12 months to 3 years), the recommendation be that for Dose 1 at routine ages (12 to 15 months). For Dose 1 at ages 4 years and older and for Dose 2, the recommendation is deferred to the ACIP General Recommendations on combination vaccines, approved in June 2009.

Discussion

Dr. Pickering noted that the recommendation approved before was for administering Dose 1 at ages 12 to 15 months.

Dr. Marin clarified that the work group proposes that the recommendation approved for Dose 1 at the routinely ages of 12 to 15 months apply for 12 to 47 months.

Dr. Ehresmann felt that the recommendation was moot, since the ACIP had chosen Policy Option 2.

Dr. Neuzil expressed concern that Policy Option 2 was distinct from ACIP's General Recommendations, which indicate a recommendation to use combination vaccines in a majority of circumstances. She agreed with the 12 – 47 month age group in this recommendation, noting that more education would be needed for parents and providers.

Motion: MMRV Vaccine for Dose 1 and Dose 2 at Ages Other Than Routinely Recommended

Dr. Neuzil moved to approve the option for MMRV vaccine for Dose 1 and Dose 2 at ages other than routinely recommended as presented. Dr. Sawyer seconded the motion. The motion carried unanimously with 14 votes in the affirmative, 0 abstentions, and 0 negative votes.

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VFC Resolution Update: Measles, Mumps, Rubella, and Varicella Vaccine

Dr. Jeanne Santoli
CDC/CCID/NCIRD/ISD

Dr. Santoli presented an update to the VFC resolution pertaining to measles, mumps, rubella, and varicella. She explained three components of the resolution. The first focuses on MMR. Eligible groups are children 12 months through 18 years of age, and the group may include those as young as 6 months of age in an outbreak or prior to international travel. She referred to the primary MMR statement from ACIP for recommended doses and contraindications. The recommended vaccine schedules, dose intervals, and precautions can be found at the following url:

http://www.cdc.gov/mmwr/preview/mmwrhtml/00053391.htm;
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5049a5.htm; and
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5522a4.htm?s_cid=mm5522a4_e

Recommended dosage can be found in the package inserts available at the following url:

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

She then turned to the varicella portion of the resolution. Eligible groups include children at least 12 months through 18 years of age. Recommended schedules for varicella vaccine can be found at the following url:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5604a1.htm

This page also includes information regarding dosage intervals, contraindications, and precautions for varicella vaccine. Recommended dosage can be found in the package inserts available at the following url:

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

Next, Dr. Santoli addressed the MMRV component of the VFC Resolution. Eligible groups include children at least 12 months through 12 years of age. Recommended schedules for combined measles, mumps, rubella, and varicella vaccine can be found at the following url:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5604a1.htm

The second element of the MMRV component of the VFC resolution would mirror ACIP's recommendations regarding Dose 1. For the first dose of MMRV vaccines given at 12 - 47 months of age, either MMRV vaccine or separate MMR and varicella vaccines can be used. The potential benefits and risks of both vaccination options should be discussed with the parents or caregivers. For the first dose of MMRV vaccines given at 4 years of age or older, the use of a combination vaccine is generally preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment, patient preference, and the potential for adverse events. For the second dose given at any age, the use of a combination vaccine is generally preferred over separate injections of its equivalent component

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vaccines. Considerations should include provider assessment, patient preference, and the potential for adverse events. Dr. Santoli called attention to a footnote to mirror the ACIP General Recommendations, which reads:

> "Provider assessment should include the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost consideration."

She indicated that dosage intervals, contraindications, and precautions for MMRV vaccine could be found at the following url:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5604a1.htm

Recommended dosage can be found in the package inserts available at the following url:

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833.

In addition, a personal or family history of seizures is a precaution for MMRV vaccine use.

In conclusion, Dr. Santoli noted that if an ACIP recommendation or notice regarding measles, mumps, rubella, and / or varicella vaccination was published within 12 months following this resolution, the relevant language above (except in the eligible groups sections) would be replaced with the language in the recommendation and incorporated by reference to the publication URL.

Dr. Beck wondered whether rather than restating the ACIP recommendation in the VFC Resolution, the VFC Resolution could simply refer to the ACIP recommendation. This way, there would be no questions regarding language.

Dr. Santoli replied that the VFC Resolution would be published on the following Monday, so there would be no document to which it could refer. The ACIP General Recommendations would not yet have been published. When they are published, then the VFC statement will refer to where the General Recommendations are published.

Dr. Snyder noted that by law, they are required to vote on the VFC Resolution, as Congress has given appropriations authority. Once the vote was complete, the resolution would become effective, and they would share the message quickly.

Motion: VFC Resolution: MMRV Vaccine

Dr. Sawyer moved to approve the VFC resolution for MMRV vaccine. Dr. Meissner seconded the motion. The motion carried unanimously with 15 votes in the affirmative, 0 abstentions, and 0 negative votes.

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Pharmacy-Based Immunizations

Stephan L. Foster, Pharm.D., FAPhA
CAPT (Ret) U.S.P.H.S
Professor and Vice Chair
University of Tennessee College of Pharmacy
Liaison Member
CDC Advisory Committee on Immunization Practices (ACIP)

Dr. Foster indicated that he had been a member of ACIP since approximately 2001, and was the first pharmacists to sit on the committee as a liaison member. In addition, he has a history with the US Public Health Service from which he is a retired Commissioned Health Officer.

He reported that pharmacists have been involved in the distribution of vaccines since the early 1900s. The American Pharmacists Association Program began in 1993 when HHS Secretary Donna Shalala asked the American Pharmacists Association (APhA) to help define the role of pharmacists in a national vaccine program for Children. By 1995, the Health Care Financing Administration (HCFA) recognized pharmacists as providers. In 1996, Mississippi recognized pharmacists as immunizers and convened the first APhA's training program, which was three days in length. Also in 1996, APhA then said through their House of Delegates that pharmacists should have three roles in the area of immunizations: 1) advocate (educating and motivating patients); 2) facilitator (hosting others who vaccinate (e.g., in most cases nurses)); and 3) immunizer(giving vaccinations themselves).

The APhA presented courses to state associations and colleges of pharmacy over next two years. The program was first licensed in 1999. The program is currently structure as a two-part program. The first component is a home self-study of approximately 12 hours on the following topics:

- → Module 1: Pharmacists as Vaccine Advocates
- → Module 2: Immunology
- → Module 3: Vaccine-Preventable Diseases
- → Module 4: Establishing a Pharmacy-Based Immunization Program
- → Module 5: Administering Vaccines
- → Self-Study Assessment

The second component consists of a one-day live seminar, which includes the following topics:

- → Importance of Vaccines
- → Shortfalls in Vaccine Delivery and Opportunities for Pharmacists
- → How Vaccines Prevent Disease
- → Vaccine-Preventable Diseases
- → Identifying Vaccination Needs
- → Establishing a Pharmacy-Based Immunization Program
- → Practice Implementation
- → Adverse Events Following Vaccination and Emergency Preparedness
- → Vaccine Administration Technique

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This program probably has more training for pharmacists than most other health care professions receive in this particular area. This program has been accepted by the majority of states in the US as a requirement before pharmacists can actually administer vaccines.

In 2002, the American College of Physicians (ACP) and the American Society of Internal Medicine (ASIM) published the following statement regarding pharmacist's scope of practice [*Ann Intern Med.*2002;136:79-85]:

> Position 4
> *"ACP-ASIM supports the use of the pharmacist as immunization information source, host of immunization sites, and immunizer, as appropriate and allowed by state law. ACP-ASIM will work with pharmacy organizations to increase immunization awareness."*

Most pharmacists in the country disagreed with physicians determining pharmacists' scope of practice, but those who had been involved in vaccinations were relieved that they supported pharmacists as immunizers, as appropriate based upon state law. The American Society of Health-System Pharmacists (ASHP) developed guidelines based upon what they thought the standards of practice should be with respect to legal authority, training, program structure, and reimbursement [ASHP. Am J Health-Pharm. 2003; 60: 1371-7]. As of June 9, 2009 Maine became the 50th state to authorize pharmacists to administer immunizations. Over 60,000 pharmacists have been trained and have delivered over 3 million influenza vaccinations.

Given that vaccines are prescription drugs, pharmacists must have the legal authority to administer them. State law governs health care practice. Each state has specific prescribing regulations, so it is imperative to know what the laws are. In the State of Tennessee, pharmacists can operate under written or verbal prescriptions, but can administer vaccines under standing orders. Most states operate under standing orders. Even in many states that do not have the laws, a physician can send a prescription to a pharmacy and the pharmacists can fill it as they would any other type of prescription. A standing order written by a physician can state that a pharmacist is permitted to administer only a particular vaccine and to whom it may be administered. Protocols can be written into standing orders for emergency administration. This is typically done in partnership with a physician in the community, through a cooperative agreement. In the case of an emergency / pandemic, a governor may sign a declaration to expand authority. During Hurricane Katrina, pharmacists in Tennessee were given prescriptive authority to immunize those who were coming into Tennessee. An immunization protocol / standing order identifies the individual who has delegated activity; identifies the pharmacist authorized to administer vaccine; indicates the types of vaccines the pharmacist is authorized to administer; describes the procedures, decision criteria, or plan the pharmacist should follow, including when to refer patient; delineates the procedure for emergency situations; and outlines record keeping and documentation procedures.

With regard to the variation in state limits to pharmacists' authority, 17 states have no age restriction, 22 restrict administration to those $\geq$ 18 years of age, 1 restricts administration to those $\geq$ 16 years of age, 4 restrict administration to those $\geq$ 14 years of age, et cetera. Many states stipulate which antigen may be administered. Two states permit influenza only, two permit influenza and pneumococcal, one permits adult vaccines only, 33 have no restrictions, et cetera. These limitations are built into the state laws as they are written.

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Another major issue with respect to pharmacists administering vaccinations regards professional liability. The physician's liability does not encompass the pharmacist's scope of practice. The physician is not liable for pharmacist's error in dispensing. Therefore, it is recommended that all pharmacists have liability insurance that covers all professional services. Pharmacists are also afforded the same protection under the federal Vaccine Injury Compensation Program (VICP) for the same types of things other practitioners are, but are protected only if documentation and event reporting occurs.

Pharmacies are in a position to make a unique contribution for a number of reasons: access, proximity, extended hours; ability to identify high-risk patients easily based upon their medications; the public's trust; and the public's enthusiastic acceptance. In general, pharmacists realistically want to be part of the health care team. Pharmacies are an ideal place to distribute medications and vaccinations during an emergency to avoid having patients congregate. Tennessee's pandemic flu laws stipulate that everyone will present to a central high school or other location where their medication will be dispensed to them by volunteers. It would be much easier for social distancing to have the medications disseminated to pharmacies in the state for distribution. This is likely to become a much easier process with the electronic medical record.

Discussion Points

Kenneth Schmader (AGS) recognized that pharmacists have been life savers for vaccines covered under Medicare Part D, and were indeed a very important part of the health care team.

Stanley Grogg (AOA) inquired as to what the protocol would be for patient who experience anaphylaxis.

Dr. Foster responded that they have Epinephrine. They had one physician who said he would not write a standing order for Epinephrine; however, the pharmacist refused to administer vaccines without it. The training program includes an emergency component. In addition to the training program, to administer vaccines in Tennessee, pharmacists are also required to maintain CPR certification.

Alan Hineman (Formerly from the National Vaccine Advisory Committee) stressed that pharmacists were going to play an important role in expanded immunization services, particularly with adolescents and the notion of annual influenza immunization for children. He pointed out that every state has an immunization registry and immunization information system; however, not all pharmacists who administer immunization are reporting them. He encouraged that this be a routine part of pharmacists' activities.

Dr. Foster responded that this is included in the training program. The training program stresses that pharmacists should not be engaging in routine pediatric vaccines, because they firmly believe in the pediatric home. This is not a course for pediatric vaccines.

With regard to increasing immunization rates, Christine Hahn (CSTE) wondered whether any health departments had reached out to pharmacies as a site through which to increase childhood immunization access.

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Dr. Foster responded that San Antonio, Texas has been particularly avid. Dr. Fernando Gurrera had signed standing orders for his entire area. There has been a great deal of difficulty in convincing health departments to write standing orders. There are still areas in Tennessee in which pharmacists do not administer vaccines because they cannot find physicians to write standing orders. Yet other areas are very much involved.

Dr. Cieslak indicated that a concern in his state was potential “cherry picking” of paying patients. With that in mind, he wondered if the national organization had any recommendations with regard to accepting Medicaid or VFC.

Dr. Foster responded that he was not aware of any pharmacies that had been in the VFC programs. Many pharmacies are involved in Medicaid programs since it pays for drugs also. It has been very difficult to convince pharmacists to administer more than influenza vaccines. That is typically not difficult to get reimbursed. Many patients who present on their own are willing to pay for the vaccine themselves. A few rural health departments in a few states have asked pharmacists to help with pediatric vaccines due to the shortage of physicians within the area. However, that is very rare.

Dr. Ehresmann noted that she did not see the issue of storage and handling addressed, which is an important part of the vaccine program.

Dr. Foster responded that there is a major component that addresses storage and handling, and pharmacists are accustomed to dealing with storage and handling issues.

Dr. Judson inquired as to whether there were any examples in which pharmacists have been able to play a continuing viable role in providing vaccines, meaning that they are reimbursed, build up a clientele, and have a volume business. In many places, pharmacy currently seems to be a very low margin / high volume operation that could not do very well on seasonal, short-term, one-time administration.

Dr. Foster responded that certain pharmacists have been involved in vaccine programs; however, it is really not an on-going patient situation. Vaccines probably make more of a margin for pharmacists than any other drug they fill. In most cases, the hesitancy for pharmacists in administering vaccines is that they are too busy and it takes too much time. Otherwise, he was not aware of any pharmacies / pharmacists building up a practice. Pharmacists are encouraged to partner with physicians. Many independent pharmacists in Tennessee send records to the patients’ physicians. Most patients present for influenza and shingles vaccine because they are Medicare Part D reimbursable. Pharmacists administer only about 7% of the influenza vaccines in the country, which is not a major percentage.

Dr. Morse inquired as to what the capacity of pharmacies might be, and whether they could solve the problem for the fall.

Dr. Foster responded that he did not know how many pharmacies had pre-filled their orders for influenza vaccine. Most chains have routine ordering departments that order / distribute vaccines for pharmacies. Several pharmacies, particularly independent ones, order vaccine for physicians’ office as well. This can be a partnership at any point. Pharmacists would very

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much like to be a part of this and really enjoy doing it. It is nice to be able to get out and touch a patient.

Influenza

Session Introduction / Overview

Kathy Neuzil, MD, MPH
Chair, Influenza Vaccine Workgroup

Anthony Fiore, MD, MPH
Influenza Division, NCIRD, CDC

Dr. Neuzil acknowledged the influenza workgroup members, pointing out their wide diversity of expertise and significant liaison representation. She reported that workgroup activities in 2009 have included a review of seasonal vaccine safety data updates; presentations from vaccine manufacturers on adjuvanted seasonal and H5N1 vaccines; discussions of antiviral issues (e.g., antiviral resistance among seasonal H1N1; interim guidelines for pandemic H1N1 treatment; and annual treatment and chemoprophylaxis recommendations); and discussions of pandemic H1N1 with respect to immunology, epidemiology, vaccine development, and program planning. This was the first year in which the recommendations for vaccines and antivirals for influenza were separated. The vaccine recommendations and vote occurred in February, while the antiviral recommendations were to be voted upon during this session.

The goals of this special ACIP influenza session were to discuss and vote on antiviral guidance for both seasonal and pandemic H1N1 virus infections; and provide background on pandemic H1N1 issues for ACIP in preparation for activities and decisions in summer and fall 2009. Dr. Neuzil noted that some considerations to keep in mind for the pandemic A/H1N1 vaccination program included: 1) The need for clear program goals, roles, and responsibilities; 2) Timelines for a vaccine program must consider the possibility of an “early wave.” What vaccines are likely to be available, when, and in what quantities? What basic information is needed to inform recommendations on use of a vaccine, preferably a licensed vaccine? When will it be available?; and 3) How might a pandemic influenza vaccine program co-exist with a seasonal program?

To orient the panelists to this session, Dr. Fiore reviewed the agenda, enumerated the presentations, and introduced the presenters.

2008-09 Influenza Epidemiology: Seasonal and Novel Influenza A (H1N1)

Lyn Finelli, DrPH, MS
Lead, Influenza Surveillance and Outbreak Response Team
Epidemiology and Prevention Branch, Influenza Division, NCIRD

Referring to the US WHO / NREVSS Collaborating Laboratories Summary (2008-09), Dr. Finelli pointed out that within the regular influenza season during, H1 was the predominant virus with a sweep through of B at the end of the season. When the H1N1 pandemic strain occurred, there was co-circulation of all of the seasonal virus with H1N1. During the week ending May 2, 2009 when novel H1N1 first appeared, there was a major increase which represented a surge in

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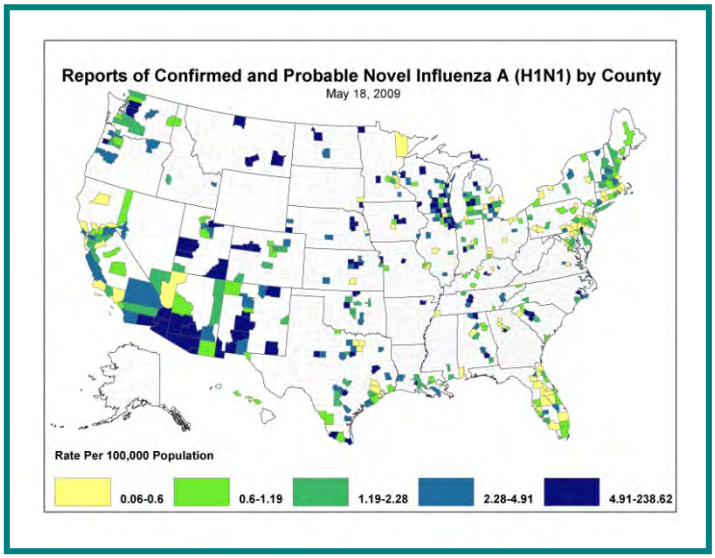
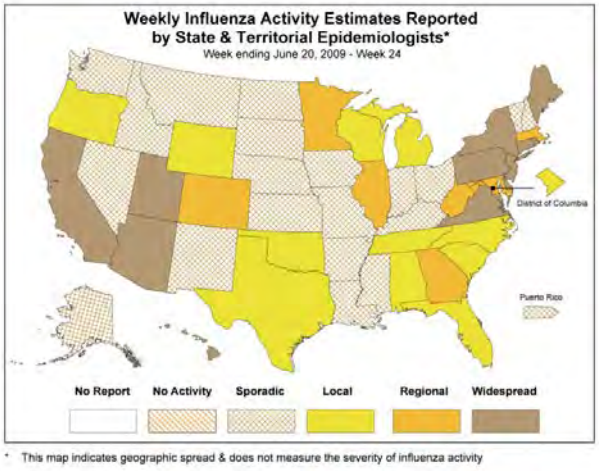
testing by state health departments. The circulation of seasonal viruses declined as the season went on, with novel H1N1 increasing to represent 97% of all influenza viruses tested.

With regard to the percentage of visits for influenza-like illness (ILI) reported by the US Outpatient Influenza-like Illness Surveillance Network (ILINet) for 2008-09 and the previous two seasons, seasonal influenza was mild in 2008-2009. However, at the end of April there was a sudden surge in ILI. That activity had declined and probably represents those who presented to the doctor to be checked, as well as the worried well who may not normally have presented to care but did when they hear the press regarding novel H1N1. The following map illustrates how focal novel H1N1 was as of May 2009:



There has been a major concentration of disease in the Southwest in California and Texas, in the Pacific Northwest, and in the Northeast in Illinois and Wisconsin. The disease has remained focal, although it is now in different areas. As of June 2009, there was a great deal of ILI activity in Massachusetts, Minnesota, New Jersey, and New York. There was also widespread activity in 11 states during this time in the Northeast, West, and Southwest as reflected in this weekly influenza map:



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During Week 18 (week ending May 9, 2009) there was a solid band of activity in several states, with the affected area changes dramatically over time.

Regarding pneumonia and influenza mortality for 122 US, the 2008-09 season was fairly mild without a lot of mortality. The percentage of pneumonia and influenza deaths did not exceed the epidemic threshold for week ending June 6, 2009. With respect to influenza-associated pediatric deaths for the 2005-06 season to the present, seasonal influenza deaths reported totaled 46 in 2005-2006, 78 in 2006-07, 88 in 2007-08, and 83 in 2008-09 of which 17 were attributable to H1N1. Given the rather mild 2008-09 seasonal flu, there would have been only about 66 deaths if not for the 17 deaths attributed to novel H1N1 in children under the age of 18.

In terms of the antigenic characterization data for 2008-09 influenza viruses in the US, between October 1, 2008 and June 12, 2009 CDC characterized 1626 influenza viruses as follows:

Seasonal influenza A(H1N1) [n=947]:
- 947 (100%) similar to A/Brisbane/59/2007 (2008-09 vaccine strain)
- Includes H1N1 resistant to oseltamivir

Influenza A(H3N2) [n=162]
- 162 (100%) similar to A/Brisbane/10/2007 (2008-09 vaccine strain)

Influenza B [n=517]
- 65 (13%) in B/Yamagata lineage
  - Similar to B/Florida/04/2006 (2008-09 vaccine strain)
- 452 (87%) in B/Victoria lineage and not similar to the B strain

Pandemic influenza A (H1N1) [n=125]
- 125 (100%) similar to prototype a/California/07/2009, which is the proposed pandemic influenza vaccine strain

With respect to the epidemiology of the H1N1 outbreak, the triple-reassortant swine virus has been circulating since about 2000-01 and has caused 13 sporadic cases over the past three to four years that CDC and its partners in health departments have investigated. Compared to the novel or pandemic H1N1 strain, this virus is triple-reassortant because it has swine, avian, and human genes. The pandemic strain genes are very different in that they have the same avian and human genes, three of the same swine genes, and two new genes that have never been seen before in either humans or swine in North America.

To summarize the events of the pandemic, between April 15 to17, 2009, two cases of febrile respiratory illness occurred in child residents of adjacent counties in Southern California. These cases were initially identified as swine influenza A (H1N1) virus and later as unusual variants of swine influenza. Both viruses were genetically closely related to each other and both were resistant to amantadine and rimantadine. Both viruses contained a unique combination of gene segments not previously recognized among swine or human influenza viruses in the US. Neither child had contact with pigs. However, this did not deter CDC from comprehensively investigating animal contact in the beginning of the outbreak. Approximately one week to 10 days into the outbreak, 10 cases were reported from three states. Ten days into the outbreak, investigations were underway in six states. One week into the outbreak, nine states were affected. Data for week ending 06 Jun 2009 have been updated. Since the 24 Jun 2009 briefing, cases reported for this week had increased by 1,749, to 3,164. This is a relatively steep increase, but represents in part cases reported by several states which had not reported

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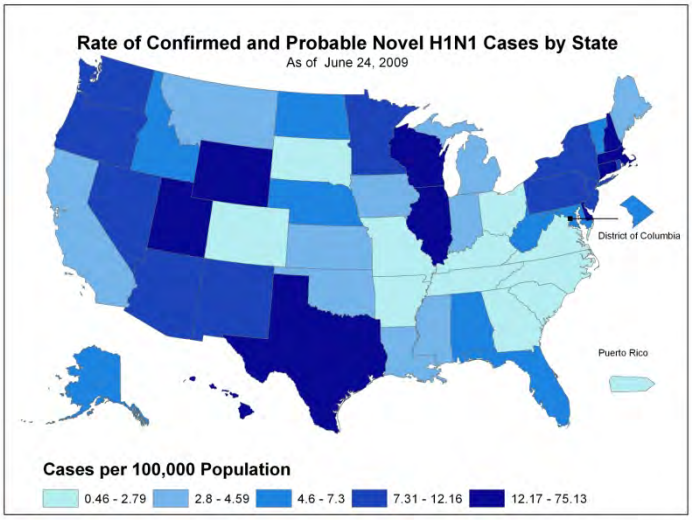
for several days previously. As of 17 Jun 2009, there were 27,717 cases reported to CDC. Of these, there were 3065 (11%) hospitalizations; 127 (0.4%) deaths; and 50% male / female. The median age in all cases was 12 years, in hospitalized cases 20 years, and deaths 37 years. The overall percentages of hospitalizes cases increased, probably due to testing practices. State health departments, which have been conducting much of the testing, are now screening primarily severely ill people because they are so overwhelmed. Thus, the proportion being screened from hospitalized people was greater over the previous few weeks.

CDC has conducted a number of epidemiologic investigation studies, and has developed secondary attack rates in households from those studies. In addition, CDC has engaged with their mathematical modeling partners who have modeled the secondary attack rate. The estimates for secondary attack rates in households are fairly consistent from all of the studies and the models. The secondary attack rate for a household member of a confirmed case is 18% to 19% for those with acute respiratory infection, and between 8% to 12% for those with ILI (e.g., fever with cough or sore throat). Generation time is used as a surrogate for incubation period. The generation time for acute respiratory infection is 2.0 to 3.1 days and for ILI is 2.4 to 3.1 days. A number of community incident studies have been conducted. One of the most difficult things about this outbreak is that when pandemic planning was done, severe morbidity and mortality were planned for. This is also what they thought they would do in terms of tracking the outbreak with surveillance. However, given the mild to moderate outbreak to date, information is being sought about the bottom of the pyramid—those who may be ill but who have not sought care. Several surveys have been conducted in an attempt to assess this. A telephone survey was conducted in New York City in May 2009, during which the proportion of people ill with ILI during that month was 6.9%. In Chicago a door-door survey was conducted, with the median percent of people ill in households was 6%, which was somewhat lower for ILI and somewhat higher for acute respiratory infection. A university survey was conducted in Delaware with two different groups, with 6% to 11% ill. The overall proportion of people sick in households was 6%. As of 24 Jun 2009, the rates of probable and confirmed H1N1 cases by state were as follows:



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CDC no longer receives date of onset for cases. Over the past few weeks 3000 to 4000 cases were report, but the week prior to the ACIP meeting over 6000 cases were reported. With the exception of one state that had not reported in a couple of weeks, all of these cases were fairly recent.

With respect to age distribution of cases reported as of 18 Jun 2009 (n=21,449), there were 2146 cases (10%) in the 0 to 4 age range; 11,720 (55%) in the 5 to 24 year age range; 4041 in the 26 to 64 year age range; 219 (1%) ≥ 65 years of age; and 3324 (15%) of an unknown age. In terms of cases rates per 100,000 population by age group as of 18 Jun 2009 (n=18,125 excluding 3324 cases with missing ages), 2146 (10.2) were reported in 0 to 4 year olds; 11,720 (14.2%) in 5 to 24 year olds; 4,041 (2.5%) in 25 to 64 year olds; and 318 (.6%) in those ≥ 65 years of age. Pandemic H1N1 hospitalizations by age group based on data reported as of 18 Jun 2009 (n=2228) included 445 (20%) ages 0 to 4; 859 (39%) ages 5 to 24 years; 756 (34%) ages 25 to 64; 86 (4%) ages ≥ 65 years of age; and 82 (4%) of unknown ages. Rates of hospitalization by age group per 100,000 population as of 18 June 2009 included 445 (2.1%) 0 to 4; 859 (1%) 5 to 24; 756 (0.5%) 25 to 64; and 86 (0.2%) ≥ 65.

In terms of differential rates of hospitalizations for various cities as of 18 Jun 2009, the US rate overall is very low. Arizona and Illinois are intermediate for those states that are heavily affected. In Massachusetts there were high rates of hospitalization, in Utah they were even higher, and hospitalizations were extremely high in New York City. The hospitalization rates in New York City approximately those for cumulative hospitalization for seasonal few, while others are lower.

Based on data from the Emerging Infections Program (EIP) sites, cumulative hospitalization for 2007-08 for seasonal influenza were approximately 42.8 per 100,000 population in the 0 to 4 age range and 75.6 in those ≥ 65. In 2008-09, seasonal flu was predominantly H1N1. During that season, the highest rate was in the youngest age group of 0 to 4 years (36.6) and lowest in those ≥ 65 (14.6). Every season is a mixed season, so the increase rates among those over age 65 during 2007-08 could also be due to influenza B and H3. The hospitalization rates were much higher cumulatively that they were thus far for novel H1N1.

Regarding the characteristics of those hospitalized, at the time of this ACIP meeting there were 3,065 hospitalizations among 27,717 cases. Detailed clinical data were available on approximately 268 patients, 21% were admitted to the ICU, 13% were placed on mechanical ventilation, and there were 17 deaths. The median time from onset of illness to hospital admission was 3 days, with a range of 1-14 days. The median length of stay was 3 days, with a range 1-53. The median length of stay for seasonal influenza is approximately 2 days. The gender distribution is approximately 50 / 50, with 128 females (48%) and 140 males (52%). The median age in this cohort is 22 years (range 21 days-86 years), which is slightly older than the median age for all those hospitalized. In terms of the age distribution of those hospitalized in this cohort, the highest percentage of people hospitalized is in the 19 to 49 year age group (n=95; 35%) followed by 10 to 18 years of age (n=55; 20%).

Underlying conditions among those hospitalized included the following: Asthma or COPD (32%), Diabetes (16%), immunocompromised (12%), chronic cardiovascular disease excluding hypertension (11%), neurocognitive disorder (8%), neuromuscular disorder (8%), current smoker (10%), pregnant (7%), chronic renal disease (8%), seizure disorder (6%), and cancer (3%). The definition for “immunocompromised” is a catch-all and represents not only those with HIV infection, but also people on long-term steroid or chemotherapy. Clinical information on those who were hospitalized reflected the following: chest radiographs demonstrating

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pneumonia at admission (35%), ARDS (16%), diagnosed with sepsis at admission (12%), mechanical ventilation (13%), treated with antivirals (73%), treated with antibiotics (78%), treated with steroids (35%), and recovered (94%). Among this cohort, approximately 180 blood cultures were done. Of Those 179 were negative and 1 was positive in an elderly man with *E. coli*.

Regarding pandemic H1N1 deaths by age group (n=87), as of 18 Jun 2009 5 (6%) deaths were reported in the 0 to 4 year old age group; 19 (22%) in the 5 to 24 year old age group; 55 (63%) in the 25 to 64 year old age group; 5 (6%) in the ≥ 65 year old age group; and 3 (3%) of an unknown age. The pandemic H1N1 case fatality ratio by age group as of 18 Jun 2009 was 5 (0.23%) in the 0 to 4 year old age group; 19 (0.16%) in the 5 to 24 year old age group 5 to 24 year old age group; 55 (1.36%) in the 25 to 64 year old age group; 5 (2.29%) in the ≥ 65 year old age group; and 3 (0.09%) in those of an unknown age.

With respect to the pandemic (H1N1) deaths reported to CDC by states as of 25 Jun 2009, limited data were available on 99 of the 111 deaths in 20 states. Of these, 49 (53%) were female and 44 (47%) were male. Race / ethnicity was known only for 47 subjects because it is not being collected at the state level, of whom 6 (13%) were non-Hispanic Black; 19 (40%) were non-Hispanic White; 19 (40%) were Hispanic; and 3 (6%) were other. The median time from illness onset to death was 7.5 days (range 0 - 40 days). The median age range was 37 years (range 2 months-72 years), broken down as follows: 0-23 months 5 (6%); 2-4 years 0 (0%); 5-9 years 7 (8%); 10-17 years 10 (11%); 18-29 years 11 (13%); 30-49 years 35 (40%); 50-64 years 18 (21%); and ≥65 years 1 (1%).

Of the 99 pandemic (H1N1) deaths reported to CDC by states as of 25 Jun 2009, 12 (12%) of persons had no underlying conditions. Some conditions may have overlapped for individual cases for the following breakdown: Asthma 11%, Other Pulmonary Disease 24%, Diabetes 13%, Chronic Cardiovascular Disease 14%, Neurocognitive Disorder 15%, Neuromuscular Disorder 11%, Pregnant 8%, Seizure Disorder 7%, Morbid Obesity 11%, Obesity 34%, Other Serious (hepatic, cancer, immunosuppressed) 13%. There have also been 5 deaths among pregnant women, of whom 4 were in their 20s. They died at various stages in their pregnancies: 1 in the first trimester, 1 in the second trimester, and 3 in the third trimester. For the most part, underlying conditions in these women are unknown. However, several of them had no underlying conditions.

In conclusion, on April 15, 2009 a novel swine-origin influenza A H1N1 virus was identified in a boy in California. At the time of this meeting, there were 27,717 reported cases in the US and 55,000 reported worldwide. The majority of persons hospitalized and who died had underlying conditions. Given the rapidly evolving outbreak, more cases are expected and transmission will likely continue into the influenza season. At this point, it did not appear that transmission was declining at all. Surveillance plans include continuing enhanced surveillance throughout the summer; convening a CSTE and CDC working group to solidify surveillance plans for fall and winter; focusing less on case counts as they grow larger and become less representative because of testing practices; focusing on more severe outcomes, syndromic surveillance data, and laboratory data; continuing enhanced virologic surveillance; and developing revised screening recommendations and guidance for prioritization of laboratory testing with CSTE and APHL.

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Discussion

In terms of reporting out for the greatest percentage in the last couple of weeks, Dr. Morse inquired as to whether there was bias toward testing, given that selective testing was being conducted more for H1N1 and not as much for other strains.

Dr. Finelli responded that CDC conducted a survey of state health departments in May, at which time it did not appear that there was a bias. This survey does need to be repeated, but it appeared at the time of this meeting that laboratories were preferentially testing for H1N1 and not testing as widely for the other seasonal viruses. That could be responsible for the 97% positive rate for H1N1 and very little seasonal flu. However, little season flu occurs during the summer. Therefore, it could be a combination of both.

When age is corrected for, Dr. Judson wondered if diabetes (13%) and obesity (34%) were over-represented in the deaths.

Dr. Finelli responded that this appeared to be true. There were so many children in the hospitalization cohort, the rate of obesity appeared to be very low. She did not show that percentage during the presentation because she thought it should be stratified by age to determine a clear percentage. Most of those with diabetes were adults.

Dr Temte thought the information presented underscored the lack of good community-based surveillance in the US for issues outside of fairly significant events. He also observed that obesity stood out as a fairly new risk factor that had not been a characteristic risk factor for influenza in the past. There is very little data in the literature to explain why that could be a risk factor, other than the possibility of some cytokine interactions. He inquired as to whether CDC had examined immunization status for seasonal influenza vaccine in these patients in terms of whether there is any potential for cross-reactivity. In addition, he wondered how much confirmed disease was acute infection. In Wisconsin, primary care is seeing many people with mild illness. They are not testing, but he suspects a lot of it is respiratory viruses.

Dr. Finelli responded that through surveys, CDC in the process of examining the bottom of the pyramid of people who are mildly ill and may not seek care. With those data and other data combined from the surveillance systems, CDC is developing a model with multipliers to give them an idea of the disease burden. They will be able to update that model on a regular basis to have an overall picture. Currently, CDC is estimating over a million cases in the US from that model. When there are more confirmed data, they will have more solid confidence limits. CDC initially examined vaccination status in these data, finding that the proportion of people vaccinated among those hospitalized looks like the proportion of people vaccinated among those hospitalized for flu every year. Among those with underlying conditions, it is higher than those with no underlying conditions. A couple of vaccination effectiveness studies were conducted, one among healthcare workers in Ohio and one among healthcare workers in Chicago in two Epi Aids. With very wide confidence limit, there appeared to be no protection from seasonal vaccine for H1N1. Regarding obesity, among the deaths, an extraordinary number of people with morbid obesity died. These individuals were in excess of 340 pounds. Lately, when CDC has been contacting the states to find out about deaths, they have been asking specific questions about obesity. In some studies going into the fall, CDC plans to examine height and weight on all patients hospitalized and patients with pneumonia to determine a quantitative measure of obesity. The data collected so far on hospitalization has just included a check box. It may be checked if the chart indicates that a patient is obese.

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Obesity is probably differentially ascertained and transcribed by providers. Thus, body mass index (BMI) should be used as a good measure of obesity, which CDC plans to do in the fall.

Dr. Baker was impressed by the burden of seasonal influenza, which can be prevented. She expressed her hope that the ACIP and public health in general would emphasize the need to prevent seasonal influenza by starting early as soon as vaccine supply is available and thinking about novel ways to get the message out to providers and the public.

Dr. Meissner asked Dr. Finelli to speculate on when H1N1 first began to circulate. The first confirmed isolates were in mid-April; however, testing is not usually conducted at the end of the influenza season.

Dr. Finelli responded that she preferred not to speculate on that, given that it was not her area of expertise. However, there was a late influenza season this year and there was more testing in April than usually because the season did not get into full swing until the second week of February. The two cases were picked up in ILI Net in CDC sentinel surveillance system. In examining syndromic surveillance data, there did not appear to be widespread disease anywhere else before these two cases were picked up. Therefore, she thought CDC's surveillance system did do its job. Both of these cases were picked up in sentinel providers that are part of the Navy. They have very good labs and conduct a great deal of testing. Because Novel Influenza A Virus is a reportable disease, state health departments do typing for Influenza A on a routine basis and send CDC data on any that are not sub-typable. CDC received several of these over approximately six months that were triple-reassortant swine, which CDC investigated. However, they received no viruses in the lab that were never typed that were not sub-typable in January or February. They heard about focal outbreaks of ILI and viral syndrome in Mexico the week preceding the discovery of the two cases and were curious with regard to whether the two cases were related to what was occurring in Mexico. At that time, CDC has information from its colleagues that there were organisms or viruses identified for the various outbreaks, so the agency had a "stay tuned" attitude.

In the 0 to 4 age group, Dr. Neuzil encouraged CDC to separate out some of the younger ages, particularly those under 6 months of age because that has a policy implication. For seasonal vaccine, there is no vaccine license. Potentially for the new vaccine, studies could be conducted to examine whether that younger age group is important. In addition, there will not be any maternal antibody for newborns. Therefore, even if they have some protection from seasonal flu, they are unlikely to have any protection from the novel influenza. With that in mind, she asked Dr. Finelli to comment on whether there was heterogeneity in the hospitalization rates for the 0 to 4 age group.

Dr. Finelli responded that CDC has some data on children under 6 months of age; however, she did not recall whether they had any significant underlying conditions. Certainly, children less than 24 months of age had very few underlying conditions.

Dr. Neuzil clarified that she also wondered whether the rates were higher. For seasonal flu, dividing 0 to 4 by finer age strata would result in a 10 times difference. That is, those younger than 1 year of age have 10 times higher rates than 3 to 4 year olds. She was curious whether this was also true with respect to H1N1.

Dr. Finelli responded that CDC had conducted such an analysis, and that as she recalled the highest rates were in children less than 6 months of age.

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Dr. Beck noticed that the age distribution for H1N1 was somewhat different than for seasonal influenza. He wondered if CDC had any comparative data from outside the US regarding whether the flu in other locations was following the same pattern as in the US, and how the clinical characteristics were similar or different.

Dr. Finelli replied that she did not have data with her pertaining to other countries.

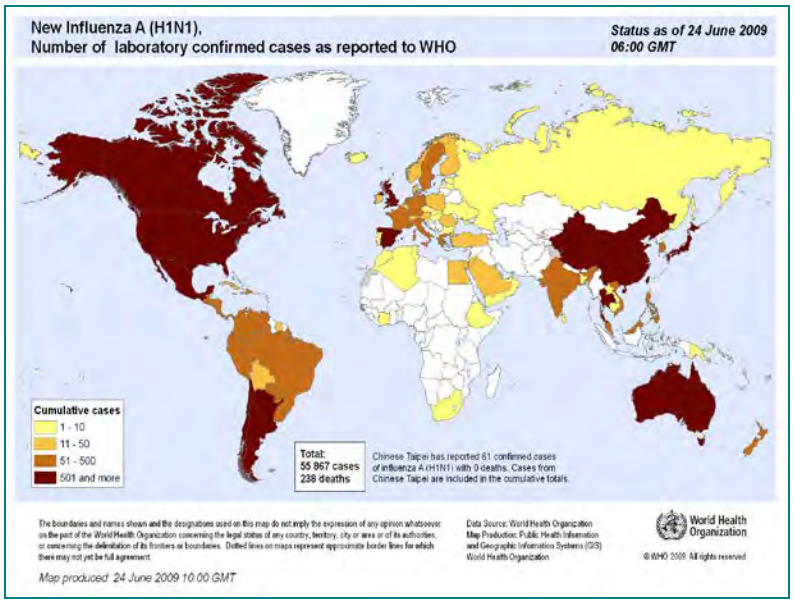
Regarding the secondary attack rate, Ms. Stinchfield (NAPNAP) requested additional information regarding the definitions being used to distinguish the respiratory component in ARI versus ILI.

Dr. Finelli responded that ILI includes fever with cough or sore throat, while ARI was any two of five symptoms (rhinorrhea, cough, fever, sore throat, coryza).

Influenza Antiviral Medications

Anthony Fiore, MD, MPH
Influenza Division, NCIRD, CDC

With regard to information from other countries, Dr. Fiore shared the following map from the World Health Organization (WHO) website illustrating cumulative cases according to country. North America had over 500 cases as of 24 Jun 2009, while across the Southern Hemisphere there were many cases in countries entering their typical influenza seasons (e.g., Argentina, Australia, Chile, et cetera).



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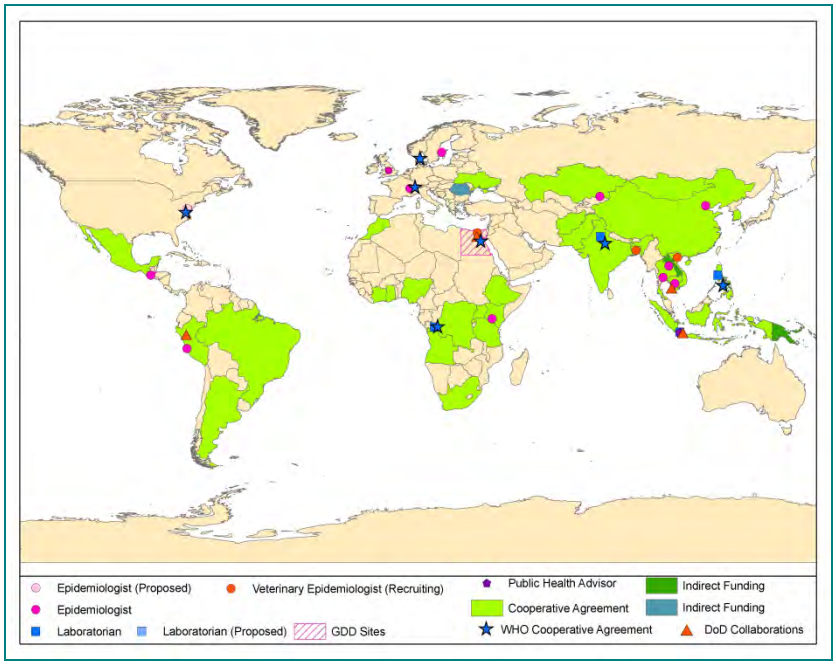
In terms of epidemiologic data that could be expected from countries with June to September influenza seasons, there are respiratory syndrome surveillance systems with influenza programs in 32 countries that have been built over last five years with pandemic preparedness funding. Most of these countries have improved laboratory capacity, and CDC has provided reagents to them to assist them in laboratory testing. The types of disease surveillance information they are capable of providing to CDC include ILI, severe acute respiratory illness (SARI), and ILI or SARI with lab confirmation. The following map illustrates where CDC personnel and influenza study sites are located throughout the world in 2009. A number of sites are located in the Southern Hemisphere in tropical areas where there is influenza circulation during June through September. CDC hopes to be able to use the existing platforms in these areas to acquire information over the next few months:



The most established information CDC receives from countries throughout the world come from the WHO Global Surveillance Network, which is a viral surveillance network that was established in 1952. The backbone of this system is the four WHO Collaborating Centres (WHO CCs), which are located in Atlanta, Japan, Australia, and the United Kingdom. These collaborating centres receive information from the National Influenza Centres (NICs). Currently, there are 126 NIC institutions in 97 countries that are recognized by WHO. NICs collect specimens in their country of approximately 175,000 patient samples annually according to the WHO website; perform primary virus isolation and preliminary antigenic characterization; and ship newly isolated strains to WHO CCs for high level antigenic, genetic, and antiviral sensitivity analyses (n=approximately 2,000 viruses sent annually to the WHO CCs). There are 25 NICs in the Southern Hemisphere, which are expected to receive viruses over the next several months. Additional NICs in countries in the Northern Hemisphere with circulation during June through September include Thailand, Bangladesh, and Central America.

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Pertaining to information expected from surveillance in countries with June through September influenza virus circulation, the most important questions six weeks before this meeting regarded whether the pandemic virus would continue to circulate. The answer to this question is a resounding "yes." Preliminary, it appears that pandemic viruses are circulating at the same time as other influenza viruses. Information has been received from Australia that H3N1 circulation has been observed. Regarding whether viruses are changing, CDC will be using the viral surveillance plans that are in place to collect these and characterize them. No changes had been observed at this time among the pandemic H1 viruses examined to date. This will be an on-going focus of study. In terms of whether the epidemiologic parameters are changing (e.g., attack rate, incubation period, et cetera), it will be difficult to obtain representative data in most countries observing current circulation. It is important remember that with on-going outbreaks in the US, there could still be a considerable amount of good data. Concerning whether the clinical manifestations are changing (e.g., severity, secondary infections), data are difficult to acquire in the US and other countries given different healthcare parameters. Obtaining viruses from unusual or severe cases is feasible to determine whether the viruses are changing. It will be possible to study whether community mitigation interventions are working in the US and other countries. These will be ecologic studies and they will be challenging to interpret. The bottom line is that there are a lot of data to examine in the US and CDC will do their best to acquire data from countries that have influenza viruses in circulation, especially from countries with co-circulation.

Turning to the ACIP antiviral recommendations, Dr. Fiore reviewed previous discussions and workgroup considerations, presented an antiviral resistance update, and explained the draft treatment and chemoprophylaxis recommendations for seasonal and pandemic influenza. In most previous years, vaccine and antiviral recommendations were approved and published together as a package. The vaccination recommendations were voted on during the February 2009 ACIP meeting and were soon expected to be published in the *MMWR*. The workgroup recommendation in February 2009 was that further assessment was needed of emerging oseltamivir resistance among seasonal influenza A (H1N1) viruses. The workgroup's recommendation was to separate the antiviral recommendations from the vaccine recommendations for the 2009-10 season and a vote was proposed for the June 2009 ACIP meeting.

The workgroup discussions from February to June 2009 examined a variety of topics. Dr. Fiore explained that the proposed recommendation reflected the workgroup's consideration of the experience with the 2008-09 influenza season and patterns of antiviral susceptibility; recent recommendations from other groups (e.g., Infectious Diseases Society of America, American Academy of Pediatrics, World Health Organization); information from antiviral experts and FDA colleagues who participated in workgroup calls; and pandemic influenza A (H1N1) clinical and epidemiologic features.

Regarding resistance to antivirals among seasonal influenza viruses in the US since October 2009, 970 of 975 (>99%) seasonal influenza A (H1N1) viruses tested were resistant to oseltamivir. All influenza A (H1N1) viruses were sensitive to zanamivir, while >99% of H1N1 viruses that were resistant to oseltamivir were sensitive to adamantanes (e.g., rimantadine and amantadine). All 169 influenza A (H3N2) viruses were sensitive to oseltamivir and zanamivir and were resistant to adamantanes. All 508 influenza B viruses tested were sensitive to oseltamivir and zanamivir. With respect to antiviral resistance among novel influenza A (H1N1) viruses in the US since April 17, 2009 all pandemic H1N1 viruses tested were sensitive to oseltamivir and zanamivir (n=184) and resistant to adamantanes (n=141). A summary of antiviral resistance during the 2008-2009 season is reflected in the following table:

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INFLUENZA VIRUSES				
Antiviral	**Seasonal H1N1**	**H3N2**	**B**	**Pandemic H1N1**
Adamantanes	Susceptible	Resistant	Resistant	Resistant
Oseltamivir	Resistant	Susceptible	Susceptible	Susceptible
Zanamivir	Susceptible	Susceptible	Susceptible	Susceptible

A number of key assumptions went into the development of the draft recommendations for antiviral agents for the prevention and control of influenza: Seasonal influenza viruses and pandemic H1N1 might have overlapping seasons. There is an inability to determine virus subtype or antiviral susceptibility in clinical settings, which makes clinical management challenging. Most antiviral treatment is empiric, given that clinicians cannot determine virus sub-type or antiviral susceptibility in a clinical setting in a way that helps with clinical management, at least in the first few days. Oseltamivir resistance among influenza seasonal A(H1N) is not associated with differences in clinical presentation or risk factors for illness. Influenza testing might be helpful, particularly if influenza B is identified. Viral surveillance data that includes influenza A subtypes might be helpful, but are often unavailable or not timely. Additional revisions of antiviral recommendations might be needed depending upon influenza virus susceptibility, influenza epidemiology and virus surveillance data, and antiviral supply.

Regarding the antiviral treatment recommendations, antiviral treatment should be started as soon as possible after illness onset. Persons for whom antiviral treatment should be considered include: those hospitalized with influenza, those with influenza viral pneumonia, those with influenza and complicating bacterial pneumonia, and those with influenza who are at higher risk for influenza complications, regardless of illness severity. Situations that merit consideration of chemoprophylaxis, and persons who should be considered for antiviral chemoprophylaxis in these situations, when influenza viruses are circulating in the community, include: Persons at higher risk for influenza complications for whom influenza vaccine is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are significantly immunocompromised); persons at higher risk for influenza complications during the two weeks after influenza vaccination (after the second dose for children aged <9 years who have not previously been vaccinated) when influenza viruses are already circulating in the community; or unvaccinated family members and close contacts (including health care workers) of persons at risk for influenza complications when influenza viruses are circulating. During an influenza outbreak in a closed institutional setting with high-risk residents (e.g., extended-care facilities) antiviral treatment should be considered for all residents, regardless of vaccination status, and unvaccinated staff. When one or more family members in a household develops suspected or confirmed influenza and chemoprophylaxis can be started within 48 hours of last exposure, this should include unvaccinated family members who are at higher risk for influenza complications. These chemoprophylaxis recommendations are somewhat reworded from last year, but are

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essentially the same groups of persons who have been recommended for chemoprophylaxis in the past several antiviral recommendations from ACIP. These boxes have footnotes, given that some information needs to be further explained.

The footnote for the Treatment Recommendations Box would include the following:

- Recommended antiviral medications (neuraminidase inhibitors) are not licensed for chemoprophylaxis of children aged <1 year (oseltamivir) or aged <5years (zanamivir).
- A recent Emergency Use Authorization provides information on use of oseltamivir for children aged younger than 1 year (see Table 4). There has been recent Emergency Use Authorization directed at use for pandemic H1N1 that provides information on use of oseltamivir for children younger than 1 year of age.
- Some experts prefer weight-based dosing for children aged <1 year, particularly for very young or premature infants.
- When using weight-based dosing for infants aged <1 year for chemoprophylaxis, those aged 9-11 months should receive 3.5 mg/kg/dose BID, and those aged <9 months should receive 3.0 mg/kg/dose BID.
- Updates or supplements to these recommendations (e.g., expanded age or risk group indications for currently licensed vaccines) might be required.
- Healthcare providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information.

The footnote for the Chemoprophylaxis Recommendations Box would include the following, with differences from treatment recommendations noted in bold:

- Recommended antiviral medications (neuraminidase inhibitors) are not licensed for chemoprophylaxis of children aged <1 year (oseltamivir) or aged <**5** years (zanamivir).
- A recent Emergency Use Authorization provides information on use of oseltamivir for children aged younger than 1 year (see Table **5**).
- Some experts prefer weight-based dosing for children aged <1 year, particularly for very young or premature infants.
- When using weight-based dosing for infants aged <1 year for chemoprophylaxis, those aged 9-11 months should receive 3.5 mg/kg/dose **QD**, and those aged <9 months should receive 3.0 mg/kg/dose **QD.**
- Updates or supplements to these recommendations (e.g., expanded age or risk group indications for currently licensed vaccines) might be required.
- Healthcare providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information.

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The recommendations for the selection of antiviral treatment are reflected in Table 3. The looks exactly like the guidance that was provided by CDC in December 2008 when first dealing with the problem of oseltamivir resistance. The footnote recommends consulting local virus surveillance data. For example, in the current situation just seeing pandemic H1N1 practitioners are selection oseltamivir or zanamivir and not using amantadine because there are no seasonal viruses being seen at this point.

Table 3. Recommendations for the selection of antiviral treatment using laboratory test results, United States, 2009-10 season*

RAPID ANTIGEN, RT-PCR OR OTHER LABORATORY TEST	PREFERRED MEDICATION(S)	ALTERNATIVE (COMBINATION ANTIVIRAL TREATMENT)
Not done or negative, but clinical suspicion for influenza	Zanamivir	Oseltamivir + Rimantadine
Positive A	Zanamivir	Oseltamivir + Rimantadine
Positive A+B	Zanamivir	Oseltamivir + Rimantadine
Positive seasonal A(H1N1)	Zanamivir	Oseltamivir + Rimantadine
Positive A(H3N2), pandemic A(H1N1), or B	Oseltamivir or Zanamivir	None

Local virus surveillance data should be consulted. Amantadine can be substituted for rimantadine but has increased risk of adverse events. Data on the effectiveness and safety of combination antiviral treatment of influenza are limited.

Table 4 provides the information from the Emergency Use Authorization that was intended for use with novel influenza H1N1 now called pandemic H1N1. This describes the recommendation for treatment according to age.

TABLE 4. DOSING RECOMMENDATIONS FOR ANTIVIRAL TREATMENT OF CHILDREN YOUNGER THAN 1 YEAR WITH SUSPECTED OR CONFIRMED NOVEL INFLUENZA A (H1N1) USING OSELTAMIVIR.*

Age	Recommended treatment dose for 5 days
<3 months	12 mg twice daily
3-5 months	20 mg twice daily
6-11 months	25 mg twice daily

*This Emergency Use Authorization was issued by the Food and Drug Administration on April 28, 2009, for a period of 1 year. While this EUA was intended for use as guidance to clinicians who were considering treatment of infants aged <1 year. However, seasonal influenza A(H3N2) and B viruses have similar sensitivity to oseltamivir. As of June 2009, nearly all seasonal influenza A(H1N1) viruses were resistant to oseltamivir.

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Table 5 addresses antiviral chemoprophylaxis recommendations, which are essentially half the frequency of the same dose (e.g., given once per day versus twice per day). For 3 month olds, FDA did not give a dose because so little data were provided and the risk-benefit for chemoprophylaxis as compared to treatment is somewhat different.

TABLE 5. DOSING RECOMMENDATIONS FOR ANTIVIRAL CHEMOPROPHYLAXIS OF CHILDREN YOUNGER THAN 1 YEAR WITH SUSPECTED OR CONFIRMED NOVEL INFLUENZA A (H1N1) USING OSELTAMIVIR.*

Age	**Recommended prophylaxis dose for 10 days**
<3 months	Not recommended unless situation judged critical due to limited data on use in this age group
3-5 months	20 mg once daily
6-11 months	25 mg once daily

*This Emergency Use Authorization was issued by the Food and Drug Administration on April 28, 2009, for a period of 1 year. While this EUA was intended for use as guidance to clinicians who were considering treatment of infants aged <1 year. However, seasonal influenza A(H3N2) and B viruses have similar sensitivity to oseltamivir. As of June 2009, nearly all seasonal influenza A(H1N1) viruses were resistant to oseltamivir.

The last component of the recommendations that are proposed to be somewhat different this year compared to last year is that some consideration is given to treatment considerations for severely ill patients. Altered regimens might be required in terms of longer duration, higher dosage, and / or alternative routes of administration. In the recommendations, none of these is endorsed, but references are provided for further guidance. In addition, information is provided to indicate that investigational drugs or alternative formulations of licensed medications might be available.

Dr. Fiore summarized that pandemic influenza H1N1 viruses have the same susceptibility profile as influenza A (H3N2) and influenza B (sensitive only to oseltamivir or zanamivir). Oseltamivir resistance among seasonal influenza A(H1N1) viruses limits antiviral options. All currently circulating viruses are sensitive to zanamivir, although various considerations limit its use. Most treatment is empiric. Zanamivir OR oseltamivir + an amantadine are recommended when oseltamivir-resistant viruses are circulating. Empiric treatment recommendations are the same as current CDC guidance (December 2008) and current IDSA guidance (March 2009) for seasonal influenza. There is a focus on treating hospitalized patients or those with an age or medical risk factor for more severe illness. The recommendations may require revision as the season progresses.

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Discussion

Dr. Baker found it very ironic that infants 6 to 12 months of age are never evaluated for certain vaccines / antivirals, but then suddenly there is an Emergency Use Authorization and dosing schedule. With that in mind, she suggested that in the future perhaps they could be more thoughtful in that area. She expressed her hope that the dosing recommendations were not made up, and requested further information regarding what pharmacokinetic and safety studies had been conducted to provide assurance that there will be very safe treatments or chemoprophylaxis for infants less than 1 year of age.

Dr. Fiore responded that David Kimberlin would be the best resource for this, given that he is one of the principal investigators on the studies from which the weight-based dosing was derived.

Dr. Kimberlin (AAP) replied that there are on-going studies being conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group that have been evaluating treatment doses of oseltamivir using an age de-escalation weight-based approach with targeted AUCs. These studies have been underway for three seasons. There are data for children between 3 months through 11 months of age. Until the Emergency Use Authorization was published, they had not gone down to the 0 to 2-month age group, so there is definitely extrapolation in that recommendation. The way CDC and FDA used those data, which were provided to them in the full dataset, and adjusted it to an age-based as compared to weight-based type approach had implications of how it would be applied across a programmatic scale. Certainly, there are data available. The data that were provided to CDC, FDA, and agencies throughout the world have been submitted to IDSA and are expected to be presented there. As more data are gathered, they may soon be able to publish a more comprehensive preliminary picture. For example, there is a recent dataset of babies in a neonatal ICU who were exposed to novel H1N1. The investigators were able to acquire blood samples, which these will soon be examined for an oseltamivir concentration determination.

Dr. Baker requested further information about the N in each of the boxes (e.g., how many patients have been studied for pharmacokinetic and safety).

Dr. Kimberlin (AAP) responded that no problems have been observed with safety. However, the numbers are relatively small. For the 6 month through 8 month age group, 15 subjects have been studied; 7 for the 9 month through 11 month age group; and 5 or 6 for the 3 month through 5 month age group. Since the ages were opened up through the Emergency Use Authorization and all cohorts by age were enrolled, there are also several 0 through 2 month olds. This is an AUC-targeted design, so the investigators knew what the target range was. For all of the children under 1 year of age, they began with 3 mg/kg/dose given twice per day as the dose being evaluated. The 9 month through 11 month age group were below the target range, which is why they were adjusted up to 3.5 mg/kg/dose. This is an on-going study, so at this time this is the best information available but it is probably not the final answer.

Dr. Baker stressed that she was not making a criticism about the Collaborative Antiviral Study Group, but was instead merely pointing out that this spoke volumes about the insufficient data available.

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With regard to novel H1N1, the chemoprophylaxis recommendations struck Dr. Cieslak as being impractical or obsolete. Based on the recommendation, a major percentage of the American public would be prophylaxed indefinitely into the future. Even for the highest risk people, it seems to say that while the virus is circulating, unlike the usual season there does not appear to be any end in sight with H1N1, so it could be interpreted as prophylaxis for a year.

Dr. Fiore responded that the preamble in the box outlines circumstances under which this would be done. They are not a full recommendation to *always* use chemoprophylaxis. This is somewhat a backing down from the pandemic H1N1 recommendation currently posted on the web. They are faced with a situation in which they have to balance between recommending prophylaxis for a very narrow group with a drug that is licensed that works quite well, with the desire to provide the option for prophylaxis in situations that are somewhat difficult to predict from a recommendations point of view. The attempt here was to prioritize the types of situations in which chemoprophylaxis might be considered. He agreed that if taken literally as a full-scale recommendation to provide prophylaxis to every person, it would involve a significant number of people. There are no safety data for a year of prophylaxis, and as the recommendations were developed, they probably did not fully anticipate that the virus would continue to circulate as much as it has over the summer.

Dr. Cieslak suggested that this needed to be addressed before voting for the recommendation.

Dr. Fiore requested suggestions for how to narrow this down. This was a very challenging recommendation for the workgroup to develop (e.g., to specifically recommend prophylaxis for one small group or to open it up to other situations in which prophylaxis might be considered).

As part of the workgroup and director of a bone marrow transplant unit with multiple people in the hospital, multiple people on ventilators, and H1N1 circulating, Dr. Englund was not willing to put a stop to prophylaxis in high risk patients. However, she thought that these antiviral issues needed to be re-addressed in August or September before it is anticipated that the flu season will begin again. She agreed with Dr. Cieslak, but was not willing to recommend stopping treatment in high risk groups while the virus continues to circulate. Perhaps they could add the phrase “while virus is circulating” because prophylaxis should not be used when virus is not circulating.

Dr. Neuzil agreed that it was very challenging for the workgroup. In the same way that ACIP likes to make recommendations early so that providers can order vaccine and prepare, the workgroup wanted to get something out for that same reason. They fully expect that this situation will have to be continually re-assessed and interim guidance will have to be offered. CDC set a very good precedent from the beginning with the communication message that this outbreak is evolving and with it the guidance must evolve. She said that while the workgroup was open to revision of the language, she did not think the workgroup thought that people would be receiving prophylaxis for 8 to 9 months at a time. Bone marrow transplants are a very specific, very high risk group.

Related to the potential volume for whom prophylaxis might be used, Dr. Sawyer requested information about what the status of the supply of antivirals was expected to be.

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Christine Hahn (CSTE) expressed confusion with regard to what would be used for prophylaxis (e.g., seasonal flu, pandemic flu, or both). She did not see any drug recommendations, nor was it clear what the intent was for the antiviral recommendation. Given that some people may not be able to tolerate long-term prophylaxis, she wondered if there would be a table just for chemoprophylaxis to address the preferred antiviral in various situations. For example, a household is probably going to be treated based on how the contact has been treated. If the contact is determined to have seasonal influenza, it would seem that the prophylaxis would be switched to match that to protect against a particular household exposure. Thus, there seemed to be considerations with respect to contacts that might need to be considered.

Dr. Fiore responded that if both viruses were circulating and there continued to be oseltamivir resistance in the seasonal H1N1s, prophylaxis would preferentially be done with zanamivir. It sounded to Dr. Fiore that some language needed to be added with regard to how one might approach a prophylaxis situation and might change it over time if the virus is identified for the original source patient, such as in an outbreak.

It seemed to Dr. Judson that there was a clear understanding of what antivirals are available, what the costs-benefits are, and that there are almost dichotomous outcomes for the various drugs against the sizable group of viruses that were tested. Therefore, he thought they had most of the information they were likely to have for the next few months.

Dr. Cieslak thought that as written, the guidelines were a “dead letter” and that Oregon would certainly not follow them. With the situation in flux, he thought it would be preferable at this point to say that chemoprophylaxis is up to the provider and that the CDC website should be monitored for further guidance. He thought something that vague and non-leading would be preferable to the recommendation suggested.

Amy Middleman (SAM) inquired as to whether there were any cost-effectiveness analyses that could help to guide which groups would be the most important to target.

Dr. Fiore responded that there are some cost-effectiveness analyses for seasonal viruses. He reiterated that the chemoprophylaxis recommendations before the committee at this time were essentially the same that had been in place for the last couple of years, although pandemic H1N1 did not have to be dealt with. However, there were certainly situations in which large numbers of people might be affected in an early influenza season, with an uncertain vaccine match, groups of people not expected to respond to the vaccine or who did not receive it, et cetera. Chemoprophylaxis is probably used infrequently and with the new focus on pandemic H1N1, chemoprophylaxis would be considered much more than in the past.

James Turner (ACHA) indicated that a consideration in the college health setting with their living conditions is perhaps being more aggressive treating an index case with antivirals, hoping to keep them from shedding the virus and then not having to chemoprophylax the entire dormitory. He wondered if discussion about index cases would be beneficial. While he understood that they wanted to limit chemoprophylaxis to high risk groups, depending upon the living environment, it may be more cost-effective to treat index cases aggressively. In addition, his impression was that the rapid antigen tests currently available at the point of care were not FDA approved for novel H1N1 testing.

Dr. Fiore replied that the rapid antigen tests were approved for seasonal influenza, not H1N1. In terms of prophylaxing an entire dorm, that would not be a recommendation because most would not likely have underlying illnesses that would put them at risk.

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James Turner (ACHA) pointed out that these students may have elderly frail parents who they could expose, they volunteer in nursing homes and schools, et cetera. The concentric circles become enormous around these students.

Dr. Julie Morita (Chicago Department of Public Health) pointed out that Chicago, being a relative hotbed of novel influenza activity, would find the chemoprophylaxis recommendations to be very useful. They had to create their own recommendations, so it would be beneficial to have ACIP's recommendations in support of their own. They do not have the sense that novel influenza is declining in Chicago. She extended Chicago's gratitude to CDC for all of the support they received in the beginning phases of this pandemic. There were several teams of EIS Officers and other medical epidemiologists who were extremely helpful and valuable to Chicago.

Dr. Baker disagreed with Dr. Cieslak, recognizing that Oregon and other states would be likely to do whatever they believe is best. However, given the media attention ACIP needs to make some recommendations with a strong caveat that these will probably be changing. If they do not continue to give guidance, they will not being doing their job.

Dr. Morse requested that the issue of supply be addressed.

Andrew Leone (GSK) indicated that at this point, GSK had reactivated all of its global sites. They have annual capacity of approximately 55 to 60 million courses of RELENZA ®. In the US, they have the capacity to produce approximately 1.6 million courses per month and is committed to producing throughout 2009. Thus, they anticipate ample supply for the upcoming influenza season.

Dr. Fiore indicated that there has not been a shortage in supply of oseltamivir through Roche and that the predominant drug in the US stockpile is also oseltamivir.

With respect to the issue of increasing resistance, Dr. Meissner requested information on the status of Peramivir and whether it was expected to be active against oseltamivir-resistant H1N1 season strain and the novel strain.

Dr. Fiore responded that the neuraminidase inhibitor, Peramivir, from BioCryst Pharmaceuticals is currently in Phase 2 trials and is currently available under an investigational new drug (IND). The advantage of this drug is that it can be given intravenously or intramuscularly. There are several thousand treatment courses available. It is active against the circulating influenza viruses. He thought it might have intermediate to full activity against the resistant seasonal H1N1s. The activity is different from zanamivir. Further information can be acquired from the FDA's and manufacturers' websites. Intramuscular Peramivir might come into play if severe infections are observed in the fall or winter for which the licensed drugs are not effective or cannot be used for some reason.

Regarding the chemoprophylaxis considerations, Dr. Sumaya said he could understand beginning prophylaxis when a member in a household has influenza or in the closed institutional setting. However, he was somewhat unclear what was encompassed by the statement "when influenza viruses are circulating in the community" and what parameters would trigger the recommendation should provide prophylaxis.

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Dr. Fiore responded that the recommendations do not include a trigger point for beginning chemoprophylaxis. Instead, practitioners should look to their state health departments for data on ILI visits, et cetera. It is very difficult to write recommendations to fit all scenarios. The purpose of the chemoprophylaxis box, which certainly had attracted the most attention during this meeting, was to offer permission as it were for people to think about the use of chemoprophylaxis in certain situations.

Danuta Skowronski (Canada) suggested that because the chemoprophylaxis recommendation was causing so much angst whether a compromise might be to provide a prescription for early treatment for those at high risk that they could have filled at the earliest sign of symptoms. That would reduce the amount of drugs required and conserve them for those who really need them.

Dr. Neuzil responded that she did not recall the working group discussing this specifically, but they discussed it extensively in the group who co-wrote the IDSA recommendations. Certainly, other professional groups have weighed in against that because there are a number of problems with this (e.g., potential supply problems, potentially using the prescription at the wrong time). She referred everyone to the IDSA and other documents to answer the question regarding why the ACIP working group did not consider that option.

Jane R. Zucker, MD (New York City Department of Health) commented about the availability of antivirals, specifically as it related to the different formulations. New York City Department of Health's experience was that there was an ample supply of the 75 mg capsules of oseltamivir, but not of the 30 mg and 45 mg capsules. They had particular problems with the availability of pediatric suspension with either short dating or pharmacies having difficulty with the supply and distributors. New York City sent communications out to pharmacies about the compounding of the capsules into the pediatric suspension. They also conducted a survey among their pharmacies, in which they learned that many of the pharmacies were not prepared to compound, although it is part of their training. Therefore, the specific request for CDC / ACIP in terms of looking at the antiviral supply is to ensure that there are ample plans in place with distribution and oversight of that, particularly for the pediatric formulations. Communication with pharmacists about compounding capsules into the correct suspension dosage is a very important part of the planning as well.

Regarding prophylaxis, it seemed to Alan Hinman that one of the issues may be that there are highly limited data pertaining to the efficacy or safety of prolonged administration of chemoprophylaxis.

Dr. Fiore responded that this was correct.

Dr. Cieslak said his issue was that the recommendations were written with the understanding that most high risk people would be vaccinated, and they call for prophylaxis either in the absence of vaccination or until a vaccine can take effect. The recommendation seems to presuppose a typical influenza season. Neither of those is operative currently.

Alan Hinman thought it sounded as though there was a desire to have a statement that one should consider chemoprophylaxis, which is a statement that has been issued in the past, and also a concern that with the continuing circulation of the novel H1N1, the circumstances are different—the virus is not necessarily passing through a community over a three to four week period. He wondered whether it would be feasible to leave the box as is and add to it a statement that "there are no or limited data on the safety or efficacy of chemoprophylaxis carried out over X period of time."

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Samual Katz (IDSA) indicated that all of the data were reviewed with regard to the IDSA guidelines, and the efficacy data for prophylaxis were found to be quite robust and consistent. One issue regards emergence of amantadine or rimantadine resistance when the index case is treated, which probably does not need to be addressed specifically. The safety data go up to six weeks for all four drugs, based on several hundred patients in randomized controlled trials (RCTs). Beyond that, there are no data although there are some on-going trials in Southeast Asia.

Dr. Pickering relayed the following comments for Dr. Lett: 1) she agreed with Dr. Cieslak's comments regarding prophylaxis recommendations; and 2) she felt that Bullet 5 for treatment regarding persons with influenza at higher risk for influenza complications regardless of illness severity should receive antiviral treatment, which may have changed or morphed somewhat since the workgroup discussed it.

Dr. Robin Robinson (BARDA Director HHS) reported that HHS is in almost daily communications with the antiviral and vaccine manufacturers regarding their supplies. The numbers given by GSK were representative of what they communicated to HHS. Roche has communicated to HHS that they can provide 8 million treatment course per month through the remainder of 2009 from their Nutley, New Jersey facility. They have a larger global supply, but accessibility and availability of that could be problematic with the global needs going forward in the fall. BARDA also supports the contract for development of Peramivir with BioCryst Pharmaceuticals. The data thus far for Phase 2 clinical trials for intramuscular administration are not favorable to go forward. However, for intravenous administration BARDA is supporting their Phase 3 studies to go forward. They do not have a large amount of data that are supportive of severe cases thus far, although they will have data from a trial they have been conducting with BioCryst's partner in Japan, Shionogi & Co., Ltd., in August. That would be critical to consider that drug in infected individuals as opposed to uncomplicated cases.

Dr. Neuzil acknowledged that Dr. Cieslak had identified a very important discrepancy that originally they had a set of recommendations for antiviral use during seasonal influenza in which the assumptions is that the majority of the US population actually receives influenza vaccine, and that influenza vaccine is available in a timely manner. Looking at the pandemic plan, there is a separate set of recommendations on pandemic influenza treatment, prophylaxis, and vaccine that relates to availability. Perhaps what they had was a confluence of both of these in an unclear situation. Unlike the vaccine recommendations made for specific groups, the headline here is situations that merit consideration. Therefore, it was not a recommendation so much as it was a guidance. What is done in the fall will depend upon a number of factors that cannot be examined in isolation (e.g., vaccine and antiviral availability in relation to an outbreak). Perhaps they should craft the language around this to indicate that "the use of antivirals for chemoprophylaxis are dependent upon the availability of vaccines that match the circulating strain and the availability of antivirals." Further into the season, that would allow CDC and others involved in pandemic response to monitor these factors and then perhaps publish more definitive recommendations.

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Litjen Tan (AMA) pointed out that one thing which helped the working group get past this was the recognition that for the remainder of the summer it would be likely that what they would be dealing with would be the H1N1 pandemic strain. Therefore, these recommendations would be appropriate. However, they also discussed that as data begin to emerge, the guidelines would have to be revised. The group recognized that these guidelines would have to shift as the season moved forward.

Dr. Morse noted that most of the discussion had focused upon prophylaxis. With that in mind, he pointed out that there seemed to be a couple of options at this point: 1) they could proceed to approve the recommendations as proposed with some minor adjustments in the wording regarding prophylaxis on an interim basis and perhaps reconsider a time during which the issues could be revisited (perhaps during a summer meeting), or 2) address treatment only and leave prophylaxis in limbo for the remainder of the summer.

Dr. Neuzil clarified that there currently is guidance on the website, and that nothing in the proposed guidance contradicted that. Thus, there was no urgency to change it.

Dr. Fiore showed a slide indicating that it reflected the current guidance.

Dr. Cieslak pointed out that the slide said that this was “Interim guidance for infection control for care of patients” versus a broader recommendation about prophylaxis.

Dr. Fiore clarified that what he was showing was the antiviral recommendations and that the link in red was for healthcare personnel exposure to refer them to the guidance to determine whether they experienced significant exposure.

Dr. Cieslak indicated that he could support the recommendation if some language was included to the effect of “Typically prophylaxis is recommended for these persons in the setting of novel influenza for which there is no vaccine, and for which the season is not well-defined. Physicians will need to consider duration of prophylaxis and supplies.”

Dr. Englund thought the information on Table 3, which she thought was a new table, was very useful for those working in a clinic or hospital setting, as well as for anyone who has access to knowing whether their patient has influenza. While some practitioners would disagree because it suggests giving two antivirals, that is the protocol until the virus is identified. Many sites, centers, and state health departments do let physicians know what is going on on a regular basis, so she knows what is occurring in her community.

Dr. Fiore responded that the table was developed from interim guidance CDC published in 2008, which was adapted by adding pandemic A(H1N1) to the bottom of the first column.

Dr. Morse suggested potentially moving ahead with the treatment vote at this time, and further developing the wording for the prophylaxis recommendation offline.

William Schaffner (NFID) suggested putting “pandemic A(H1N1)” on a separate line as it was somewhat buried on the table as it stood.

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Motion: Treatment Guidelines Recommendation

Dr. Sawyer made a motion to approve the treatment guidelines as stated and for the group to develop compromise language for the prophylaxis recommendation by the next morning. The motion was seconded. The motion carried with 13 affirmative votes, 0 abstentions, 2 not present (Lett, Baker), and 0 negative votes.

At the end of the day, the committee revisited the antiviral prophylaxis issue. Dr. Neuzil indicated that during the break further information was obtained. As a model, the Red Book addresses treatment for influenza. It has only a very short paragraph regarding chemoprophylaxis, in which a website is referred to. Perhaps this is a good option, given that it is user-friendly and adaptable. If the group generally agreed, the working group would draft language that refers to a CDC website and disseminate to members separately for review.

Discussion

After discussion with Dr. Campos-Outcalt, Dr. Temte suggested that the prophylaxis section be divided into post-exposure and general chemoprophylaxis because they are separate issues and there is better evidence for one than the other.

Dr. Sawyer inquired as to whether ACIP or CDC would be responsible for the content of the website.

Dr. Fiore responded that upkeep of the website would be CDC's responsibility.

Dr. Neuzil stressed that it was termed as "guidance" versus "recommendation."

Motion: Antiviral Prophylaxis Guidelines Recommendation

Dr. Meissner made a motion to include a brief paragraph that defers the reader to CDC's website. The paragraph should also address the issue of chemoprophylaxis in the absence of a vaccine and in the absence of an anticipate cessation of influenza virus circulation. Dr. Baker seconded the motion. The motion carried with 13 affirmative votes, 0 abstentions, 2 not present (Lett, Judson), and 0 negative votes.

Novel Influenza A (H1N1) Vaccine Development and Progress

Robin Robinson, PhD
HHS / ASPR / BARDA Director

Dr. Robinson explained the 2009 US H1N1 vaccine strategy. The epidemiology of H1N1 suggests that it can be expected to persist throughout the summer, fall, and winter along with what is observed for seasonal influenza. The moment that the novel influenza virus became apparent, the US went into the normal pandemic preparedness mode of vaccine development of

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the strain. CDC engaged in isolating the strains, preparing the virus reference strains, and engaging in master virus seed preparation. Those strains (e.g., classical reassortants and reverse genetics reassortants) were essentially manufactured the last week of May, within a couple of days of the designated time and with the original plans and estimates for pandemic preparedness that had been done for H5N1. From there, the manufacturers began developing investigational lots to be moved into clinical studies in July. Vaccine manufacturing began at the same time the manufacturers received the reference viruses because they needed to start with commercial scale. It is known with new viruses that it takes a number of passages at commercial scale to move forward.

Through numerous inter-departmental discussions, the decision was made to use Tier 1 manufacturers, which are those manufacturers that have licensed seasonal influenza vaccine products, 4 which are inactivated and 1 which is live attenuated. In addition, if the severity of the pandemic were such that the transmissibility was so increased that a vaccine was needed for everyone as soon as possible, the adjuvant and bulk antigen would need to be made sooner than September. In anticipation of that and as part of the preparedness plans, they have gone forward with adjuvants. On May 27, 2009 Secretary Sebelius announced that HHS was moving forward not only with the vaccine development with the clinical studies, but also with the purchase of bulk antigen and bulk adjuvant for vulnerable populations, critical workforce, et cetera. Also needed are syringes and needles to move forward with a campaign, and vaccine administration activities must be addressed. Thus, some decisions have already been made while others will be made moving forward through the summer.

For H1N1 vaccines, HHS has been working from the *National Strategy for Pandemic Influenza* (Nov. 2005), the goal of which is to provide influenza vaccine to everyone in the US within 6 months of pandemic onset. The H1N1 Vaccine Strategy follows the pandemic playbook for vaccine development, production, and administration with multiple decisions and on / off ramps. With two exceptions, the playbook is in tact: 1) The pandemic did not begin in Southeast Asia or some other part of the world, but began in the Northern Hemisphere in North America; and 2) It was not clear whether there would be a distribution system or what that would be. An earlier advisory group from NVAC worked with state and local health officials to point out problems with the vaccine distribution system that was in place. Clinical studies will inform vaccine formulation and safety profile. The vaccine could be licensed as an antigen-alone formulation, which may be afforded as strain changes, or under pre-EUA packages in preparation for the vaccine with adjuvant. Unfortunately, manufacturers who worked very hard on this had not filed their BLAs yet with their H5N1 vaccines, so they are not licensed. While these are mature in their development, but they are not currently licensed in the US. Key decision issues include prioritization of vaccine for special populations (e.g., children, critical workforce, et cetera), vaccine type, Thimerosal preservative, oil-in-water adjuvant, and post-immunization adverse event safety monitoring.

The products from different manufacturers would include a standard antigen-alone formulation that would be in a multi-dose vial or a single dose syringe that would be Thimerosal-free or mixed with an adjuvant, either oil-in-water emulsion or with GSK (3.4%) it would be a combination of two vials with the adjuvant in one vial and the antigen to add to the vial from CSL (18.7%). From MedImmune (5.8%) would come the standard sprayer inhalation type of delivery system without adjuvant or Thimerosal. From GSK there would be a combination vaccine with their own antigen and adjuvant mixed at the beside. From sanofi pastuer (26.4%) there would be standard multi-dose vials, single dose syringes, Thimerosal-free without adjuvant. The adjuvant they would use is GSK ASO3 adjuvant mixed with their antigen. Novartis Vaccines (45.7%) will have a multi-dose vial standard without adjuvant or a single dose vial with the

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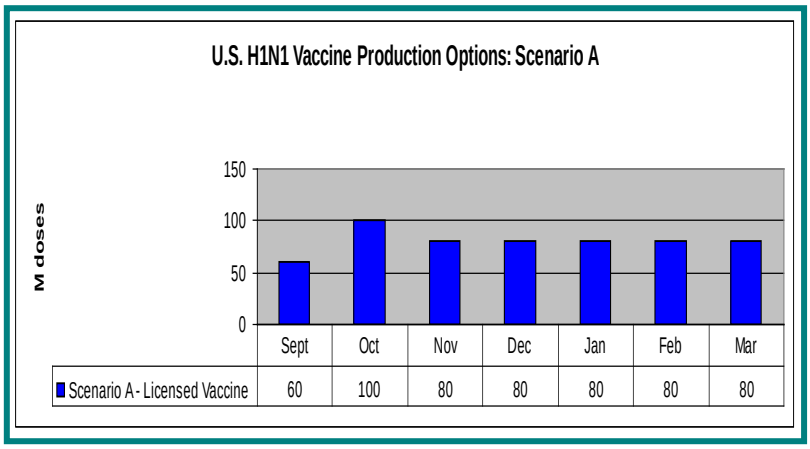
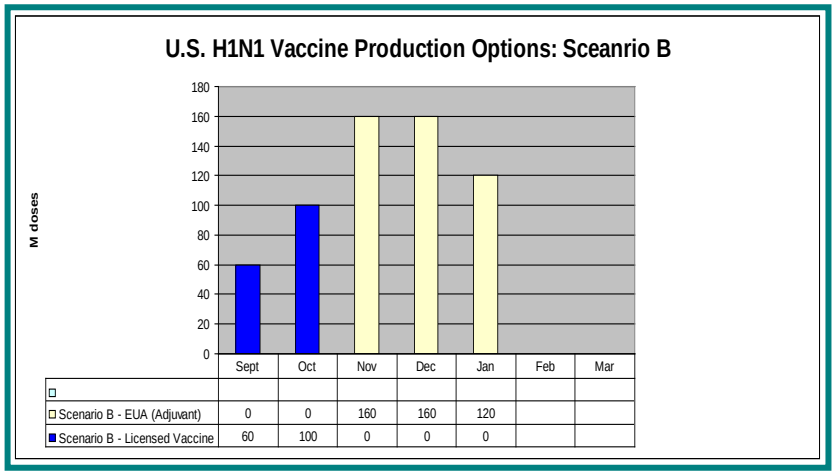
adjuvant pre-formulated. If the virus continues as it has thus far, Scenario A for licensed vaccine is anticipated for H1N1 vaccine products and output, illustrated as follows (although this had changed four times in the last few days):



If the pandemic is more severe and morbidity and mortality warrant the use of an adjuvant, Scenario B will be followed. In this case, the licensed vaccine can be available early and then shift to use of the adjuvant when support by clinical data:



Regarding H1N1 vaccine distribution options, CDC working with HHS, manufacturers, and others, is building the seasonal influenza vaccine distribution system already. With this systems, states order through a central CDC ordering system and then place orders with manufacturers moving forward. This was an adaptation that resulted from the 2004-05 influenza vaccine shortage. The five vaccine manufacturers would produce the product, send it to McKesson (with whom CDC currently has a contract), from which it would go to states. An attractive aspect of this model is that McKesson could receive vaccine, syringes, needles, and fact sheets from different manufacturers, package it all together, and send it each “ship to site.” Recipients would then receive everything ready to go to begin vaccinations. McKesson has approximately 30 to 50 distribution sites available throughout the country, and could be more if they contract with other wholesale distributors. Capacity is about 40,000 to 90,000 parcels per

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day. Part of this set-up was in response to assisting states in the current crunch. Ultimately, the desire would be to have this system available for 300 million people. Prioritization will depend upon severity of the disease, transmissibility, and whether drug resistance occurs.

FDA Recommendations for Clinical Evaluation of Novel H1N1 Vaccines

Norman W. Baylor, Ph.D.
Director, Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Dr. Baylor presented a high level overview of FDA evolution of novel H1N1 vaccines. He emphasized that the FDA is examining all options in an effort to provide a flexible regulatory approach, which allow availability of H1N1 vaccine as rapidly as needed. At the same time, the FDA must ensure safety and public confidence in the vaccines licensed by the FDA or permitted for use under Emergency Use Authorizations. FDA actions to address H1N1 vaccine have included developing needed pathways and regulatory processes to speed vaccine availability; assuring safety and public confidence; facilitating vaccine manufacturing and availability; addressing scientific and related technical needs (e.g., growing H1N1 virus and preparing reagents needed for production); enabling current and evolving technologies; and working with other global national regulatory authorities and the World Health Organization.

With respect to regulatory guidance, the regulatory pathway for H1N1 vaccines is similar to that of annual influenza vaccine. Dr. Baylor emphasized that a guidance document is posted on the FDA website. What this document was based upon in terms of evaluating pandemic influenza vaccines began with H5N1. Because there is more experience with H1 subtypes historical, the FDA believes that there can be somewhat more flexibility with H1N1. For H1N1 vaccines manufactured using US licensed processes, applicants must submit a new BLA for administrative purposes, but can cross-reference their existing BLA for the seasonal vaccine. A data package is required that is similar to a “strain change” with the addition of limited data from dose-ranging studies. Under a declared emergency, an Emergency Use Authorization may be pursued for products manufactured by an unlicensed manufacturing process, but whose benefits likely outweigh risks. Currently, none of the US-licensed influenza vaccines contain adjuvants.

The objectives for clinical evaluation of H1N1 vaccines primarily include: 1) dose-finding; rapid dose-finding necessitates a sample size adequate to assess the proportions of subjects that achieve the study endpoints; 2) safety evaluation (e.g., reactogenicity) and immunogenicity; and 3) investigational adjuvant evaluation to provide data on their utility in dose sparing and enhanced immunogenicity.

Concerning the clinical evaluation of H1N1 vaccines, the FDA recommends that subjects include healthy adults 18 to 64 years of age and >65 years of age, and children 6 months to 3 years of age and 3 years to 9 years of age. Also under discussion is whether an age group of 10 to 17 should be included or whether extrapolation can be done from the 3 to 9 year olds. Additionally, FDA is open to investigators who are considering conducting clinical studies involving children less than 6 months of age. The design must be randomized, double-blind, and controlled. The interventions include two intramuscular doses of H1N1 separated by 21 days and studying 7.5 mcg, 15 mcg, and 30 mcg doses. The endpoints include safety (e.g.,

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solicited and unsolicited adverse events) and immunogenicity (e.g., neutralizing titer of 1:40, which has historically been the target).

In terms of special considerations for clinical studies with adjuvants, manufacturers may consider multiple dose-ranging adjuvant arms: 3.8, 7.5, 15 mcg of hemoglobin antigen. FDA is trying to emphasize the added benefit of the adjuvant in that if there is no added benefit, there is no reason to include the adjuvant. Clinical studies may be conducted concurrently in the adult and pediatric age groups, with some exceptions. Subjects should be monitored for 12 months for serious adverse events (SAEs), deaths, and new onset of chronic medical conditions. This is primarily for those products with the novel adjuvants. Safety laboratory evaluations should be assessed at baseline and at early and late time points post-vaccination. The emphasis here is also on the adjuvanted products.

Regarding international collaboration, FDA is working with EMEA, Health Canada, and other international regulatory agencies to harmonize approaches to vaccine development, multiple regulatory requirements for vaccine manufacturing (e.g., “Consensus” Protocol), and post-authorization surveillance and risk management plans.

In summary, development of monovalent H1N1 inactivated or live attenuated vaccines using licensed manufacturing processes is the most straightforward approach; however, the FDA will evaluate other vaccine types. The FDA is using flexible regulatory approaches to expedite the availability of H1N1 vaccines. Given the unpredictable nature of the pandemic, the FDA will evaluate adjuvants and other antigen sparing strategies.

H1N1 Vaccine Trials: NIH Update

George Curlin, MD
OD / DMID / NIAID

Dr. Curlin explained that NIAID is the vaccine development extramural part of the NIH. With their institute, the Division of Microbiology and Infectious Diseases, is the principal focus for vaccine development and extramural funding to control and prevent infectious agents except HIV. Vaccine and Treatment Evaluation Units (VTEUs) is a consortium of individual contracts. NIH’s VTEUs were established in 1962. These are a ready resource for the conduct of clinical studies, which are located in academic centers and other organizations. There are eight sites throughout the US, including: Group Health Cooperative in Seattle, Children’s Hospital Medical Center in Cincinnati, University of Maryland in Baltimore, University of Iowa in Iowa City, Baylor College of Medicine in Houston, St. Louis University in St. Louis, Vanderbilt University in Nashville, and Emory University in Atlanta. There is a broad range of capabilities in the VTEUs: phase I, II, III, and IV trials; bacterial, viral, parasitic vaccines (novel delivery systems, compare formulations / dosing schedules), therapeutics, immunotherapeutics; and targeted surveillance studies. They also have access to a wide range of populations: healthy adults, elderly, pediatric populations, and special populations (e.g. immunocompromised, pregnant women). The VTEUs have conducted over 160 Phase I, II, and III clinical trials since 1995 of seasonal vaccines, pre-pandemic vaccines, and antivirals.

The initial steps in the H1N1 outbreak were for FDA, DMID, and BARDA to begin discussions on vaccine issues immediately. FDA engages in active discussions with manufacturers to develop core elements for clinical trials, receive proposals, and provide feedback. BARDA addresses the vaccine supply issues. NIAID’s role in the consortium is to provide the clinical

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trial data that supplements the large Phase III trials, which are the principle element and source of information for the products that they hope will be deployed in advance of the next epidemic.

NIAID's area of support specifically for H1N1 Vaccine Trials I is to assist licensed vaccine manufacturers in generating clinical data needed for licensure for more rapid availability of data in populations within a company's license, and to generate data in groups for which H1N1 vaccines may be used under Emergency Use Authorizations. NIAID is standing by to supplement the large scale trials with special trials to generate data in "special populations" (e.g., infants < 6 months of age, pregnant women, immunocompromised subjects). For H1N1 Vaccine Trials II, NIAID's role is to generate clinical data to help inform policy decisions and / or address "gap" areas: more efficient use of vaccines in different populations, compare different H1N1 vaccines using a standard assay, and assess "real world" scenarios for mass vaccination. For example, do shorter versus longer dosing intervals result in comparable immune responses presuming two doses are needed? Co-administration of TIV with H1N1 vaccines raises a series of issues that must be address (e.g., adjuvanted, unadjuvanted; inactivated, live-attenuated). NIAID will also address prime / boost with adjuvanted vaccines from different companies (AS03-H1N1, MF-59-H1N1). Another NIAID area of support for H1N1 Vaccine Trials III is to generate data on mixing stockpiled vaccine antigen and adjuvants from different manufacturers (e.g., GSK's AS03 adjuvant mixed prior to administration with CSL or sanofi H1N1 antigen vs. GSK antigen). Pre-clinical data are likely to be required prior to clinical trials.

Negotiations with FDA are on-going, as are discussions with other global regulatory groups and companies. NIAID has initiated contact with companies directly regarding vaccine availability and regulatory documents needed to mount clinical trials. NIAID is also developing the new assays and preparations are underway with the VTEU sites to address capacity, access to populations, et cetera. The first set of vaccine protocols were expected to be finalized within two weeks, with other sets to follow. The VTEUs had already developed specimen collection protocol, enrolling patients, positive control samples, assay development, research reagent, clinical outcome, sequencing, shedding, humoral and cellular responses, et cetera. The VTEU protocol to assess safety and immunogenicity of TIV in pregnant women enrolled the first subject the week before this ACIP meeting.

NVPO's Role and the Guidance on Allocating and Targeting Pandemic Influenza Vaccine

Dr. Bruce Gellin
National Vaccine Program Office

Dr. Gellin reported that last week when Secretary Sebelius met with Margaret Chan, one of her requests was that the information that is coming out of these clinical trials and the system (e.g., surveillance, biologic) be shared with WHO and others who will have to make similar decisions. Needless to say, the Secretary readily agreed to this. Many decisions have already been made, such as the decisions to begin vaccine production, the clinical trials, and a potential immunization program.

On May 22, 2009 the Secretary announced the purchase of an allotment of over $1 billion to begin the production of the vaccine ingredients to have an ample supply for the clinical trials, and to have the ingredients for antigens and adjuvants. On June 11, 2009 Secretary Sebelius and Secretary Duncan (Secretary of Education) sent a letter to Superintendents to begin to work with the Department of Education about what may occur in the fall. The letter addressed some of the contingencies schools need to deal with in the fall (e.g., dealing with ill children and

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faculty, conducting education if schools are disrupted, et cetera). On June 24, 2009 President Obama signed the supplemental appropriation for $7.65 billion to better prepare the country for what might occur in the fall. Broadly, those funds are to support the purchase of additional vaccine and antigen, prepare for a potential immunization program and its execution, and to broadly support public health measures to better prepare for preparedness and response. There are a number of federal advisory committees within HHS and other departments that have a piece of this. There have been a number of regularly scheduled meetings to address the issues, with many of the discussions addressing what each of the committees brings to the table given their process and expertise.

NVAC will examine overall program implementation and will take a specific look at the vaccine safety monitoring pieces of this. NCAC will convene monthly calls that will be considered official public meetings. A special working group will assess vaccine safety monitoring, looking at the national system—not just the HHS component, but also the components of the DoD and the VA. The National Biodefense Science Board has been in existence for approximately a year and a half. This advisory committee reports to the Secretary essentially on preparedness issues, and it has a Pandemic Influenza Working Group. This group will also be convening conference calls. Dr. Gellin encouraged people to participate in these calls to better understand everyone's roles and responsibilities, as well as the advice that they are giving to the departments. The DoD has its own system, the Defense Health Board and a subset of that. They have had a similar set of discussions about their preparedness for the military. The Department of Homeland Security has a committee called the National Infrastructure Advisory Council, which advises the President on critical infrastructure. This endeavor was begun by the Secretaries of HHS and the Department of Homeland Security who went jointly to this advisory council to ask them for help in identifying critical parties within the critical infrastructure, particularly in the setting of a severe pandemic when there would likely be absenteeism and disruption of schools, the economy, and society at large. The Department of Homeland Security provided a report that fed into this process "Guidance on Allocating & Targeting Pandemic Influenza Vaccine."

The "Guidance on Allocating & Targeting Pandemic Influenza Vaccine" speaks to some degree on the goal of developing and implementing a vaccine program. It is important to distinguish the goals to ensure vaccine preparedness and the amount of vaccine that has been sent forth that might potentially be needed as a country from the goals pertaining to an immunization program. Obviously, there cannot be an immunization program without a vaccine, but just because there is a goal of making a substantial amount of vaccine does not necessarily mean that it will be used.

Referring to the following chart, Dr. Gellin stressed the importance of becoming familiar with the "Guidance on Allocating & Targeting Pandemic Influenza Vaccine," particularly with regard to the Severity of Pandemic chart reflecting the various tiers of severity. He explained that the idea of chart was that based on the severity of a pandemic, every American would find their place on this chart regarding where they would get in line. What is important about this is the preamble. This is part of the preparedness activity because there was no crystal ball. A lot of it was driven by the experience with H5N1 and the concern that should that become transmissible what it might mean. Moreover, pandemics past do not all look like 1918. Hence, there must be a range of different responses appropriate to pandemic severity. With that in mind, Dr. Gellin shared the following passages:

> "…it is important that plans are flexible as the guidance may be modified based on the status of vaccine technology, the characteristic of pandemic illness, and risk groups for severe disease – factors that will remain unknown until a pandemic actually occurs."

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> "At the time of a pandemic, national leaders will obtain advice from scientific and public health experts to determine whether the guidance should be modified based on the characteristics of the emerging pandemic."
>
> "Guidance on pandemic vaccine allocation and targeting will be reassessed periodically before a pandemic occurs to consider the new scientific advances, changes in vaccine production capacity, and advances in other medical and public health response measures."

The final piece of this was the recognition that this effort needs to engage many people outside the Beltway and conference rooms to talk to real people about their expectations and values. There was a long process in which input was obtained from stakeholders and the public, out of which came the following four goals of a program: 1) Protecting those who are essential to the pandemic response and providing care for those who are ill; 2) Protecting workers who are at greater risk of infection due to their job; 3) Protecting those who maintain essential community services; and 4) Protecting children.

Review of Existing Vaccine Prioritization Guidance

Tom Shimabukuro, MD
Centers for Disease Control and Prevention

Dr. Shimabukuro reviewed the existing pandemic vaccine priority groups, the process that went into generation the document titled, "Guidance on Allocating and Targeting Pandemic Influenza Vaccine," and what work was done previously and how the work was conducted. He emphasized that the guidance was an initial starting point for developing a prioritization process and for determining priority groups for receipt of vaccine during an influenza pandemic. Although the guidance covered various severities of a pandemic, it focused primarily on a severe pandemic with H5N1 in mind. This document was released in July 2008 prior to the emergence of the pandemic H1N1 virus.

The US pan flu vaccine strategic goals in the HHS pandemic plan are to: 1) establish and maintain a dynamic pre-pandemic influenza vaccine stockpile available for 20 million persons (2 doses / person) or more persons depending on vaccine manufacturing capacity and results of dose-sparing adjuvant studies and prime-boost immunization studies: H5N1 vaccine stockpiles; and 2) provide pandemic vaccine to all US citizens within 6 months of a pandemic declaration: pandemic vaccine (600 million doses) [*National Strategy for Pandemic Influenza (Nov 2005) and HHS Pandemic Influenza Plan (Nov 2005)* www.pandemicflu.gov]. Under the current guidance, the goal of pandemic influenza vaccination program is to vaccinate all persons in the US who choose to be vaccinated. However, the vaccine supply will not be available all at once. Therefore, decisions regarding who will be vaccinated first will have to be made. The overarching objectives are to reduce the impact on health and minimize disruption to society and the economy.

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With respect to the process, this guidance was drafted by a federal interagency working group whose members represent all sectors of the government. This group received input from federal, state, and local public health agencies; other public sector agencies; and private sector partners as well. This was an 18-month long systematic process that included a historical analyses of previous pandemics, public engagement and stakeholder meetings, and a formal decision making process. Though not part of the development process, there was a provision for review and reassessment during a pandemic in the context of the current epidemiologic data and a provision for periodic review in general.

The specific objectives of the vaccination program would be to protect those who are essential to the pandemic response and provide care for persons who are ill (e.g., primarily healthcare workers); protect those who maintain essential community services; protect workers who are at greater risk of infection due to their job (e.g., emergency responders); protect those who maintain homeland and national security; and protect children (based primarily on feedback from public engagement and stakeholder meetings). Again, this is focused on a severe pandemic.

With respect to general principles, the guidance takes into account a “pandemic severity index” (PSI); provides for pro rata allocation of vaccines to states that is allocated and distributed according to population; strongly recommends state and local governments follow national recommendations; includes provisions that vaccine priority groups will be evaluated in the context of current epidemiologic data; and specifies that the guidance will be reassessed periodically in general. The framework of the document is organized around four categories, the first three of which are occupationally defined: homeland and national security, health care and community support services, critical infrastructure, and general population. Within each category there are specific target groups, which include: specific occupations / occupational groups, and age / risk-based groups (general population). There are 5 Tiers, with Tier 1 being the highest priority, follow by 2, 3, 4, and 5. The guide recommends vaccinating sequentially by tier and simultaneously within a tier. That is all target groups within a tier should be vaccinated simultaneously both within the categories and within the target groups. The primary objective of vaccination of critical infrastructure / key resources workers is not to reduce absenteeism in general, but is rather to protect workers with critical skills, knowledge, and licensure or certification whose absence would create bottlenecks or collapse of critical functions; and to protect workers at especially high occupational risk (e.g., direct patient care, first responders). The following is the main table in the guidance:

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Tier 1 | Tier 2 | Tier 3 | Tier 4 | Tier 5 | Not Targeted**

Category	Target Group	Estimated Number*	Severity of Pandemic: Severe	Moderate	Less severe
Homeland and national security	Deployed and mission critical personnel	700,000	Tier 1	Tier 1	Tier 1
	Essential support & sustainment personnel	650,000	Tier 1	Tier 1	Tier 1
	Intelligence services	150,000	Tier 2	Tier 2	Tier 2
	Border protection personnel	100,000	Tier 2	Tier 2	Tier 2
	National Guard personnel	500,000	Tier 2	Tier 2	Tier 2
	Other domestic national security personnel	50,000	Tier 2	Tier 2	Tier 2
	Other active duty & essential support	1,500,000	Tier 3	Tier 3	Not Targeted**
Health care and community support services	Public health personnel	300,000	Tier 1	Tier 1	Tier 1
	Inpatient health care providers	3,200,000	Tier 1	Tier 1	Tier 1
	Outpatient and home health providers	2,500,000	Tier 1	Tier 1	Tier 1
	Health care providers in LTCFs	1,600,000	Tier 1	Tier 1	Tier 1
	Community support & emergency management	600,000	Tier 2	Tier 2	Not Targeted**
	Pharmacists	150,000	Tier 2	Tier 2	Not Targeted**
	Mortuary services personnel	50,000	Tier 2	Tier 2	Not Targeted**
	Other important health care personnel	300,000	Tier 3	Tier 3	Not Targeted**
Critical infrastructure	Emergency services sector personnel (EMS, law enforcement and fire services)	2,000,000	Tier 1	Tier 1	Tier 1
	Mfrs of pandemic vaccine & antivirals	50,000	Tier 1	Tier 1	Tier 1
	Communications/IT, Electricity, Nuclear, Oil & Gas, and Water sector personnel	2,150,000	Tier 2	Tier 2	Not Targeted**
	Financial clearing & settlement personnel		Tier 2	Tier 2	Not Targeted**
	Critical operational & regulatory government personnel		Tier 2	Tier 2	Not Targeted**
	Banking & Finance, Chemical, Food & Agriculture, Pharmaceutical, Postal & Shipping, and Transportation sector personnel	3,400,000	Tier 3	Not Targeted**	Not Targeted**
	Other critical government personnel		Tier 3	Not Targeted**	Not Targeted**
General population	Pregnant women	3,100,000	Tier 1	Tier 1	Tier 1
	Infants & toddlers 6–35 mo old	10,300,000	Tier 1	Tier 1	Tier 1
	Household contacts of infants < 6 mo	4,300,000	Tier 2	Tier 2	Tier 2
	Children 3–18 yrs with high risk condition	6,500,000	Tier 2	Tier 2	Tier 2
	Children 3–18 yrs without high risk	58,500,000	Tier 3	Tier 3	Tier 3
	Persons 19–64 with high risk condition	36,000,000	Tier 4	Tier 3	Tier 2
	Persons >65 yrs old	38,000,000	Tier 4	Tier 3	Tier 2
	Healthy adults 19–64 yrs old	123,350,000	Tier 5	Tier 4	Tier 4

http://www.pandemicflu.gov/vaccine/allocationguidance.pdf

The table includes a column of the estimated number of individuals in each of the target groups. These numbers were determined in cooperation with the industry sector, councils, HHS, and DHS. A tier is assigned to each target group within each category. The estimated numbers add up to $300 million residents, which is the total population of the US. As noted, vaccination is done sequentially by tier and simultaneously within a tier. The blank boxes represent the "not targeted" category, which does not mean not included. Instead it means in a moderate or less severe pandemic, those specific occupationally defined groups will move into the general population category and will then be reassigned to those tiers and target groups within the general population. There is a balance act between critical infrastructure and security goals (e.g., maintaining key services, preventing societal disruption, preventing damage to the economy, maintaining homeland and national security) and public health goal (e.g., protecting the public's health and preventing morbidity and mortality). In a severe pandemic, a vaccination program would be more weighted toward critical infrastructure and security needs. In a less severe pandemic in which critical infrastructure and security goals may not be compromised by disease, logically the goals would be re-weighted more toward the public health goals. These are not necessarily mutually exclusive. For instance, keeping school children healthy and in school may prevent a lot of societal disruption. So, there is really a mix of goals within the two broader goals.

The following table illustrates that assigning a tier to a target group is not just a blanket statement in which healthcare workers are Tier 1. Included in Tier 1 are healthcare and emergency services. In working through the Industry Sector Councils, DHS, and HHS the determination was made that of all healthcare workers roughly 60% would be considered Tier 1. Some healthcare workers would not fall into Tier 1, 2, or 3. Of emergency service workers, the determination was made that approximately 90% would fall into Tier 1 primarily because of the increased risk burden. For Tier 2 target groups, the determination was made that 25% would be critical to maintaining services.

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Tier	Infrastructures	Allocation	Rationale
1	Healthcare Emergency services	~60% 90%	• High risk exposures • Increased burden
2	Communications/IT Electric & Nuclear Oil & Gas Water	25%	• Products/services essential to all sectors • Products cannot be stored • Little fungibility
3	Banking & Finance Chemical Food & Agriculture Pharmaceutical Postal & Shipping Transportation	7.5%	• Products may be stored • Demand may decrease • Greater fungibility

Discussion

Dr. Morse inquired as to whether assessment was being done of the potential for 1 dose in the older age groups due to the potential for protection, such that they may not require 2 doses in certain age groups.

Dr. Baylor responded that FDA has recommended examining the data for adults when it is ready. They will attempt to review the data early so that decisions can be made early if possible. If they observe a robust immune response, some decisions can be made at that point that can be extrapolated to all of the groups. In some of the studies, the data will be reviewed 7 days post dose 1; 14 days post dose 1; and the same for post dose 2 to have an early idea of effectiveness.

After hearing the list of all of the committees that will be working on this, Dr. Baker inquired as to what committee would be responsible for deciding the recommendations for novel H1N1 influenza vaccine. Until now, this has always fallen with the purview of the ACIP.

Dr. Gellin replied that the idea behind this was that the guidance was created based upon the assumptions that were observed with the recognition, and then they had to gauge it as they saw it at the time. To him, this was what ACIP did all of the time. That is, ACIP looks at the vaccine, the epidemiology, and then makes recommendations on how to match that. Because the members have seen novel H1N1 information in pieces, the purpose of this session was to put all of this in front of the ACIP so that they could begin to think about the data needs ACIP has to fulfill their role. The short answer was that CDC was asking ACIP to consider how to manage the situation, particularly with an emerging epidemiological pattern. In some ways this may be similar to ACIP's role in the management of vaccine shortages. ACIP would continue to make recommendations.

Dr. Baker noted that all of the information pertaining prioritization included children at the bottom; however, the boxes do not stipulate all children. It is children by age or youngest children and pregnant women are left off every time in Tier 1. With regard to the severity index, she asked whether there was a scoring index for severity.

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Dr. Gellin responded that this was part of the difficulty WHO had in ratcheting up their pandemic phases, because that is a geographic determination versus a severity determination. The recognition along the way was that a response should be tailored to the magnitude of the problem and that while there was endless discussion about 1918, there was also discussion about 1957 and 1968. Hence the idea of a modulated response appropriate to the problem. The Pandemic Severity Index was the construct for that.

Dr. Schuchat added that the general pre-pandemic planning attempted to use a framework with graded severity because decisions on short supply would be different in different circumstances. Clearly, what has been observed thus far is not a 1918 scenario. WHO has talked about what is being observed as a moderately severe pandemic. That does not necessarily correlate with the Pandemic Severity Index included in many of the documents submitted to ACIP. The principle issue for ACIP was that as they often consider influenza vaccinations in terms of who should be vaccinated, whether recommendations should be strong or permissive, et cetera. It is likely that vaccination would be carried out in a setting of limited supply, at least initially, which would require input from ACIP about the target populations for an initially limited supply. The NVAC committee will focus on how safety would be monitored. They have a Safety Working Group that has been considering that type of issue for years, and they are going to take on that piece of the larger pie.

Dr. Baker asked for clarification with respect to whether the Severity Index was a quantitative trigger or if it was 15 committees' debating a trigger.

Dr. Schuchat replied that ACIP did not really need to worry about the Severity Index. The Severity Index was helpful for planning purposes. Based on what is observed as the season goes forward, ACIP will considering who is most at risk, the rates, potential for increased illness in a second wave, et cetera. ACIP will be examining actual data from the pandemic.

With respect to seasonal influenza, William Schaffner (NFID) pointed out that there was an army of providers in place monitoring what is occurring and wondering how much they are going to have to revise their usual activities. With that in mind, he wondered who would decide whether an H1N1 program was going to be started, when, whether it would be early, and when this would be made known.

Dr. Neuzil replied that one of the principles from her introduction pertained to how a pandemic influenza vaccine might co-exist with a seasonal vaccine program. The first step was to understand the timelines for when pandemic vaccine might be available. She proposed that this issue be put off until the next day at which time they would hear more detailed plans on vaccine program implementation. Then they would have all the pieces to weigh in.

Regarding the FDA presentation, Dr. Ehresmann noted that McKesson is the distributor used for the Vaccines for Children program. With that in mind, she expressed concern that if there is an overlap between seasonal influenza and the H1N1 vaccine, there may be volume issues with McKesson.

Dr. Santoli agreed that this is a critically important question. In addition to seasonal influenza vaccine, half of the nation's pediatric vaccine supply goes through the centralized distributor. CDC is happy with this and wants to protect it. CDC is wrestling with this question, and has asked McKesson to help them understand how risks to the routine seasonal flu and routine childhood distribution program and can be mitigated because these matter greatly, even in the midst of a novel response.

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Regarding the clinical studies for adjuvants and the statement that subjects should be monitored for 12 months for serious adverse events, Dr. Ehresmann wondered whether that meant to have licensed vaccine with adjuvants it would take at least a year.

Dr. Baylor replied that there will be surveillance post-license as well with the adjuvanted products. Most likely the products with novel adjuvants will be available through an Emergency Use Authorization. They probably will not be licensed vaccines.

Dr. Curlin indicated that two of the manufacturers that produce the adjuvants have already presented plans for long-term clinical studies that would span several years and would include hundreds of thousands of subjects, beginning in Summer 2009.

Dr. Neuzil stressed that a key issue regarded the timelines. Looking at Dr. Robinson's timeline, the critical piece pertains to when ACIP will be able to acquire the first clinical trial data in a variety of age groups following one dose of vaccine.

Dr. Baylor responded that they would have to know when the vaccine would be available, which it was not at the time of this meeting. As soon as vaccine is available, the FDA's goal is to begin the clinical trials. Although he did not have a calendar date, if they attempt to collect early data 7 to 14 days post dose 1 in a small group, that could possibly be three to four weeks after the trial begins. However, he stressed that no clinical trials could be conducted until the manufacturers produce a vaccine.

Dr. Neuzil was pleased to hear that the goal was to get a minimal dataset as quickly as possible. Along those lines, she wondered if there was a clear pathway for the live attenuated vaccine to be licensed and whether that would be considered a strain change.

Dr. Baylor responded that the pathway is the same. However, it is a strain change as defined in his presentation, with a limited amount of dose ranging data. In the US, no clinical data are required for annual strain changes. That would be the difference.

Dr. Meissner raised the issue of Guillain-Barré Syndrome, pointing out that in 1976 when the vaccine was recommended the association with Guillain-Barré Syndrome was not appreciated. He wondered whether this might be a generic problem with swine influenza, and whether anything was known about the degree of homogeneity between the hemoglobin molecule of the 1976 swine strain and the California 2009 H1 strain.

Dr. Neuzil indicated that there would be presentations the next day regarding virus characteristics and the safety monitoring plans.

Phil Hosbach (sanofi pasteur) stressed that a reality check was needed, given that the discussion was focused on all things working perfectly, on time, moving quickly, aggressive plans, et cetera. Even if they do add to the protocols a 7- or 14-day blood draw, they will have to go back to their IRBs, draw the blood, bring it back in house, run it through assays, make sure that they have the right reagents for formulation of the vaccine, et cetera. Many assumptions had not been discussion, so he wanted to ensure that people understood that things would have to go perfectly in all of the groups, organizations, agencies, manufacturers, et cetera.

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Dr. Morse agreed, noting that Dr. Robinson had outlined potential production capabilities that seemed much more optimistic than what he had heard previously.

Dr. Robinson replied that there are always assumptions. One important component that was built into preparedness is redundancy. They have five vaccine manufacturers that are going to produce different amounts to support what is available to the US. In 2004, this would have been a much different situation. With redundancy, they are now able to engage in conversations as to what is available. They took a very conservative estimate on many of the production yields and other assumptions, and would see over the next 30 days how those play out. It is not clear yet whether there will be more or less than needed.

Once the tiers are reviewed and fine-tuned and production is underway, Dr. Morse wondered how decisions to move successfully through the tiers would be managed.

Dr. Gellin responded that they had to analyze the situation as it unfolded and not focus on the tiers specifically. The construct of the tiers is a helpful starting point, but the unfolding epidemiology must also be examined carefully from the data coming out of the clinical trials to consider how to direct certain products to certain populations.

Dr. Sawyer wondered how, given the recent history of vaccine supply, manufacturers could suddenly turn out 600 million doses without blinking an eye and whether money was usually the missing ingredient.

Dr. Robinson responded that basically, the $5.6 million has been appropriated and used over four years has permitted them to be in this situation. Four years ago, these adjuvants were not available. Similarly, there were just one or two manufacturers at that time and now there are five. The manufacturers have also increased their facility production. For example, GSK has two facilities that are producing influenza vaccine—one is producing seasonal and the other is producing H1N1 currently. Facilities have been retrofitted to enhance their capabilities so that existing facilities can produce larger amounts.

Doug Campos-Outcalt (AAFP) requested that someone address the issue of prioritization in terms of how that will be enforced and how much leeway states may have to deviate from that.

Dr. Gellin replied that this is like guidance that ACIP gives all of the time. It is guidance for those who are implementing the programs to follow. It is not enforced. When this process began, there was a desire by the states for such guidance so that not everyone had to do this on their own. Determining who should be in line first is not an easy task. Thus, this large national process was put in place to provide guidance for providers to follow as best they can depending upon the situation. While the guidance is important, following the implementation plan is also essential. The idea is for the guidance to be read by states and localities in concert with a range of others.

Dr. Ehresmann said from a state perspective, the guidance is welcomed because consistency is very important. Using Minnesota as an example, the Twin Cities border Wisconsin; the Morehead area borders directly with Fargo, North Dakota; and in the Southeast corner of the state the healthcare system is centered in South Dakota. For Minnesota not to be consistent in other states would be highly problematic. While each state will face different issues in terms of their decisions, Minnesota will follow the guidance, and she believed other states would very much value and follow the guidelines as well for the importance of consistency throughout the country.

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Danuta Skowronski (Canada) noted that if the situation continued to evolve as it had been over the summer, it is likely that a substantial part of the population will already have been affected, infected, and rendered immune by the fall. To what extent will that be taken into account in planning for immunization programs, perhaps through planned population sero surveys to assess population susceptibility moving into the fall.

Dr. Schuchat responded that the concept of everyone being immune has been discussed but is not considered to be very likely. A number of studies are underway, including serologic surveys to understand asymptomatic infection and how often that is occurring. H1N1 has a very focal nature. Even in locations such as New York City, the burrough-specific attack rates are not the same and it is likely that the vast majority of people have not yet been exposed to this virus.

Andy Pavia said he was still hearing to some degree that the guidance document on prioritization is being viewed as if it were "carved in stone." He stressed the importance of ACIP thinking about the document as preparatory work that identified the size of the groups at risk and obtained some sense of public values, but does not consider the epidemiology of the H1N1 outbreak which does not match the scenarios that were constructed or the reality of what vaccine there will be. Instead, ACIP should be considering how to fine tune prioritization because everyone would be looking to ACIP's prioritization.

Dr. Gellin said that ACIP should review the epidemiology of what is in front of them, which is what they do every time they make a decision about a vaccine use.

Dr. Schuchat suggested that ACIP think about target populations, given that they may or may not recommend any tiering. There are a number of ways recommendations may evolve in terms of groups that might be recommended for vaccine, expected vaccine availability, timing of ability to deliver vaccine, et cetera. ACIP's role was to be fully briefed on the particular real world scenario, factoring in uncertainties of how this might change by the time recommendations are being implemented, and then engaging in the committee's usual work of determining target population recommendations for what might be a licensed vaccine.

With regard to consistency between states, Christine Hahn (CSTE) reminded ACIP that unlike the earlier discussion about physicians wanting a choice, if novel H1N1 escalates many others will jump in to tell states where to direct vaccine. Given the uncertainties, she suggested strongly worded recommendations from ACIP to help states keep their priorities the same.

Dr. Chilton thought they were appropriately concerned about the coming 2009-10 influenza season, but he wondered if any consideration was being given beyond that to the next season with respect to a quadrivalent or pentavalent vaccines.

Dr. Gellin replied that this issue has arisen at the last two strain selection Vaccines and Related Biological Products Advisory Committee (VRPAC) meetings. As noted, several vaccine manufacturers now have greatly enhanced capacity such that consideration is being given to producing a seasonal vaccine that may provide broader protection. In the licensure of the H5N1 vaccine, there was only a licensure pathway for a vaccine that had 90 mg to be given twice. So, there is a pathway through which a vaccine can be licensed.

Dr. Baylor responded that it is not simple when adjuvants are added or quadrivalent products are being produced. This gets into supply issues because the vaccine virus that grows the least is going to dictate how much vaccine can be manufactured. Conceptually it may seem like a

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straight path, but in reality it not necessarily that simple. With respect to the regulatory mechanism data can be considered from a chemistry manufacturing and control perspective and a clinical outline, but there are other issues involved as well.

Dr. Schuchat noted that regarding the virologic surveillance, as well as the strain selections that occur twice every year, Dr. Cox would be presenting the next day. For decades, Dr. Cox has been helping to select the strains that go into seasonal influenza vaccine for the Northern and Southern Hemispheres. At this point, it is not know how many seasonal strains will be circulating this year, what the long-term circulation of the novel H1N1 will be, et cetera. It is very immature to determine how many strains will actually be needed. While it is exciting that there is greater capacity and better virologic surveillance worldwide, it is far too soon to understand what the formulation of vaccine would be for future Northern and Southern Hemisphere seasons.

Dr. Sumaya inquired as to whether there was any possibility that the focus on influenza vaccine may hamper work on other vaccine programs.

Dr. Robinson responded that considerable effort has been made to ensure that H1N1 production does not affect seasonal vaccine production, and that influenza production as a whole does not affect other vaccine programs. An attempt was made to build the infrastructure such that influenza vaccination production would be independent of production of other vaccines or other biological products.

Dr. Englund pointed out that the epidemiology CDC provides ACIP will help them direct where they believe the priorities are. As a pediatrician she recommended that there be more specific age group definitions, particularly in children less than 4 years of age and in children less than 12 months and 6 months. In her hospital, 30% of H1N1 cases that have been diagnosed are under 4 years of age. Because this epidemic is not as severe overall as was first thought, she believes that the cases affecting medical care and tying up the medical system need high priority. Once they have the data, ACIP can base their decisions based not only on severity and mortality, but also on cases that present to physicians' offices and hospitals.

Public Comments Day 2

Claire Hannan, MPH
Association of Immunization Managers (AIM)

Ms. Hannon reported that AIM continues to have on-going concerns about the Hib vaccine supply and reinstatement of the fourth dose. AIM represents the 64 immunization grantees of 50 states, 8 territories, and 6 cities. AIM convened a conference call earlier in the day, during which the grantees had an opportunity to discuss their supply situations and the new Hib vaccine allocation that they received for July. While the overall supply has increased for July, the supply of monovalent Hib vaccine appeared to be decreasing. Many states indicated that their allocation of monovalent Hib vaccine decreased in July, which they were not expecting. This is important because providers may not choose to use the combination vaccine in children who only need the Hib component. At least 10 states reported that they do not have sufficient Hib vaccine to meet their needs and are not ready to move to the 4-dose series. Thus, there is a need to monitor this issue closely at the program and provider levels, not just at the aggregate

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or national levels. It is as if an announcement had been made about a product, but the product remained at the factory. In a supply situation, the overall number of available doses is not the only determining factor in deciding whether there is enough vaccine. It is also important to take into account how those doses are spread across providers, and the providers' ability to use and manage the doses. More information is needed from the manufacturers about the individual products and the presentations they are planning to release. There is a major difference between monovalent Hib vaccine and the combination Pentacel® vaccine. If there is a significant shift in the ratio of one to another, immunization programs need to prepare and to work with the providers to change ordering and practice behaviors.

June 26, 2009

Novel Influenza A (H1N1)

Virology and Immunology

Nancy J. Cox, Ph. D.
Director, Influenza Division
Director, WHO Collaborating Center for Influenza Reference and Research
Influenza Division, NCIRD

Dr. Cox reported on the laboratory characterization of the novel H1N1 viruses and vaccine development, given that these have been such a critical piece of the influenza response. Events unfolded very quickly, with the first US case of novel H1N1 detected on April 15, 2009. By about April 29, 2009, real time polymerase chain reaction (PCR) kits had already been assembled and were being distributed to US labs. This was possible because there was already a five-target real time PCR assay that could detect influenza A, influenza B, H1, H3, and H5. CDC had this assay because the agency was preparing for an H5 pandemic, with a considerable amount of response preparation predicated on the potential for an H5N1 pandemic. Referred to as "swine flu" at the outset of the pandemic, novel H1N1 was a surprise. Nevertheless, CDC was able to develop primers and probes rapidly, acquire an Emergency Use Authorization, and obtain permission from FDA so that those primers and probes could be included in the five-five target assay.

By about the middle of May, CDC had already developed a number of vaccine candidate viruses that had been generated by reverse genetics or by classical reassortment, tested for their antigenic properties, and sequenced. The necessary safety testing had still not been conducted; however, CDC was permitted by all regulatory authorities and agreement of the World Health Organization (WHO) to ship these vaccine candidates to the manufacturers who could work under Biosafety Level 2 (BSL-2) conditions with BSL-3 enhancements. Thus, numerous efforts were being made in parallel to respond rapidly. By mid-June, real time PCR kits had been distributed to over 230 US laboratories and well over 300 international laboratories.

Dr. Cox shared the following example to illustrate the very complex picture of the number of influenza A viruses currently circulating in pigs in North America:

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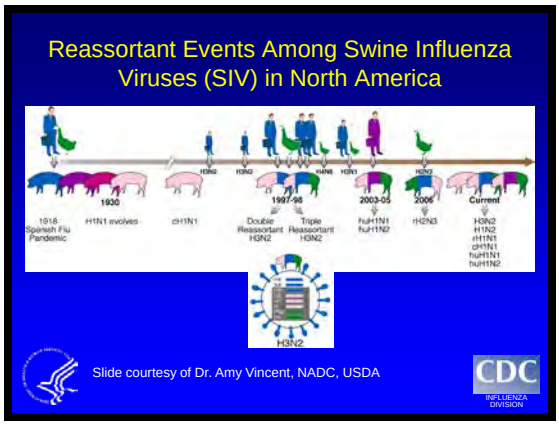

This does not take into account the diversity of influenza viruses circulating in Europe, Asia, or the rest of the Americas—this is just in the US where H3N2, H1N2, reassortant H1N1, classical H1N1, and human H1N1 and H1N2 viruses are circulating. Dr. Cox reported that Dr. Amy Vincent of NADC / USDA and her colleagues have found that this internal gene cassette consisting of PB1, PB2, PA, NP, M, and NS were very stable. This cassette of genes seemed to accept hemagglutinins and neuromitidaises of a variety of different subtypes with no problem whatsoever. Dr. Cox emphasized that this was important to keep in mind moving forward, given that this stable replication complex plus cassette could accept, for example H5N1.

In the last few years, CDC has been concentrating on wild birds introducing their viruses into domestic poultry. Those viruses were subsequently transmitted to humans and there was a fear that there would be reassortment in humans between human influenza viruses and avian influenza viruses. But then, "out of left field" came the novel H1N1 viruses which combine a variety of gene segments from human influenza viruses, swine influenza viruses, and classical swine influenza viruses. Thus, it is extremely important to keep this total picture in context and focus carefully upon what is occurring with novel H1N1.

When the first novel influenza H1N1 case was recognized in California, CDC quickly knew that there was something different about this virus. The agency obtained a number of isolates of the triple reassortant H1N1 viruses from humans that had been transmitted from pigs in a variety of settings, and began developing primers, probes, and sequencing protocols so that these viruses could be examined rapidly to determine whether there had been any changes that might indicate that they would be more transmissible to humans. When the triple reassortant H1N1 viruses were transmitted to humans, they did not transmit beyond one or possibly two generations. Humans appeared to be a dead end host. However, it was immediately apparent that the novel H1N1 virus did not behave in the expected manner with the real time primers and probes that the agency had been using to characterize triple reassortants. Much to their surprise, CDC found a gene type for this new virus that had not been described elsewhere in the literature.

And if you look at the origin of the various genes, you can see that the PB2 and the PA genes were introduced in about 1998, were circulating in swine, they're present here. The PB1 gene was introduced into humans in about 1968, introduced into swine in 1998, and that's the origin of the PB1 gene. The HA, NP and NS date back to the 1918 virus and have been evolving in pigs during the period from 1918 to the present time. And the NA and M interestingly were the two new genes in this virus, and their original was avian influenza viruses that were introduced into swine at about 1979. First identified in Belgium and then they evolved this lineage of avian

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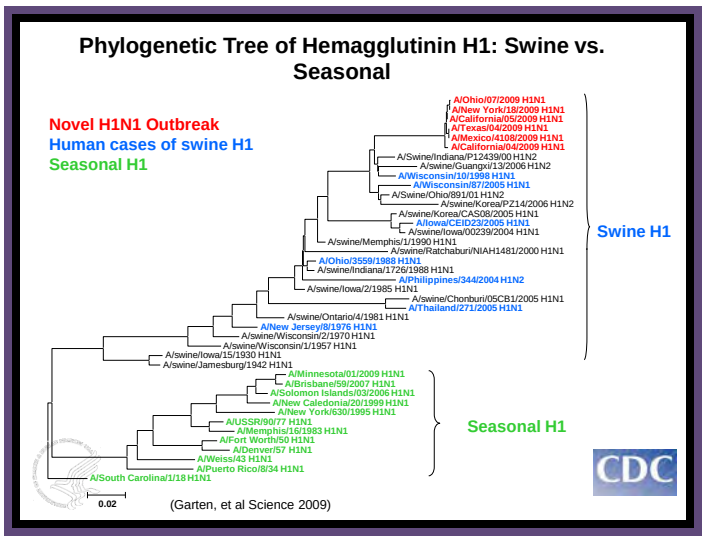
H1N1 viruses became established in pigs and evolved until the current time. So in this new virus, we have this novel gene constellation that had not been seen before. People have been digging through their freezers, very carefully looking for the predecessors of these viruses among their swine influenza virus collections and so far, no one has been able to find the predecessor.

Looking at the evolutionary tree, Dr. Cox pointed out a number of things about this particular evolutionary tree for the hemagglutinin gene; she noted in one place there was the 1918 virus. South Carolina/1 1918 H1N1, this is one of the viruses that was sequenced from preserved lung tissue by Jeffery K. Taubenberger. Everyone working on influenza is very familiar with older viruses such as Puerto Rico/34, Weiss/43, Denver/57, et cetera. The human seasonal influenza viruses have evolved.



Looking at the phylogenetic tree of hemagglutinin H1 with respect to swine versus season influenza, the hemagglutinins for novel H1N1 are on a long branch on the evolutionary tree. Many data points are missing because very little surveillance is being conducted for novel H1N1. While there is more surveillance in the US and Europe than in any other part of the world, and there is some surveillance being conducted in Asia (particularly in Hong Kong), much of the rest of Asia and most of world do not currently conduct any surveillance.

Referring to the following table, Dr. Cox made several points about the importance of conducting haemagglutination-inhibition tests in terms of vaccine development and seeking cross-reactivity with seasonal vaccines:

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STRAIN DESIGNATION	NJ/8/76	WI/10*	IL/9*	CA/07	MX/4108	NY/18	TX/15	AS/59
A/NEWJERSEY/8/1976	**640**	10	10	5	5	5	5	5
A/WISCONSIN/10/98*	80	**1280**	1280	640	640	640	640	5
A/ILLINOIS/9(33304)/2007*	160	1280	**5120**	2560	2560	1280	1280	5
A/California/07/2009	10	320	1280	**2560**	1280	1280	1280	5
A/Mexico/4108/2009	10	320	1280	2560	**640**	640	640	5
A/New York/18/2009	5	320	640	1280	640	**640**	640	5
A/TEXAS/15/2009 FATAL	10	640	2560	5120	2560	1280	**1280**	5
A/BRISBANE/59/07	5	5	5	5	5	5	5	**160**
TEST ANTIGENS								
A/CALIFORNIA/7/09 X-179A	5	640	2560	2560	1280	1280	2560	5
A/TEXAS/5/2009 XPR8-IDCDC RG15	5	640	1280	2560	1280	1280	1280	5
Utah 249817 FATAL	5	160	1280	2560	1280	1280	1280	5
Washington V19-4347 FATAL	5	160	1280	1280	640	640	640	5
Arizona PV09124151 FATAL	5	320	1280	2560	2560	2560	2560	5
Montana 723335	10	320	1280	1280	1280	1280	1280	5
Maine VSP-001799	10	640	2560	2560	2560	2560	2560	5
Nevada 1050	5	640	1280	2560	1280	1280	1280	5
Utah 243727	5	640	1280	2560	1280	1280	1280	5
A/NONTHABURI/102/09	10	640	2560	2560	2560	1280	2560	5
Guatemala 450	5	320	1280	2560	1280	640	1280	5
Colombia 330	5	640	2560	2560	2560	2560	2560	5
El Salvador 351	5	320	1280	2560	1280	1280	1280	5
Mexico/4593/2009	40	1280	2560	5120	2560	1280	2560	5
A/AUCKLAND/1/2009	5	640	1280	2560	1280	640	1280	5
A/ENGLAND/195/2009	10	640	2560	5120	1280	1280	2560	5

The A/New Jersey/8/1976 ferret antiserum and its homologous antigen have a nice homologous haemagglutination-inhibition titer of 640. With respect to how this antiserum inhibits these viruses, novel H1N1 viruses are really quite different from A/New Jersey. A/Wisconsin/10/98 and A/Illinois/9(33304)/2007 are triple reassortant swine influenza viruses that were isolated from humans. There is more similarity between the current strains and these two viruses than with the A/New Jersey/8/1976; there is a lot of homogeneity. The reference strain, California/7, has a homologous titer of 2560. If within 2- to 4-fold in terms of titer, the conclusion is that the virus is not varying from the referent virus. The reference strain from Mexico likewise has a lot of homogeneity in terms of the titers represented, as do A/New York/18/2009 and A/Texas/15/2009. With regard to the seasonal H1N1 virus, A/Brisbane/59/07, there is really no inhibition of this virus by any of the swine influenza ferret antisera and likewise antiserum to this virus does not inhibit any of the novel influenza viruses.

Of the two top candidates (A/California/7/09 X-179A; A/Texas/5/2009 XPR8-IDCSC REG15), the A/California/7/09 X-179A is perhaps the leading contender among the various vaccine candidate viruses that have been produced, given that it seems to grow the best. It certainly has very similar antigenic properties to all of the novel swine influenza viruses. It is always possible to check whether the candidate vaccine viruses have the same antigenic profile as their wild type viruses. A number of fatal cases have been examined to determine whether there are any differences antigenically or genetically between the fatal and more severe cases and the milder cases. Certainly in terms of antigenicity, no difference is observed whatsoever.

In summary of genetic and antigenic analyses, the combination of gene segments of nH1N1 viruses had not been reported previously and has still not been found in any frozen specimen collections. Re-assortment had occurred between Eurasian swine influenza viruses and North American swine lineage triple reassortant viruses. It is not clear at this time whether the reassortment event occurred in North America or in Asia and then was exported from Asia. No genetic markers for severe disease in viral genes has been detected yet. The virulence markers identified for the H5N1 and 1918 Spanish Flu viruses are not seen in the novel H1N1 viruses. However, a caveat to that statement is that not all of the virulence markers for influenza viruses are known, and they can vary depending upon the gene constellation.

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Genetically and antigenically homogeneity suggests a single introduction in humans with onward spread and evolution. Homogeneity made selecting a reference vaccine virus relatively easy compared to seasonal influenza. However, it has been demonstrated that passage in eggs that limit dilution to select viruses that grow to high titers in eggs can result in antigenic and genetic variation in the viruses. Thus, vaccine manufacturers will have to be very careful as they work with these viruses.

Naturally, determining the antiviral resistance profile or antiviral susceptibility profile to oseltamivir, zanamivir, and the M2 blockers (e.g., amantadine and rimantadine) is important. In The current seasonal H1N1s are largely resistant to oseltamivir but sensitive to zanamivir, and mainly sensitive to the M2 blockers. On the other hand, H3N2 viruses are sensitive to oseltamivir and zanamivir, but resistant to the M2 blockers. Influenza B viruses are sensitive to oseltamivir and zanamivir. Of the novel H1N1 viruses, 216 were tested that were isolated from many countries globally. All of them are sensitive to oseltamivir and zanamivir, but are consistently resistant to the M2 blockers.

Many questions have been raised about whether seasonal influenza vaccine would afford any level of protection against novel H1N1 virus because the seasonal virus does contain H1N1 components. Therefore, Jackie Katz and her group immediately began soliciting panels of serum that were available through a number of sources, with many collaborators providing serum. Pediatric subjects 6 months to 9 years of age who had seasonal influenza vaccines were found to have no detectable antibodies to the novel H1N1 virus following vaccination. They did have a detectible micro neutralization titer of 42. Micro neutralization is much more sensitive for picking up antibodies to novel influenza viruses than HI titers (haemagglutination-inhibition). Although following vaccination there was no increase in antibody whatsoever to the novel influenza virus, as expected, there was a robust response to the vaccine virus. This was true for all of the panels, and was true for trivalent inactivated vaccine as well as live attenuated vaccine. While the hope was that a more robust response would have been observed post-vaccination in those children who received a live attenuated vaccine, unfortunately that was not the finding. There was a slightly different picture for adults 18-64 years of age in that pre-vaccination, there was detectible antibody. When further stratified by age to examine individuals over 60 years of age, higher levels of cross reactive antibody was observed in their serum with a slight rise in titers. Thus, there is not a very promising picture with regard to cross protection afforded by seasonal influenza vaccines, and the conclusion is that there would be minimal to no protection afforded by seasonal vaccine against novel influenza H1N1. Some data have been gathered in Japan and in the United States to examine vaccine effectiveness of seasonal vaccine against novel H1N1 virus. Although the data are not robust yet, a signal has not been found to indicate there is protection in either country.

Another component of public health risk assessment is to determine pathogenesis and transmissibility of the novel H1N1 viruses. For this assessment, a ferret model was used because that is the best model and best predictor to examine what will occur in humans. This model has been used to examine H5N1, 1918 viruses, and seasonal influenza viruses. While this model will not necessarily answer all questions regarding what will occur in humans, it will offer interesting hypotheses to consider. When seasonal H1N1 viruses were compared with two novel H1N1 viruses, increased morbidity was observed in the ferrets. The novel H1N1 viruses replicated to very high titers in lung tissue and could be recovered from the intestinal tract of internasaly inoculated ferrets. The results that although some labs have somewhat conflicting results, the results suggest that there may be higher virulence of novel H1N1 viruses compared to their seasonal H1N1 counterparts in this ferret model.

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The investigators also wanted to try to measure the efficiency of transmission of these viruses compared to seasonal influenza viruses, so they assessed transmission through direct contact in which an inoculated ferret was joined by a contact ferret one day post-inoculation in the same cage. The contact ferret was then monitored for infection. With seasonal viruses, they always observed that the contact ferrets are all infected and begin to shed virus early after contact. Cages were designed in an effort to develop a ferret model for transmissibility. The cages are perforated, with infected ferrets and inoculated ferrets placed in one cage and contact ferrets placed in an adjacent cage to be monitored for infection. What was consistently observed with seasonal H1N1 and H3N2 viruses was that the inoculated ferrets began to shed virus one day post-inoculation. All three ferrets in this experiment become infected, shed viruses to high titers, and then experienced titer decline to return to baseline by day seven. The contact ferrets began shedding virus the day after exposure and there was a similar pattern, just delayed by a couple of days since they were the contact ferrets. This was respiratory droplet transmission, with no directional airflow in these experiments. With novel H1N1 viruses, a different pattern was observed in that not all of the contact ferrets in the adjacent cages are infected (e.g., only 2 out of 3 of the ferrets were infected). There was also somewhat of a delay compared to what was observed in the contact ferrets for seasonal influenza viruses. The conclusion for the work going forward is that novel H1N1 viruses exhibit less efficient respiratory droplet transmission in comparison to seasonal H1N1 viruses. Given that transmission occurred in only 4 of 6 droplet contact pairs and that infection was delayed compared with seasonal H1N1, these data suggest a hypothesis that perhaps additional virus adaptation in humans may be required to reach the high-transmissible phenotype observed with seasonal H1N1 and H3N2 viruses. This may be reflected in the fairly low secondary attack rates that have been observed in households in California and Texas.

In conclusion, genetic and antigenic characterization of viruses, serologic assays, animal models, and epidemiologic assessments are all critical components for public health risk assessment. To date, there has been substantial consistency between laboratory and epidemiologic results, which suggests that novel H1N1 may not be fully adapted to humans. Epidemiologic and virologic surveillance are important for identification of future changes in antigenic characteristics, transmission characteristics, severity of disease, antiviral resistance, and intensity (e.g., surge) in US cases. There is a limited understanding of diversity of influenza viruses in pigs globally, which is a major gap in pandemic preparedness. USDA's efforts to initiate surveillance should be supported and encouraged by public health, putting the "One Health" concept into action. Ensuring virus sharing between public health, animal health, academia, and industry is a key component of planning.

Key questions remaining for the 2009 H1N1 response include: What is the timing of the expected fall wave of 2009 H1N1 in the Northern Hemisphere? What will be the timing and dosing for 2009 H1N1 monovalent vaccine, if recommended, based on clinical trial data? Who are the target populations for 2009 H1N1 vaccine? Will reassortment occur with 0-resistant seasonal influenza viruses or with H5N1 viruses? It is known that a novel H1N1 is circulating in Egypt where there are cases of H5N1 occurring in the populations that seem to be most susceptible to novel H1N1viruses. How will antiviral drugs be used, assuming they are effective? What will be the effectiveness of non-pharmaceutical interventions? The question most frequently asked is: What is the difference between bird flu and swine flu? To that Dr. Cox quipped that that for bird flu, tweetment is needed and for swine flu oinkment is needed.

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Discussion Points

An inquiry was posed regarding whether in the ferret model investigators had any data on viremia and / or stool shedding of the virus.

Dr. Cox responded that they continue to work on this, but have no evidence for viremia. There is no evidence for a virus in other organs (e.g., brain, spleen, et cetera). They have information only for the intestine at this point. Additional data are expected from more detailed examination of the tissues.

Dr. Morse requested information about the status of the development of rapid tests for novel H1N1 virus and their potential application for the fall seasons.

Dr. Cox responded that the rapid tests commercially available are being compared for their ability to detect novel H1N1 virus. It is known that many of the commercially available tests do detect novel influenza virus. The sensitivity is not as high as would be expected, so the real-time PCR assay will probably be an assay of choice. It is not as rapid and is not a bedside test, but it can be utilized by laboratories accustomed to using real-time PCR. There is, of course, a lot of work going on in industry and with various partners to try to develop bedside tests. However, so far none of them are as sensitive as the real-time PCR assay and are not nearly as sensitive as viral culture. CDC has been working diligently with many partners to try to develop a simple, inexpensive, rapid test that can be used at the bedside.

Gus Birkhead (NVAC) requested further information pertaining to the comment made earlier that CDC had sent out candidate vaccine strains to the company without the usual safety testing.

Dr. Cox explained that there is new safety testing done for seasonal vaccine candidate viruses; however, because this is a novel strain and it is unknown how it will behave, and because safety testing was required for the H5N1 candidate vaccine viruses, it was determined within the WHO network that the novel viruses should be tested using the same kinds of assays used for H5N1 to ensure that the vaccine manufacturers could work with these candidate vaccine viruses safely in their facilities. The agency had to demonstrate that the reassortant viruses were less pathogenic in ferrets and similar to the donor of the internal genes in terms of the pathogenicity. They had to look for ability to replicate in eggs and not kill the embryos. Because increased pathogenicity has been observed in ferrets, CDC felt that this was very important. Once the agency was able to develop a safety dossier and submit that to WHO, and engaged in some consultation, it was agreed that these viruses were attenuated relative to their parent wild type viruses and that they could be used by vaccine manufacturers.

Dr. Temte inquired as to the current status on serological assays for this virus in patients, and what the plans were for conducting any serological surveys in the population.

Dr. Cox responded that CDC is first planning to examine what was occurring in Mexico in certain areas to try to determine the bottom part of the pyramid. It is known that fatal and severe cases are much more likely to be detected than milder cases. Therefore, CDC is conducting sero-surveys in partnership with its Mexican colleagues to try to determine the denominators as accurately as possible. They are having to use a micro neutralization assay, which is a difficult assay in that it is time- and labor-intensive. There is also the complicating factor with the pre-existing cross reactive antibody that exists in older populations. That is, the

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older someone is, the more likely they are to have cross reactive antibody. Intensive work will be required to ensure that the proper cut off is used so that denominator is being measured well. Sero-surveys are also being conducted in populations in the US to better understand the denominators. CDC is examining serum that has been banked from blood donors to achieve a much finer analysis of exactly what the age break is for cross reactive antibody. While it is known to increase by age, CDC wants to go decade by decade to assess which epitopes cross reactive antibody might be reacting to.

Dr. Meissner pointed out that one of the questions anticipated to arise with a novel H1N1 vaccine strain will regard Guillain-Barré Syndrome (GBS), particularly if this strain retains its sensitivity to antiviral agents. He noticed that the phylogenetic tree included the 1976 New Jersey isolate, although he could not tell how much homology there might be between the hemagglutinin from the 1976 strain and the current strain that is circulating. With that in mind, he wondered if there were any thoughts on the degree of relatedness among the critical epitopes on the hemagglutinin molecule and what the risk might be of another association of GBS in this vaccine.

Dr. Cox replied that there was a great deal of difference genetically in the HA between the New Jersey virus and the new viruses. The average number of amino acid differs, and the neuromitidaise is totally different because it resulted from introduction of a different avian H1N1 virus into swine in Europe, and then with subsequent evolution in pigs in Europe and Asia. There has been no identification of specific epitopes on the HA that were responsible for the association of GBS with the swine influenza viruses with the New Jersey vaccine. There have been a variety of hypotheses, including one that has to do with a monitor of neuromitidaise activity and the amount of acid for that which might have been contained in the vaccines made in 1976. CDC is carefully assessing the neuromitidaise activity of these viruses compared to the swine New Jersey viruses, particularly given that there is not a solid hypothesis for why GBS was associated with the swine flu vaccine in 1976 and not with subsequent vaccines.

Dr. Lett inquired as to whether shedding studies were being conducted in humans or whether the ferret studies might help to inform the exclusion period now used for H1N1. The 7-day exclusion period is causing a lot of disruption. People are asking whether CDC is going to consider changing the recommendations, especially since children recover faster.

Dr. Cox responded that shedding studies are on-going, though it will take some time for them to be completed. These are very important studies because it is critical to know how long people might be shedding and at what titers. If shedding occurs at very low levels, people may not be infectious. Thus, CDC is trying attempting to quantitative detection of virus. They hope to have this information by the fall.

Dr. Schuchat added that epidemiologic data carefully evaluate the period of transmissibility, which may be updated.

It was noted that the understanding from animal model studies appeared to be that the virus was not transmitted as easily under conditions of high temperature or high humidity. With that in mind, an inquiry was posed regarding whether there were unique physical or chemical characteristics of the novel virus.

Dr. Cox responded that what has been observed in the past when a novel influenza virus has been introduced into the human population were focal outbreaks during the summer months. In 1957 and 1968, there was an introduction during the late spring / summer. Focal outbreaks

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were observed then, but the epidemic did not really get going until the following fall. There appears to be a different pattern this year with this particular virus. It is believed that it is spreading in schools where there is a high density of highly susceptible individuals who are in very close contact with each other. The same is being observed in summer camps and other high density, close contact settings. In terms of activity in the population overall, it appears to be declining. However, CDC hears from its Mexican colleagues that activity has been increasing in the Yucatan where it is currently very warm. The Yucatan was relatively spared during the first wave of infections. CDC expected to see a seasonal factor and decrease of influenza activity earlier than they did. The weather has been somewhat cooler in the Northeast, which could have contributed. However, a consistent pattern has not been observed for this virus.

Kathleen Coelingh (MedImmune) requested further information about immunogenicity in humans. From MedImmune's experience with the live attenuated reassortants, novel H1N1 is quite immunogenic in ferrets. However, she had not heard anything about how inherently immunogenic this particular hemagglutinin might be in humans. She noted that all of the manufacturers will be conducting immunogenicity tests on the human vaccines. She wondered what sort of assay would be feasible to measure the immune response following the vaccine. She also wondered whether there were any post-infection data from people infected in Mexico, California, or elsewhere.

Dr. Cox replied that what is observed in ferrets cannot be completely extrapolated to what will be observed humans. Therefore, the inherent immunogenicity of the antigens is unknown. CDC expects that because a large portion of the population will have been exposed to an H1N1 virus previously in their life, the novel H1N1 vaccines may be a lot better than the H5N1 vaccines were in terms of their immunogenicity. This will not be known for certain until the human studies are conducted. CDC hopes to be able to use haemagglutination-inhibition assays, but has been using micro neutralization simply because they were trying to detect antibody with the most sensitive test possible. They hope in the CDC laboratory to be comparing haemagglutination-inhibition assays to micro neutralization assays even to a greater extent as they move forward. CDC will be working with partners to provide information that develops as time go on. Post-infection and post-vaccination data can be different. With the live attenuated, similar types of responses might be expected, but not enough sera have been tested yet for CDC to be able to say anything about inherent immunogenicity.

Vaccine Program Implementation Plans

Pascale Wortley, MD, MPH
Immunization Services Division, CDC

Dr. Wortley reported on key aspects of CDC's implementation planning for H1N1 vaccination. The situation planned for in pandemic planning differs from what is occurring. CDC is looking forward to having larger amounts of vaccine than hoped for in the past. The illness does not appear to be as severe as it was in 1918. The disease that began in the US was really not the scenario that had typically been planned for. To top it off, there will be a confluence of seasonal and pandemic vaccination, which really complicates the process and was never discussed in terms of pandemic planning.

Pandemic planning always includes discussions about uncertainties. Interestingly, CDC is potentially 3 to 4 months away from a vaccination campaign and is still faced with many uncertainties. This make the task highly complex for planners. CDC is still not able to tell state

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planners specifically how much vaccine they can expect to have or exactly when. There is expected to be vaccine available from five manufacturers, not all of which make pediatric formulations. Therefore, issues remain about when the vaccines will come online, for what populations they can be used, and how that relates to priority groups. Also not known is exactly what the vaccine formulations will be and whether they will be adjuvanted. CDC is waiting to hear more about the priority groups for vaccination. It is not known whether severity of illness will change or remain as observed to date. One of the complicating factors from an implementation point of view regards the timing of the H1N1 vaccine and the seasonal vaccine and how those will relate to each other. That has implications for implementation. Another major unknown pertains to what the demand will be for these vaccines. It is understood from every year of seasonal vaccine implementation, demand is very difficult to anticipate and / or control for. The upcoming vaccination effort could be quite large. To put it into perspective, depending upon who the vaccine is recommended for, there could be as many as 600 million doses for administration, accounting for 2 doses per person. To put that into context, about 150 million doses of pediatric vaccines are distributed annually, including Vaccines For Children (VFC) vaccine and private sector vaccine. There is a maximum of 115 million doses of seasonal influenza vaccine. It is important to keep in mind that this would be in addition to the doses of novel influenza vaccine, given that shipping of the other vaccines is not expected to cease during this period.

Another important challenge is that the public health infrastructure at the local and state levels has been reduced, particularly over the last year. The National Association of County and City Health Officials (NACCHO) conducted a survey to determine the proportion of staff and budget cuts in local health departments, with 27% reporting lower budgets in 2008 compared to 2007 and 44% (n=1,079) anticipating cuts for 2009 and similar patterns expected in terms of staff layoffs. Local health departments are a foundation for the response to H1N1. At the state level there has been a considerable amount of discussion about utilizing a delivery model that blends vaccination in public health run clinics, which is always the model thought of traditionally in a pandemic setting, with delivery through the private sector. “Private sector” is meant in the broadest sense of the word (e.g., provider offices, workplaces, retail settings, et cetera).

Key issues involved in preparation include identifying and engaging providers (e.g., public, private, community). It is probably fair to say that in the past, providers probably would not have anticipated that they would be engaged to deliver a pandemic vaccine. Immunization programs naturally think of their VFC providers because those are the ones with which they have close relationships. Other providers need to be brought into the fold as well, which is more difficult because there may not be existing relationships. To determine what the capacity might be, conversations are underway between immunization programs and local chapters of medical societies to determine willingness, feasible, et cetera. Given the number of children to be vaccinated, consideration must be given to what gap public health must fill. There are numerous issues pertaining to payment mechanisms for vaccinating. Because of the challenges at the state and local levels in terms of running clinics, there is a need for funds to augment staffing either through directly augmenting local health department staff or making funds available to them to establish contracts with others (e.g., community vaccinators) who can assist in running these clinics and provide the manpower for such an effort. In addition, if vaccine is going to be administered through the private sector, reimbursement for administration needs to be addressed. Based on preliminary conversations with America’s Health Insurance Plans (AHIP), it appears that this will not be problematic in the provider setting. There also will be issues regarding uninsured children and adults.

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There are also key issues with respect to distribution, allocation, and ordering. Distribution is a major issue given the amount of vaccine that will need to be delivered. Two main options are currently being explored. One option was the basis of pandemic planning in the past, which was direct distribution from manufacturers or distributors to sites that are referred to as "Ship To Sites" that would be designated by states. At the state level, this would entail breaking down of packing / packages and repackaging and distributing the supply throughout the state to a considerable number of end users. With five manufacturers, this could become extremely complex. The second option is centralized distribution, which is the process used for the VFC program. That process has just come online in the last couple of years and is fairly new. CDC is in the process of exploring whether this would be feasible. Obviously, it would be a much better solution from the perspective of state and local planners. In either case, the end users have to be identified, which remains a major component of the work to be done. This harkens back to 2004 to allocation and ordering of vaccine. Regardless of the distribution used, public health will control where vaccines go. In that respect, this differs from centralized distribution when providers order. While public health will not physically handle the vaccine in a centralized distribution system, it will control distribution of vaccine to ensure that it is allocated to providers designated as end users based on the amount of vaccine relative to demand. Again, this is very difficult to predict. There will obviously be a considerable amount of complexity in creating systems that will allow the allocation / distribution effort to function smoothly.

There are also inventory capacity issues. Distribution of novel H1N1 vaccine will be occurring at the same time as seasonal vaccine distribution. If pediatricians are receiving pre-loaded syringes, there are space implications that must be considered. Ordering procedures would differ for novel versus seasonal vaccine, which also must be addressed. It is also imperative to monitor doses administered. One key aspect of this is providing a denominator to be able to evaluate adverse events. Therefore, it will be very important at the beginning that doses administered are monitored and systems must be created to do this. This is currently referred to as Countermeasure Response Administration (CRA). If both the public and private sectors are to be involved in administering vaccines, stipulations will have to be placed on reporting because it will be critical that the doses administered be reported according to the protocols that have been established. Priority groups must also be respected. It is known from 2004 that this can be challenging in a private sector setting. Policies will have to be established to support physicians in being able to respect priority groups. The issue of a second dose may also have to be addressed. Also not clear is whether the novel vaccine will be administered under Emergency Use Authorization. If so, this is likely to create further complications.

Contingency planning also poses a major difficulty. Consideration must be given to what is reasonable to expect with respect to private sector delivery. The situation in the fall could be incompatible with private sector administration. Therefore, an approach that is not dependant on the private sector must also be planned for. There is a basic issue of capacity. It is already known from previous work related to the expansion of the pediatric influenza guidelines that pediatric offices cannot absorb all school-aged children, so there must be alternatives for those children. There could potentially be a situation in which diseases are occurring at the same time as vaccination. Depending upon the severity of disease, there would not only be an increase of sick visits, but also an increase in "worried well" visits that would really make it challenging from a provider perspective. Plans need to be developed in such a way that they can be dialed up or down with involvement of public sector and private sector depending upon the situation as it plays out in the fall.

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Overarching issues include coordination between programs at the state level, and between state, local, and federal levels. At the state level in particular, this is a joint endeavor between immunization programs and preparedness programs, which will play out differently in different locations. Coordination will be especially critical in relation to communication. Messaging is probably going to be the most complicated ever faced. Another issue is expectation management. Potentially a lot of vaccine could come available at once, so consideration must be given to the expectation in terms of how quickly it can be administered. Undoubtedly, there will be variations across states related both to differences in infrastructure and differences in demand.

Supplemental funding is expected for accelerated planning and early implementation, which CDC is hoping to be able to allocate to states very quickly. The agency has formed a Vaccine Implementation Steering Committee with representatives from key public health partners (e.g., ASTHO, NACCHO, AIM, Preparedness Directors, CSTE, and NPHIC). They are also working with provider organizations and others. Distribution planning is a key activity, and CDC is working to develop scenarios to help people think through how they will establish these programs. Scenario planning includes permeations of disease severity, timing of disease with respect to timing of vaccine, and getting people to think ahead to how they would tackle different population groups.

Plans to Assess the Effectiveness of Seasonal and Pandemic Influenza Vaccines 2009-10

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Influenza Division, NCIRD, CDC

Regarding some background and assumptions, Dr. Shay reiterated that pandemic H1N1 vaccine would be purchased by the US government. Safety and limited immunogenicity studies will be conducted for currently licensed vaccines before use. The adjuvanted and other non-licensed vaccines may require Emergency Use Authorization before use. The preliminary estimate is that 60 million doses of monovalent H1N1 vaccine will be available for distribution as early as September 2009. There are initial contracts with each of the 5 large producers, which are for inactivated and live vaccines and bulk adjuvants. It is expected that 2 doses of monovalent pandemic vaccine will be offered, and that concurrently or subsequently a seasonal campaign will also be conducted.

In thinking about vaccine effectiveness, consideration has to be given to whether illness is prevented by the pandemic vaccines, and whether clinical vaccine effectiveness differs for receipt of one versus two doses of vaccine and whether that varies by age, presence of underlying illnesses (e.g., obesity), or by vaccine type. Also important to consider is whether vaccine effectiveness varies by outcome measured (e.g., symptomatic illness, medically attended acute respiratory illness, hospitalization). Rapid vaccine effectiveness assessment will be required for some outcomes, and there will be a need to evaluate absolute vaccine benefits versus absolute risks for adverse events, particularly for rare but important events like GBS.

CDC plans to use lab-confirmed influenza outcomes whenever feasible to improve the validity and comparability of vaccine effectiveness estimates. Sensitivity and particularly specificity of clinical outcomes is fairly low, and specificity varies by age group and during the course of an outbreak. Vaccine effectiveness must be estimated for pandemic H1N1 and seasonal influenza (e.g., H3N2). CDC plans to leverage existing platforms developed over the past five seasons

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using lab-confirmed outcomes for seasonal vaccine effectiveness to estimate pandemic vaccine effectiveness as well.

Vaccine effectiveness assessment for prevention of reverse-transcription polymerase chain reaction (rRT-PCR) confirmed medically attended influenza is now underway in four community-based sites (e.g., Marshfield Clinic, University of Michigan, University of Rochester, and Vanderbilt University; referred to as the 4 MMRV sites). In terms of vaccine effectiveness for prevention of influenza hospitalizations, CDC has a system in the emerging infections program (EIP) in 10 EIP sites in which influenza hospitalizations as diagnosed by provider-ordered clinically available tests are being examined. There will also be early assessments of vaccine effectiveness among health care workers and perhaps others at high priority for receipt of vaccine who may not be well-captured in the community-based studies. Some crude vaccine effectiveness assessments will be conducted basically by the screening method. For example, there was interest early on before some of the serology data were available about the effectiveness of receipt of 2008-09 seasonal vaccine for the novel H1N1 strain.

Community assessments cases address patients seeking medical care for acute respiratory illness who consent and test positive for influenza again by PCR. The comparison group is basically those who seek care, but test negative for flu. Vaccination data is collected by a variety of means according to the sites, but it depends on either self-report, electronic medical record, or record review. CDC has developed a system to make interim and final vaccine effectiveness estimates for each season. Similar methods will be used to assess vaccine effectiveness for outpatient outcomes for next season.

Referring to data for 2351 subjects enrolled at the four MMRV sites during the December to February time frame, Dr. Shay reported that in terms of outcome of all influenza (n=319), vaccine effectiveness for the early part of last season was roughly 55% with a confidence interval of 37%-68%. Against influenza A (n=208), effectiveness was approximately 66% with a confidence interval of 50% to 79%. Against influenza B (n=111), effectiveness was 21% with a confidence interval of -31% to 53%. Vaccine effectiveness was adjusted for study site, age group, presence of high-risk conditions, and 2-week enrollment interval. Through supplemental funding, testing for rRT-PCR for influenza (including nH1N1) continues. Rochester has enrolled 116 cases of nH1N1 through 25 June 2009, and ascertainment of vaccine status on-going. These cases have been predominantly in children and young adults.

In the EIP system, cases include hospitalized patients in 10 EIP sites who test positive for influenza by clinical tests (most either rapid antigen or immunofluorescence tests). Controls are age- and community-matched persons who are not hospitalized with an acute respiratory illness up to the date of admission of the corresponding case. Case and control interviews and medical record reviews are conducted. The first study of vaccine effectiveness for lab-confirmed hospitalizations among young children was conducted in the 2005-06 through 2007-08 seasons. The first study for similar outcome among older adults started during 2008-09 season. The large catchment area is strength of EIP system, given that it permits vaccine effectiveness assessments for the more severe outcomes, like hospitalization, that have driven expanded vaccine recommendations. Studies to address other needs are also planned, such as those assessing vaccine effectiveness among those who receive vaccine early. Assessments are also planned among civilian health care workers and others who may be vaccinated early. CDC is going to work closely with the Department of Defense (DoD) to coordinate plans and methods for vaccine effectiveness studies for pandemic and seasonal influenza. There are expected to be special situations that may require rapid results. For

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example, early in the nH1N1 outbreak, there was interest in whether receipt of seasonal vaccine was associated with protection from infection with new virus.

Investigators have been working on a rapid case cohort analysis for vaccine effectives. Cases were RT-PCR positive for novel H1N1, aged 18 years and older, with a vaccination history available in the line listing data that were collected early on in the outbreak. These are state-level analyses that were restricted to states that had 5 or more cases with this type of information (e.g., Arizona, Colorado, Connecticut, Kentucky, Pennsylvania, and Virginia). Vaccine status in cases was compared with Behavioral Risk Factor Surveillance System (BRFSS) influenza vaccine coverage estimates for 2008. Those data were only available for individuals aged 18 and above, so that was the age restriction. The current analysis only has the data for 169 cases, but more data are being accrued and are adjusted for only broadly by age category. The vaccine effectiveness was not positive (-26%) with a very wide confidence interval (-78% to 11%). Certainly, there was no indication that vaccine was associated with any protection. These data are consistent with those from serology studies Dr. Cox presented, which do not suggest cross-protection with seasonal influenza antibodies.

In summary, CDC is monitoring for pandemic H1N1 at the four community-based sites that have been established, with plans to continue this effort. The agency hopes to expand to include some additional sites west of the Mississippi River; however, it is not clear whether this will be feasible, certainly before the fall. Larger studies using nationally reported cases are in progress. Several methods will be used by CDC to provide estimates of vaccine effectiveness during the next season for both pandemic and seasonal vaccines. It is important to keep in mind that even with PCR-confirmed outcomes, the number of possible circulating strains and the potential use of multiple vaccines are going to present challenges, particularly for rapidly assessing vaccine effectiveness. As an example, an 18-month child could receive up to 4 doses of influenza vaccines during the course of the season, and all that would have to be coordinated with the timing and diagnosis of influenza in that child.

Influenza Vaccine Effectiveness: DoD Approaches and Plans

COL (Ret) Jose L. Sanchez, MD, MPH
Armed Forces Health Surveillance Center (AFHSC)

Dr. Sanchez indicated that he represented the Department of Defense (DoD) Armed Forces Health Surveillance Center (AFHSC). He reported on the military's past approaches for determining vaccine effectiveness, and what DoD's future plans are. Some of the data presented by Dr. Sanchez have been published in the peer-reviewed literature, to which he invited those present to refer.

The first method to which Dr. Sanchez referred was pioneered by the Armed Forces Health Surveillance Center in which introspective analyses were conducted of pneumonia and influenza and influenza-like illness (ILI) rates as well as influenza-related hospitalizations. This is done routinely for active duty military personnel for the last 5 years. There has been good catchment in terms of diagnosis, hospitalizations, and out-patient visits for these conditions. Thus, it is a very complete assessment that allows the military to compare vaccine effectiveness for both inactivated and live attenuated vaccine. The military uses both products in different types of active duty populations. One drawback is that the military represents a highly immunized group, with many seasonal vaccines being used. Therefore, the military is primed or seasoned. Thus, there are low levels of susceptibility. Unfortunately, the military does not have good vaccination and encounter data on dependents to conduct similar analyses, given that

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many visits and hospitalizations occur for dependents out of network (e.g., outside of the 400+ military treatment facilities that comprise the defensive program system). Hospitalizations and outpatient visits were coded as ICD-9 codes for fever, cough, and sore throat, which may be diagnosed by the clinician with a rapid test. However, these are not PCR or culture proven endpoints, which must be kept in mind.

Recently published in the *Journal of the American Medical Association (JAMA),* DoD examined the period of 2004-2007. Investigators were able to demonstrate very consistently the morbidity reduction for trivalent and activated vaccines. That level of reduction is more aggressive for live attenuated influenza vaccine (LAIV) in active duty populations among non-recruits or seasoned individuals. When the split of the active duty population was examined between recruits (18-21 years of age) versus non-recruits, a clear pattern was observed in which LAIV appears to be more effective than trivalent inactivated influenza vaccine (TIV) in recruits. Conversely, among non-recruits, TIV appears to be somewhat better than LAIV. Again, the caveat is that these are highly immunized populations and this resource may not be generalizable to the larger US population.

Another approach utilized by the military in the past has been screening methods to monitor field effectiveness in which vaccination coverage in the cases is compared to the vaccination coverage in the target population at large. The Air Force system is known as the Air Force Complete Immunization Tracking Application (AFCITA). This system has been in place for the last 12 years. There are a number of assumptions that have to be taken into consideration. The analyses that have been conducted do not include efficacy or effectiveness against novel H1N1 since this occurred after the April 2009 time frame after the bulk of the vaccination program had taken place. Another caveat is that “vaccination” is arbitrarily defined as being protected 14 days or more after vaccination and not protected within the first 14 days. Another drawback of this system is that the analysis is limited to the period of high vaccination coverage. Normally in the military, depending upon the branch of service, 80%-90% vaccination rates are not achieved in active duty until late December. Thus, to determine the effects of vaccination reliably, examination must be made of what occurs after December. The estimates of vaccine effectiveness vary considerable when a lesser proportion of the population is being immunized. Effectiveness by subtype can also be assessed. For the Air Force, there is confirmation by culture or RT-PCR and cultures, so it is possible to determine effectiveness against Influenza A and against which subtype.

A third approach utilized by the military for the last 6 years, which was pioneered by the Navy Health Research Centers, is the conduct of a program at 8 training centers throughout the US. This is prospective population-based fever or respiratory illness surveillance in which there is laboratory confirmation of cases, screening by RT-PCR and confirmation by culture. Thus, it permits subtype-specific vaccine effectiveness estimates. Again, this is a highly immunized group. Recruits are required to receive influenza vaccine upon arrival, which usually occurs between the periods of October through the end of the expiration date of the vaccine, which is usually June or July. An assumption is made that for the first 14 days of being in camp, a recruit is assumed to be susceptible. It is assumed that there will be enough cases of novel H1N1 to go into the full winter timeframe, since recruits will be vaccinated with the new vaccine as soon as it becomes available in about September. The data in this system can be examined by effectiveness against the different subtypes, and by any area of the country. Of the 8 training centers, there are good data for 7. The 8th did not have enough data at the time of this presentation.

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With regard to the future, the military intends to continue to perform population-based assessments of seasonal vaccine effectiveness using hospitalization data. They may be able to include vaccination effectiveness estimates against H1N1 vaccine if it is used next season. The military is also planning cost-effectiveness analyses comparing LAIV versus TIV and a new study among DoD beneficiaries to assess vaccine effectiveness against both seasonal and novel H1N1. Colleagues will continue to measure seasonal vaccine effectiveness on military basic trainees and could estimate what the impact is of the seasonal vaccine against novel H1N1 among basic trainees. The military would like to establish a multi-site tri-service cooperative effort to measure effectiveness and efficacy over multiple years in active duty children, spouse, family members, and retirees.

There have been predictable outbreaks in clusters in both recruits and non-recruits of the novel H1N1. The military intends to follow study protocols on a standardized CDC approach so that they can compare results. The emphasis will be on young (18-30 year old) vaccinees and recruit to recruit in Advanced Individual Training (AIT) posts where there have also been outbreaks. Immunogenicity and safety can be examined for the first 8-12 weeks. Dr. Sanchez showed a series of 10 maps to illustrate the military clusters of novel influenza. There have been at least 7 shipboard outbreaks to date. There have also been outbreaks among trainees at Lackland Air Force Base in San Antonio, at the Naval Recruit Training Center in Great Lakes, and in some of the other installations in the Southeastern part of the United States. Cases have also been reported from Kuwait among troops deployed to Southwest Asia. The onset of those cases or the actual seeding of those cases occurred from two locations in the Southern US at Fort Bliss in Texas. There were also cases from Fort Wiley, Kansas who were deployed eventually to Kuwait. Apparently, many of them have started over-incubating at these two transition sites, which soldiers pass through before deploying to the Southwest Asia theater.

The joint DoD / CDC collaboration to supplement the new and on-going vaccine evaluation being performed by others mentioned earlier will include a retrospective influenza diagnosis-based case-controlled study to examine effectiveness of the MMRV approach as well as the consideration of prospective randomized control trial (RCT)-based trials among specific groups at risk such as recruits, shipboard populations, and other special groups. The military population is at risk, with young military personnel who have acquired this novel strain and will probably predictably have the same type of problems in the fall and winter. The DoD has good data collection and laboratory-based systems and offers a unique opportunity to conduct real-time evaluation of both seasonal and novel vaccines.

Monitoring the Safety of a Pandemic H1N1 Influenza Vaccine

Cindy Weinbaum MD, MPH
Acting Director, Immunization Safety Office
CDC, National Center for Infectious Diseases

Dr. Weinbaum reported on monitoring the safety of the pandemic H1N1 influenza vaccine, noting that as with the distribution methods, there are also many uncertainties about safety monitoring. Decisions are still pending about the full production and use of a pandemic H1N1 flu vaccine. If the vaccine is recommended, vaccine safety monitoring will be an important aspect of the program. Thus, planning has already begun and in fact, began when the first case was identified, to implement safety monitoring if vaccination is undertaken. There is a great deal of uncertainty about the program, which makes planning for safety monitoring really challenging. There is also uncertainty about when the vaccine will become available, who the target groups will be for the initial use of the vaccine, and in which settings the vaccine will be

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administered. If it is administered through the settings that are used for routine influenza vaccination, it will be very difficult to have adequate lot and manufacturer information for every vaccinated individual.

Other planning challenges for safety monitoring include the probability of concurrent use with seasonal influenza vaccine, so if there is any safety signal, knowing whether it is associated with the new seasonal flu vaccine or with the new novel flu vaccine will be difficult. There will be five manufacturers, so tracking which person received which manufacturer's vaccine will be difficult. There will be 8 or 9 total vaccine products, including the possibility of using an adjuvanted vaccine, that might be used under an Emergency Use Authorization. This will further limit the pre-utilization data. There is the distinct possibility of limited pre-utilization data and particularly of limited data for some sub-populations of particular interest, which might include children and pregnant women. Moreover, there is an anticipated need for two doses for at least some individuals. That would mean that safety monitoring would have to be done not only after a first dose, but also after a second dose in case there is a two-dose effect, which would delay the ability to make any conclusive statements about the safety of this vaccine until the 21-day period between doses passed. One the other hand, the need for two doses also will provide an opportunity for a provider to see an individual who already received a dose of vaccine again and inquire about any adverse events that might have occurred in the interim. In addition to those adverse events that are being prepared for, which are adverse event that have been observed previously with other seasonal flu vaccines as well as the swine flu vaccine, there is the possibility of unanticipated adverse events that will have to be monitored for.

There will be vaccination of a large number of people in a short time period. In a seasonal flu vaccination campaign, 80% to 90% of individuals who are going to be vaccinated in a given season are vaccinated within the first about 4 weeks after vaccination is initiated. Therefore, safety monitoring will have to be done very quickly and might be challenging. As noted, the historical experience with the 1976 swine flu vaccine makes everyone extra cautious about utilizing this vaccine. GBS, an acute inflammatory demyelinating polyneuropathy of unknown origin, was observed after vaccination was initiated in 1976 with swine flu vaccine. GBS may be triggered by antecedent infections and about 30% or 40% is associated with infection with Campylobacter jejuni, but is also seen after respiratory infections. Some recent studies have illustrated an association of GBS with influenza-like illness (ILI) or confirmed flu, which again will make monitoring for GBS even more challenging in the context of people getting the flu and receiving vaccine. The background incidence rate in adults is about 1 per 100,000 person-years, and is much higher in people over the age of 50.

The 1976 vaccination program against swine flu was initiated in October of 1976 and was suspended in December of 1976, once preliminary data suggested an increased risk of GBS among vaccinees and the threat of the pandemic had passed. The current situation is somewhat different because, in fact, infection is on-going. Subsequent analyses of these GBS cases suggested an attributable risk of vaccine-related GBS among adults on the order of about 1 case per 100,000 vaccinees. There were a total of about 500 vaccine-related GBS cases out of the 40 million doses that were distributed. This risk was not associated with any one of the 4 manufacturers, and studies have been conducted to examine remaining vaccine from the 1976 vaccine to look for the presence of Campylobacter antigens, which was one of the theories of this association. Campylobacter antigens were not found in the vaccine. Ganglioside antibodies were found to develop after vaccination with the 1976 vaccine in mice, but subsequent seasonal flu vaccines also induced these antibodies in mice. The answer to the question of why this occurred after that vaccine is still not settled, which makes it important to continue to monitor that. Continued monitoring has been done to look for GBS after seasonal

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influenza vaccines. Consistent association has not been found, although with the 1992-1993 and 1993-1994 seasons, a slight increased risk in GBS after vaccination was noted. However, was on the order of about 1 case per million persons vaccinated, or a much less frequent association.

Safety is an element every step of the way. Because the vaccine will be used in such large numbers, post-marketing safety monitoring is where the rare adverse events will be found. The objectives for post marketing safety monitoring include timely identification of clinically significant adverse events following vaccination, rapid assessment of the significance of these adverse events that are identified, and the evaluation of the risk of vaccine-associated GBS. Timely identification should be able to be done with enhanced surveillance through the Vaccine Adverse Event Reporting System (VAERS); using the active surveillance with sequential analytic methods through Vaccine Safety Datalink (VSD) sites; and the Defense Medical Surveillance System (DMSS)), as the military will be an early user of vaccine. Also, special studies are being planned to examine hospital admission and discharge data and surveys of neurologist and others.

VAERS is a volunteer reporting system that is national in scope; that is flexible in that it can receive reports by internet, phone, fax, and mail and can assimilate all of those reports in real time; and is scalable. CDC is currently working to increase the staffing of nurses, coders, and analysts at VAERS to meet possible need. VAERS is also designed to accept reports not only from providers through electronic medical records or from manufacturers, but also directly from vaccinees or families. VAERS is going to require some enhancements to better quickly identify adverse events, although VAERS has been very useful in identifying adverse events associated with vaccines in the past. The enhancements that are under way or that are needed include communications efforts to support reporting, which will have to include providing information at the time of vaccination. CDC is also working to figure out ways by which to facilitate reporting of manufacturer and lot number, and this might be by providing written record to the patient and / or by bar coding vials so that information can be scanned directly into a patient record.

Another way to identify possible signals for adverse events is through active surveillance using managed care organization as sequential analytic methods, which allows rapid assessment of pre-specified adverse events. CDC will be able to perform a simultaneous analysis with appropriate comparison groups through these methods, and chart confirmation is feasible. This will allow quick identification of events that are highest priority for further investigation; however, this will require that accurate information on vaccination be available in managed care databases and also that sufficient numbers of individuals are vaccinated in managed care systems, so that there will be sufficient numbers necessary to identify rare adverse events. Active surveillance also includes a number of possible collaborations inside and outside the federal government, some of which are established and some of which are very new for CDC.

After these signals are identified, it will be necessary to assess the significance of adverse events. Certain pre-specified adverse events can be assessed through a sequential analytic approach. A list has already been developed based on experience with prior flu vaccines, the 1976 vaccine, and biological plausibility of adverse events that CDC would like to monitor. Background rates are currently being collected so that CDC will know as quickly as possible whether the rates being observed exceed background rates. As noted, CDC also anticipates that there will be other adverse events that have not been pre-specified. These will need rapid study utilizing linked immunization and outcome records. The agency expects to do a comparison of observed cases with expected cases based on known incidence rates and is

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prepared to conduct field investigation in collaboration with state health departments if necessary.

The third prong in CDC's strategy involves evaluating the risk of GBS associated with the pandemic flu vaccine. Of course, there is no particular reason to think that this should be associated. They are not very homologous, but CDC is planning to engage in active case finding of incident GBS cases in multiple areas. Ascertainment of vaccination status and other risk factors for GBS will be done when a case found. This is expected to be done using the assistance of the Emerging Infections Programs and state and local health departments. CDC is trying to enlist the assistance of the American Academy of Neurology (AAN) to created a listed surveillance with neurologists for GBS.

There remain unresolved issues regarding safety monitoring. The role of the VSD sites in vaccine administration under state and local plans is important, given that only if sufficient numbers of people under surveillance are vaccinated will a definitive association or lack thereof with possible adverse events be permitted. CDC is also still working on how to facilitate collection of accurate information on manufacturer and lot number after vaccination.

In summary, the established surveillance systems (e.g., VAERS, VSD, military) are going to be utilized and enhancements are planned for all of these systems. There are new collaborations being developed and that need to be developed so that CDC can extend the number of individuals under surveillance for adverse events. There is a need to consider vaccine safety monitoring when planning vaccine distribution in terms of tracking, manufacturer dose, and who is vaccinated. Vaccine-related risks will eventually need to be assessed in light of the severity of the pandemic. If the pandemic is wide spread and severe, the threshold for accepting mild vaccine associated risks will be much higher than if the pandemic is not as bad as predicted and the risks associated with vaccine are significant.

Discussion

With 5 manufacturers producing vaccine, Dr. Morse inquired as to whether consideration had been given to trying to stratify allocations geographically by region, state, and manufacturer to make it easier to track administration, monitor adverse effects, minimize changes in product between first and second dose, optimize data from the VSD system, et cetera.

Dr. Wortley responded that the thinking in the past has always been the opposite of that for risk management to distribute every manufacturer's vaccine across the country. The thinking was that if certain states were assigned to certain manufacturers and there was a glitch, there would be a major problem. However, she thought Dr. Morse's suggestions should be considered in terms of pros and cons.

Regarding the infrastructure of the plan to deliver vaccine, Dr. Sawyer indicated that his local health department, as had many others, experienced significant cuts in the last year. With that in mind, he requested further details pertaining to the magnitude of supplemental funding CDC was trying to obtain to build back up the infrastructure not only to deliver novel H1N1 vaccine, but also to assist in all other efforts including monitoring for safety. He also requested further information about potential provider administration fees, particularly for providers not actively engaged in government sponsored health care.

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Dr. Wortley deferred the first question to Dr. Schuchat, given that there were some issues still in flux. With respect to the second question, CDC envisions that vaccine that would be delivered in a provider's office and the provider would actually bill either Medicaid or private insurers just as if it were a regular vaccination. Preliminary conversations with America's Health Insurance Plans (AHIP) have indicated that insurers will likely cover this vaccine. Interestingly, even under Emergency Use Authorization, CDC initially thought this might be a problem. What may be trickier, just as it is for seasonal vaccine, is being vaccinated at a local pharmacy or other venue outside the practitioner's office. There are issues regarding contracts that exist between those entities and the health plans. In the doctor's office, one thing that will vary just like it would for any other vaccine is the state-to-state variation in Medicaid rates.

Dr. Schuchat added that CDC, the administration, and Congress are well aware of the fiscal challenges that states have in terms of the public health infrastructure. Congress passed a supplemental war bill and a contingency bill that would include additional funds. The administration is in discussions with Office of Management and Budget (OMB). The lack of ability to engage in this kind of vaccination program without additional support is well-recognized, and the magnitude of support is likely going to vary depending on the size of the program.

Dr. Neuzil stressed that it is certainly one goal of this program to get vaccine out and lessen morbidity and mortality from the pandemic virus. It is also important for this program to be strengthened such that it will not undermine the seasonal vaccination program in general. She agreed that safety surveillance is really critically important, noting that there are a number of lessons other than GBS from the 1976 swine flu having to do with temporally but not causally related events (e.g., the cluster of deaths that occurred in Pittsburgh during the 1976 influenza campaign). At some point, ACIP would like to hear about the detailed communication plans that will go along with risk management. Speaking to Dr. Sanchez, she said she was really quite impressed with the system that has been built and expressed her hope that they could capitalize on that for innovative safety assessments.

Dr. Marcy agreed that the 1976 GBS vaccine relationship was a cautionary tale about how real or perceived adverse events can affect an entire immunization program. It seemed to him that notably absent was the role of the Clinical Immunization Safety Assessment (CISA) network. It seems very important to specify and accurately delineate an adverse event and prevent what could be a mining of VAERS by the media. The media is just waiting to find something that is going to appear. If "it bleeds, it leads" and when it leads, it leads all over the country in the news.

Dr. Weinbaum responded that CDC anticipates CISA's involvement in reviewing adverse events reported to VAERS. There will be a major need to assure that any signal that comes up in VAERS is validated by record of use of that individual and on a population basis through the VSD managed care organization data. In terms of the question about communicating, the media, and damage control, CDC will do its best to make sure that they are aware of all signals and that they follow them up appropriately.

Dr. Schuchat elaborated that hopefully people are aware of how high a priority CDC gives to communication and to the H1N1 response to date. It has been among the agency's highest priorities to support state and local health departments, as well as the media, to get good information to people quickly. During this panel, several components of vaccination planning were presented, although the Communication Team did not present. This team includes a

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number of experts in this area. The agency views communications as critical, both for vaccination planning and the entire response in terms of what the country will continue to go through over the summer and in the fall. They will be happy to share communications plans the committee in the future. These plans are much more extensive than just vaccine safety risk management. There are also issues of supply, demand, flow, early deaths, et cetera. Focus groups have been initiated, and extensive plan are in place to get good information to people, when they need it, where they need it, and in as open and transparent a manner as possible.

Dr. Temte stressed that the potential safety issues could not be over-emphasized. There is a potential perfect storm of very rapid development and deployment of a new vaccine, over an incredibly wide target, in a medical care system that is terribly broken and very disparate. He had an experience with a gentleman who received travel vaccines from a travel clinic, who was later seen by a neurologist. Two months later, it was Dr. Temte who finally decided look into this and file a VAERS report because nobody else thought it was their duty. He was concerned that if they looked at only one group (e.g., neurologists), signals may be overlooked if they are not neurological. There must be a wider approach and the VAERS system needs to be more user-friendly. No one has the 45 minutes it takes to enter information into this system.

With respect to improvements, Dr. Weinbaum indicated that a new web interface for VAERS is due to be rolled out in September, which is intended to facilitate web-based reporting for VAERS. Some of the communications campaigns planned pertain to soliciting and increasing reporting to VAERS. Hopefully, through a combination of publicizing VAERS and making it easier to utilize for reporting, the amount of reporting that actually occurs will be enhanced.

Dr. Ehresmann noted that Minnesota uses a system that was developed in Wisconsin as do a number of other states. She wondered if there was a key constellation of information that CDC wanted to collect to have real time data on vaccine adverse events.

Dr. Weinbaum responded that using those information systems has not been a core part of the Immunization Safety Office's (ISO) planning. The VSDs have 9.2 million people in managed care, and they have a vaccine registry that is linked with their electronic health record data. CDC is definitely planning to use those. Based on the discussions during this meeting with respect to the possibility of using other immunization information systems, ISO needs to pursue and flesh that out. Others in the Immunization Services Division may have worked on this more than ISO has.

Dr. Schuchat added that the primary way in which immunization information systems have been considered in terms of denominator information was with the thought that adverse events would be presented elsewhere. However, if there are places in which electronic health records have been linked with severe adverse event registries, this would be worth exploring.

Dr. Chilton noted that several weeks ago, Secretary Sebelius and Education Secretary Duncan sent a letter to school superintendents about schools' involvement in an effort this fall. He did not hear anything in the presentations about the place of school immunization.

Dr. Wortley replied that if school aged children were at the front of the line for vaccine, schools will have to be considered as potential vaccination venues. There are various ways of doing that, either according to the model for seasonal flu in which vaccination occurs during school hours, or through clinics held at schools. Schools are familiar locations and using them would alleviate some of the complexities pertaining to collecting consent in advance, which is a

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challenging issue with regard to school-based vaccination. CDC is in the process of working with the Department of Education, with CDC staff planning to attend a joint meeting organized by the Department of Adolescent and School Health (DASH) and NACCHO. Many partners were also expected to attend from educational-related organizations. This meeting was expected to offer a good chance to hear about concerns, which CDC could think about as they prepared guidance for vaccinations related to school-aged children.

Regarding the recruitment of private providers to administer vaccine, Dr. Birkhead (NVAC) requested further information about the comment that there have been discussions with AHIP which suggested that reimbursement should not be a problem. NVAC's Finance Working Group issued a report last September illustrating problems with such reimbursement. New York has tried to explore how managed care reimbursement occurs for vaccine administration, finding that this is a "black box." New York negotiated provider-by-provider in terms of how payment would occur. Reimbursement for administration of vaccines ranged from $2 to $20. In some practices, there was not a specific reimbursement amount, given that it was basically included in the per capita payments that were made to the provider for those patients. If they really were trying to encourage providers to take on the role of vaccinating, telling them that two additional vaccines would be required in their existing rate would do little toward convincing providers to sign on. The complicating factor is that providers typically have arrangements with multiple plans, so they do not know exactly what reimbursement they are going to get. There seems to be a role for CDC and AHIP to communicate affirmatively with plans in the US about this problem. There needs to be transparency in how the reimbursement is going occur if providers are actually going to sign on. CDC and CMS need to drive home the issue that providers are simply not going to volunteer their time for no payment. There have been many reports of Tamiflu not being covered by plans, which highlights the issue that as many plans as there are, there are that many different arrangements for how payment occurs. There is not unified and does not instill confidence that there will be widespread recruitment of the private sector.

Dr. Wortley agreed, clarifying that what she intended to convey was that in preliminary conversations, CDC has been told that the insurance industry intends to support this. However, it is not a uniform industry and it is incredibly complicated to work within, particularly given that there are many insurance plans and products. CDC intends to tackle these issues and is forming a group to focus just on this issue.

Steve Foster (APhA) said he thought they were underestimating the ability / willingness of patients to pay for their own medication. Many times patients present at pharmacies whose plans will not cover what they take, yet many of them are willing to pay themselves. During the vaccine shortage a few years ago, people were walking in and they did not care that they had to pay themselves as long as they could obtain their vaccine. Other potential groups / venues to consider for distribution include colleges of pharmacy, colleges of medicine, and the vast number of students who are willing to help. Perhaps this could be coordinated through health departments.

Sandra Fryhofer (ACP) said she was convinced that there would be a vaccine for H1N1 virus in the fall, and that she was impressed with the plans to evaluate vaccine safety and effectiveness. However, she remained concerned about distribution even though McKesson is a large company that is used to distribution. She also remained concerned about getting people vaccinated. While ideally it would be prudent to administer seasonal influenza vaccine as soon as possible, the reality is that this does not always occur. She stressed the importance of making both seasonal and novel vaccine available to patients, who already have limited time to

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obtain their vaccines (e.g., time off from work, et cetera). Also of concern is that during these economic times, patients may not be as willing or able to pay for vaccines themselves. It is highly likely that an increasing number of patients will not have health plans; therefore, consideration should be given to how these vaccines might be acquired at cheaper prices.

Dr. Santoli indicated that she works in the branch within the National Center for Immunization and Respiratory Diseases (NCIRD) that supports the current contract with McKesson for distribution, under which half of the childhood vaccine in the US is distributed, including seasonal vaccine. On the public side, that is a relatively small amount of seasonal influenza vaccine. Given that after three years, this system for distribution can meet the needs of many providers, it seemed to be a good place to start. One of the thoughts when the system was created was to determine whether this might be a way to assist in response to emergencies. Clearly, the magnitude of novel influenza vaccine to be distributed and the time frame absolutely dwarf what occurs every year. CDC approached McKesson because they are a much larger distributor than the group CDC works with, and because CDC has a system that they know can work. McKesson has been given all of the assumptions and is aware of the very uncomfortable uncertainty of going from 0 doses to 600 million. With this information, they have been asked to consider what they can leverage within their own company and what they might leverage through partnerships with other distributors. She expects McKesson to develop a plan that will work.

Sandra Fryhofer (ACP) encouraged the agency to have a Plan B in place. “Putting all eggs in one basket” could result in a scenario similar to what occurred a couple of years ago when there was only one company producing influenza vaccine.

Harry Keyseling suggested reviewing the oral polio community campaigns as a model for community campaigns, stressing that they should not underestimate the opportunity to ask healthcare professionals to volunteer.

William Schaffner (NFID) pointed out that a major stumbling block in 1976 was liability coverage, which he had not heard mentioned.

Geoffrey Evans (HRSA) responded that legislation was passed in 2005 known as the Public Readiness and Emergency Preparedness (PREP) Act, which sets up liability protection for makers of covered countermeasures as declared by the Secretary of Health and Human Services (HHS). The pandemic H1N1 vaccine and Relenza and Tamiflu have been declared covered under this authority. Funding has recently been authorized to put into effect the compensation elements of this act, which would be an administrative program modeled after the Smallpox Vaccine Injury Compensation Program. The Health Resources and Services Administration (HRSA) has the responsibility for administering and putting that into effect. This is all very embryonic at this point.

William Schaffner (NFID) thought there needed to be some discussion about seasonal influenza administration and its timing. He wondered whether the manufacturers were going to have an opportunity to indicate how much seasonal vaccine they have and when they plan to begin shipping.

Geoffrey Evans (HRSA) suggested that if possible, it would be beneficial to have a separation of the seasonal program from the H1N1 supply and distribution to clarify safety.

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With respect to nomenclature, Patsy Stinchfield (NAPNAP) pointed out that numerous terms were being utilized to describe novel influenza (e.g., swine flu, H1N1 influenza, novel influenza, pandemic H1N1, pandemic virus) and soon that would be overlaid that with "seasonal H1" and pick your "N1 combination." With that in mind, she thought it was time to move to something broader, such as "2009 pandemic influenza" perhaps shortened to "pan flu." This is going to affect public communication and media messages. The media is already stumbling over H1N1 and what that really means. It is going to be very difficult to separate the various vaccines, particularly if people are presenting four times in one season. Even the manufacturers' labeling of those vaccines for medication errors and safety issues will be affected by nomenclature.

Dr. Schuchat agreed with the priority of clear communications. There is mixed information currently about what people understand and what messages will be the clearest.

As the co-chair for the National Influenza Vaccine Summit, Litjen Tan (AMA) reported that CDC's Communications Team would be presenting during the Summit's H1N1 session. The goal of the Summit is unification of messages pertaining to influenza. The Summit is seeking guidance from everybody in terms of messages (e.g., community immunizers, distributors, manufacturers, et cetera).

Kelly Moore (Tennessee Immunization Program urged the committee and others to reflect on the debacle of 2004. Many of the suggestions currently being discussed were attempted then, with many challenging logistical issues that resulted ultimately with only 60 million doses being distributed and millions of doses unused despite best efforts to get it to the right people. Her department is much less capable of administering vaccine now than it was then because of personnel cuts. Therefore, she stressed that they could not permit distribution and trying to manage the product too carefully get in the way of actually administering the vaccine. States must get out of the way. When her state dictated where vaccine was to be distributed, vaccine shipments were delayed dramatically. Nursing homes were waiting a month after they placed their orders through the state.

Dr. Santoli responded that there was centralized distribution in 2004-2005 that was drastically different from the current system, in that there were 12-15 distributors. The effort was to attempt to share equitably among planners to distribute flu vaccine. There was no coordination among them, and there was not a good method for getting information back from them. That quasi-centralized distribution was invented during the shortage. There is, indeed, a lot to learn from that experience. The discussion about centralized distribution is drastically different from what occurred in 2004-2005.

Regarding the cross strain effectiveness of A/BRISBANE/59/07, Robert Malone (Focus Diagnostics) said he assumed that with respect to the aggregated analysis across all vaccines, the database is not large enough to support a break out of TIV versus live attenuated in terms of the T-cell component to potential protection.

Dr. Shay responded that most of the vaccine that is still distributed in the US is TIV. In the analysis done so far, conclusions can probably only be drawn about TIV. That will probably be true for the data received from community-based sites as well.

Robert Malone (Focus Diagnostics) thought it would be very useful to actively capture data relating to potential effectiveness of the live attenuated vaccine.

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Dr. Lett agreed that states needed to be taken out of the way to a certain extent to allow the vaccine to get to the private sector. In her state alone there are probably 20,000 private providers who are not enrolled in a VFC program. She thought every state was probably in a similar situation. While states may need to have some control over public clinics and emergency dispensing sites, it is imperative to widely disseminate this vaccine. With that in mind, perhaps CDC needs to think about other contracts with other distributors such that shipping can occur directly from the manufacturers to the private sector.

Dr. Wortley replied that potentially the system could evolve into this; however, the unknown at this point is that it is not entirely clear how much vaccine there will be in the beginning. Because vaccine must be allocated across the country, the system must be flexible.

Dr. Santoli added that the discussions so far have pertained to states controlling what occurs in the beginning, using a centralized distributor. Consideration must be given to how to subsequently transition from state control to non-state control. That has yet to be mapped out, but should probably be taken under advisement with the group of states CDC converse with on a regular basis regarding planning.

Summary of Issues / Next Steps

Anthony Fiore, MD, MPH
Influenza Division, NCIRD, CDC

Dr. Fiore summarized that in terms of the epidemiology and virology, circulation of novel H1N1 continues in the US, although it appears to be declining. Morbidity has largely been among younger adults and children. It is believed that a large proportion, and perhaps virtually all of the younger population, is susceptible and co-circulation of both seasonal and pandemic viruses is expected. Therefore, plans need to be in place for co-circulation. Vaccine development appears to be proceeding as planned. The timelines for availability and the supply are not certain and depend upon yet unknown production constraints and formulations that are ultimately chosen. However, the initial vaccines are likely to be similar to seasonal vaccine formulations and not adjuvanted, depending upon immunogenicity studies. In terms of implementation goes, planning has been done for near simultaneous seasonal and H1N1 vaccine programs. Communication is expected to be a major challenge, and perhaps a new session will be needed on that during the next ACIP meeting. The uncertainties about availability, formulation, program scale, and demand continue to make planning challenging. Assessment plans are in place, including vaccine effectiveness and safety plans.

In terms of early use of seasonal vaccine, current ACIP guidelines indicate that use can begin when vaccine is available and that this will provide protection even when there is early circulation of influenza viruses. There is no evidence for clinically important waning immunity among those vaccinated in late summer and early fall. Early vaccination will reduce overlap between pandemic and seasonal vaccine campaigns. Manufacturers estimate that there will be approximately 120 million doses for the upcoming season. There might be as many as 15 million doses available by mid-August, 40 million by September 1, and over 90% of doses shipped by November 1. This offers a great opportunity to plan on early vaccination using seasonal vaccine, perhaps earlier than the usual planning that occurs in October and November. Early availability of vaccines includes both preservative-free vaccines and infant and toddler doses, which will be important especially since a lot of those have to be given twice in a season.

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ACIP's role in the next few months includes the usual role of epidemiologic data review; review of vaccine studies; and review of program plans. It appears that ACIP has a major role in developing and reviewing the plans for vaccination targeting, and will be working to re-assess the vaccine prioritization plans that were made as part of pandemic planning over the past couple of years. Certainly, ACIP suggestions are welcome about ways to reduce impact on seasonal vaccination program. The current ACIP guidance is a start toward that. ACIP and the vaccine workgroup will begin development of guidance for pandemic influenza vaccine use as more is known about what that vaccine will look like. It is likely that there will be a need for an off-cycle meeting prior to the standing October meeting, perhaps in July or August.

Pneumococcal Vaccines

Pneumococcal Vaccine Work Group

S. Michael Marcy, MD
Clinical Professor of Pediatrics
UCLA Center for Vaccine Research
Harbor-UCLA Medical Center

Dr. Marcy reported that in 1919, Abrahams, Hallows, and French described a condition which began with relatively mild flu-like illness, but rapidly progressed to a purulent bronchitis and then what they called influenza pneumonic septicaemia [Abrahams A, Hallows N, French H. A further investigation into influenza pneumococcal and influenza-streptococcal septicaemia: epidemic influenzal "pneumonia" of highly fatal type and its relation to "purulent bronchitis." *Lancet* 1919; 1: 1–11]. They drew three faces (red, white, and blue), the first of which they described as "An early case in which the facial colour is frankly red, and the patient might not appear ill were it not for the drooping of the upper eye-lids and a half-closed appearance to the eyes." They explained that this could progress to "Cyanosis in which the colour of the lips and ears arrests attention in contrast to the relative pallor of the face. The patient may yet live for twelve hours or more." This was followed by "The heliotrope cyanosis. The patient is not in physical distress, but the prognosis is almost hopeless." This was their recognition of the fact that secondary bacterial infection is a common problem with influenza respiratory disease, particularly lower respiratory disease.

The pathophysiology of influenza with secondary bacterial infection is better understood today as Brundage has illustrated and as Morens indicated in his paper in 2008. Secondary bacterial infection, particularly with pneumococcus, is an important aspect of the morbidity and mortality of influenza illness. It is understood that influenza infection alone may cause serious, indeed fatal, pulmonary illness and that pneumococcal illness alone can do so as well, but the two together create "a perfect storm." Indeed, when the two come together, the influenza predisposes patients to pneumococcal infection by destroying / damaging physical barriers, increasing adherence (NA medicated), decreasing mucociliary activity, immune cell dysfunction, immune system disregulation, and upregulated gene expression (toxins) [Brundage J F: Interactions between influenza and bacterial respiratory pathogens. Implications for pandemic preparedness. Lancet Infect Dis 2006; 6: 303-12; Morens D M, et al: Predominant role of bacterial pneumonia as a cause of death in pandemic influenza. Implications for pandemic influenza preparedness. J Infect Dis 2008; 198: 962-970].

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With that background in mind, the pneumococcal vaccine working group approached the problem of how pneumococcal vaccine should be integrated into the program of novel H1N1 vaccine. The group recognized that influenza plus pneumococcus yields pneumonia in many cases, but it also results in a fairly significant fatality rate when the two are present in large numbers. The working group discussed the epidemiology of novel H1N1; evidence of secondary bacterial infections; vaccine safety, effectiveness, and cost-effectiveness; vaccine supply and allocation; distribution and control; and implementation of new recommendations. Taking somewhat of a turn, the group also discussed the role of immunization; antivirals; antimicrobials; and the supply of antivirals and antimicrobials. Dr. Marcy reminded everyone how Cipro disappeared off of every pharmacist's shelf during the anthrax scare and became virtually impossible to obtain. Thus, there is a potential for antimicrobials and antibacterial agents to be a problem that will have to be dealt with during the upcoming possible pandemic. The group also deliberated the 13-valent pneumococcal conjugate vaccine (PCV13), which may be available sometime in September to October in time for inclusion in the program for the H1N1 vaccine program, in terms of serotype specific pneumococcal disease, potential expanded prevention that this vaccine may offer, and options for catch up immunization. The group also discussed the status of the investigational 13-valent pneumococcal conjugate vaccine and the public health and economic impact of PCV13 (e.g., direct and indirect benefits; routine immunization in children ages 1 through 5 years; and catch-up program for children <5 years old).

Planning for Use of 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) to Prevent Pandemic Influenza A (H1N1)-Associated Pneumococcal Pneumonia

Matthew R. Moore, MD, MPH
Commander, USPHS

Dr. Moore first offered a recap of the February 2009 ACIP meeting with respect to policy options considered by the ACIP Pneumococcal Vaccines Working Group. He stressed that they were in a very different place in terms of thinking about pandemic influenza preparedness then. At that time, three potential policy options were discussed:

- Assuming that a pandemic will occur in the near future, expand current recommendations for use of PPV23 as soon as possible
  - Unclear target groups, unclear benefit
  - Programmatic challenges to expanding target groups
  - Concerns about re-vaccination and hyporesponsiveness

- Encourage implementation of current recommendations (http://www.pandemicflu.gov/vaccine/pneumococcal.html)

- Administer PPV23 to critical infrastructure personnel targeted for pre-pandemic influenza vaccine when a pandemic is declared
  - Relatively young, healthy population likely to respond to PPV23
  - Programmatic efficiency with pre-pandemic influenza vaccine
  - Fulfills planning objective of maintaining critical response functions

Option 1 is no longer an option, Option 2 is still very much an option, and Option 3 needs to be modified because currently consideration would be given to administering PPV 23 to critical infrastructure personnel very soon and would need to think about whether there is a way to do that without disrupting distribution and administration of seasonal and pandemic influenza

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vaccine. In choosing from among the options, the working group considered the epidemiology of pandemic H1N1 infection, including bacterial complications; safety, effectiveness, and cost-effectiveness of PPV23 in persons with pandemic H1N1 infection; supply of PPV23 and prioritization among potential new groups targeted for vaccination; and implementation of any new recommendations.

In terms of the evidence of bacterial infections among hospitalized cases of H1N1, a *Morbidity and Mortality Weekly Report (MMWR)* was published several weeks ago from California in which they described their first 30 cases of confirmed or probable novel H1N1 individuals who were hospitalized for at least 24 hours between late April and mid-May. These data are very consistent with Dr. Finelli described the previous day in her presentation of data on hospitalized cases. Most notable is that of the 30 cases, none had any evidence of bacterial infection. However, since the publication of that *MMWR*, CDC became aware of a 45 year old male who was found dead in his home. He was obese and had cardiovascular disease and sleep apnea. At autopsy, his lungs showed heavy consolidation consistent with bacterial pneumonia. The tissue specimens from his lungs were positive for novel H1N1, *S. pneumoniae*, and group C streptococcus. Soon after this initial publication came out, California became aware of a fatal case associated with secondary bacterial infection [MMWR 2009; 58(19):536-541; Personal communication, Dr. J. Louie, California Dept. of Public Health].

In terms of the epidemiology of the pandemic H1N1-associated hospitalizations, 142 (71%) of 201 hospitalized cases of confirmed novel H1N1 infection had $\geq$1 risk factor for influenza-related complications (e.g., chronic lung / cardiovascular disease, diabetes, immunocompromised, smoking, chronic renal disease). Conversely, among the 59 patients with no underlying conditions, 20 were healthy children <5 years old. This is a group who would not normally be thought of in terms of administering PPV23, but is currently receiving the 7-valent pneumococcal conjugate vaccine (PCV7), and if and when it becomes available would receive the 13-valent conjugate vaccine (PCV13). Among the same cohort of hospitalized cases, about 1/3 had abnormal chest x-ray findings consistent with pneumonia, about 2/3 of those had bi-lateral infiltrates and 2/3 had at least one underlying medical condition. The median age was about 24 years. At least from this cohort, it appears as though most patients who are admitted to the hospital had existing indications for PPV23 vaccine, and among those who are diagnosed with pneumonia upon admission, most also had indications for PPV23 vaccine.

From this same cohort, there was evidence of bacterial infections among the non-fatal hospitalized cases in two instances (n=184). Within this group, a 23 month old male with empyema had a pleural biopsy performed and group A streptococcus was identified by immunohistochemistry (IHC) and by molecular assays. Also included in this group was a 58 year old female who was previously healthy, had chest x-ray confirmed pneumonia and streptococcus pneumonia grown from culture collected at the time of a bronchoalveolar lavage (BAL). When CDC first began hearing about these kinds of cases, it occurred to them that these are fairly invasive procedures and are not the most common way to diagnose pneumococcal pneumonia or even bacterial pneumonia. The situation is evolving very rapidly.

The age range of these cases is broad. These are fatal cases with evidence of bacterial infections, and they range from a couple of months old to about 57 years of age. The duration of illness is on the order of between 1 day and about 9 days. A large proportion of these patients had underlying conditions, but not all of them. Roughly 1/3 of them had no known underlying condition as far as is known; however, this information is evolving and could change. The autopsy cases were diagnosed largely by IHC.

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The working group also discussed the safety, effectiveness, and cost-effectiveness of polysaccharide vaccine in persons with pandemic H1N1 infection. From a safety standpoint, it is known that polysaccharide vaccine is safe when it is co-administered with seasonal influenza vaccine; therefore, it is assumed that it would be safe when administered with pandemic H1N1 vaccine. Obviously, this will remain unknown for certain until the vaccine is available. Effectiveness, as discussed at length during the February 2009 ACIP meeting, depends upon the age of the person receiving the vaccine and whether they have any co-morbidities. From the standpoint of cost-effectiveness, also discussed at length in February, there was some agreement that most scenarios suggested that polysaccharide vaccine would be cost-effective under a wide range of assumptions. A key driver of the cost-effectiveness was the effectiveness of pre-pandemic H1N1 vaccine, which may be important moving forward in the discussions about polysaccharide vaccine.

In terms of vaccine supply issues, one way to think about supply is in terms of how many people in the country are currently unvaccinated but who have existing ACIP indications to receive the vaccine: 30 million individuals who smoke in the US, 21.6 million individuals who are between the ages of 2 and 64 years who have underlying illnesses that increase the risk of pneumococcal disease, 14.7 million individuals who are 65 years of age and over, and 3.4 million individuals who have asthma. That is, it is currently estimated that there are about 70 million people in the US who have indications for polysaccharide vaccine but have not been vaccinated.

If the recommendations were expanded to include additional groups outside of those listed, consideration must be given to who those groups might be and how many individuals this would include. One way to look at this is to consider the “Draft Strategy and Guidance for Pre-Pandemic Influenza Vaccination,” which is related to but different from the prioritization scheme discussed the previous day. Approximately 8.1 million persons are included in “Tier 1” of the “Draft Strategy and Guidance for Pre-Pandemic Influenza Vaccination.” Of these, 3.2 million are front-line hospital-based healthcare providers (HCP) and 2.3 million are front-line outpatient HCP. The working group considered whether HCP should receive PPV23 to minimize time off from work. It would be a good idea to keep healthcare workers on the job as much as possible and perhaps, the administration of polysaccharide vaccine would be a good way to approach that.

Then the obvious next question regards whether there is evidence of bacterial complications of pandemic H1N1 infection among healthcare personnel. The following is the first paragraph of a recently published *MMWR* on novel influenza infections among healthcare personnel in the US:

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Novel Influenza A (H1N1) Virus Infections Among Health-Care Personnel — United States, April–May 2009

Soon after identification of novel influenza A (H1N1) virus infections in the United States in mid-April 2009, CDC provided interim recommendations to reduce the risk for transmission in health-care settings. These included recommendations on use of personal protective equipment (PPE), management of health-care personnel (HCP) after unprotected exposures, and instruction of ill HCP not to report to work (*1*). To better understand the risk for acquiring infection with the virus among HCP and the impact of infection-control recommendations, CDC solicited reports of infected HCP from state health departments. As of May 13, CDC had received 48 reports of confirmed or probable infections with novel influenza A (H1N1) virus* (*2*); of these, 26 reports included detailed case reports with information regarding risk factors that might have led to infection. Of the 26 cases, 13 (50%)

MMWR 2009;58(23):641-645

The bottom line for the purposes of this discussion was that at this point, there is no evidence of increased risk of pandemic H1N1 infection among healthcare personnel. That is not to say that there have not been any infections. There clearly have been. It is just not clear that healthcare workers are at increased risk compared to the general population. There is also no evidence of increased risk of bacterial complications among healthcare personnel who have pandemic H1N1 infection.

Returning to the policy options and thinking about the advantages and disadvantages, Policy Option 1 was simply to encourage the implementation of the existing ACIP recommendations. The advantages of that option are that these are groups are already known to be at increased risk of pneumococcal disease; administering vaccine now may provide additional benefit to those individuals in the context of the pandemic; and it is an opportunity to increase coverage in a group that has relatively low coverage at this time. The disadvantages are that historically it has been very difficult to increase coverage among that group, which will be even more difficult in time when resources are stretched; and there is inconsistent evidence of effectiveness against pneumococcal pneumonia among persons with co-morbidities.

Policy Option 2 regards administering polysaccharide vaccine to critical infrastructure personnel (e.g., healthcare personnel). This has several advantages including the potential to keep healthcare personnel on the job during a fall wave or perhaps even during the summer if the epidemiology continues; these are largely healthy individuals who would be expected to respond well to the vaccine; and there is some evidence of cost-effectiveness, especially in the absence of other interventions. Relatively speaking, implementation in healthcare workers may be somewhat easier than implementation in other groups. The disadvantages are that there is currently no evidence of increased risk of pandemic H1N1 or associated complications among healthcare personnel; there is the issue of hypo-responsiveness; despite this group being relatively easier to reach than other groups, it would still be challenging to administer

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polysaccharide vaccine to this group given the likely need for 2 doses of pandemic H1N1 vaccine and 1 dose of seasonal influenza vaccine; and this could divert the supply from other individuals who they have been trying to reach for many years.

The conclusions of the working group were that the current epidemiology does not suggest a need for expansion of polysaccharide vaccine recommendations to include these additional target groups; healthcare personnel may be a logical group for expanded recommendations if the epidemiology of pandemic H1N1 suggests an increased risk of pneumococcal pneumonia; existing recommendations should be reiterated for use of the vaccine among persons known to be at increased risk of pneumococcal disease; monitoring of the epidemiology of the pandemic (including bacterial complications) should be continued moving forward through summer and into the fall. The issues should be revisited as additional information becomes available.

Acting on the advice of the working group, interim guidance was posted on CDC's website for the use of PPV23 during the novel influenza A outbreak. Essentially, this guidance reiterates the existing ACIP indications, but the working group wanted to give it a prominent place so that people could keep this in mind going forward. The group also discussed possible triggers for expansion of polysaccharide vaccine recommendations. Development of antiviral resistance among pandemic H1N1 strains might make administration of polysaccharide vaccine more attractive. There is not an available or effective pandemic H1N1 vaccine. Obviously, if elevated secondary pneumococcal pneumonia attack rates are observed, perhaps from the Southern Hemisphere going forward into the fall, this would be a trigger. Other triggers would be increased risk of pneumococcal pneumonia among specific populations with pandemic infection (e.g., healthcare personnel); or increasing severity of disease, including mortality.

In conclusion, the following questions were posed to ACIP:

- Does the ACIP have additional comments on the policy options discussed by the Working Group?

- What additional information or "triggers" should push the ACIP to consider expanding current recommendations for PPV23 to minimize pneumococcal pneumonia as a complication of pandemic H1N1 influenza?

Discussion

Dr. Baker thanked the group for their nice review and congratulated them in coming to what she thought were very reasonable conclusions, with the flexibility to make changes as necessary depending upon evolving epidemiologically.

Alexis Elward (HICPAC) indicated that this information was presented to HICPAC during its June 2009 meeting, at which time HICPAC agreed with the pneumococcal working group's conclusions that expansion of recommendations was not indicated at this time. The primary drivers behind that included the lack of severity of novel H1N1, and the lack of evidence of increased risk among healthcare workers. HICPAC also agree the conclusions should be revisited if the data change.

James Turner (ACHA) recalled that the pneumococcal recommendation had been changed to include smokers and asthmatics 19 years of age and older. He also inquired as to whether the pie chart showing 70 million included new cohorts of 19 years olds who smoke and have

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asthma. He pointed out that link (http://www.pandemicflu.gov/vaccine/pneumococcal.html) provided to the current recommendations for pneumococcal vaccine needed to be updated.

Dr. Moore responded that the pie chart showing 70 million includes new cohorts of 19 years olds who smoke and have asthma, and that the correct link for the website would be provided.

Noting that there seemed to be a lot of recent data on deaths, Dr. Morse wondered whether this meant that the potential for new information was increasing and the same monitoring was taking place in the Southern Hemisphere.

Dr. Schuchat responded that international monitoring efforts are diverse. There are virologic surveillance systems that track influenza strains, but there are also many places where severe acute respiratory infection is being monitored, which would include invasive pneumococcal infection. There are sites such as those in South Africa where CDC has been collaborating for many years to conduct intensive surveillance for influenza and severe illness, but they have also had a national system for invasive pneumococcal infections. That is a very special population at very high risk for pneumococcal infections due to the HIV epidemic. Australia also has good pneumococcal tracking, so more information is likely to be forthcoming.

Dr. Pickering noted that obesity seemed to be a major underlying risk factor, and requested that Dr. Moore comment further on this issue.

Dr. Moore responded that obesity was indicated as an underlying condition in some of these cases. One individual had asthma as a co-morbidity with obesity, while another had cardiovascular disease as a co-morbidity along with obesity. However, there were individuals who appeared to have obesity without other underlying conditions. It is just too early to tell whether obesity is a risk factor for pneumococcal disease complicating H1N1 infection.

Dr. Schuchat added that some additional comparisons have been done of obesity in the general population and obesity in hospitalized patients. It is really morbid obesity that is over-represented rather than just general obesity. It is fairly universal that people who are morbidly obese have respiratory compromise, restrictive respiratory problems, et cetera. While there are patients in the general H1N1 surveillance who have obesity as their only apparent medical problem, this is being considered as a subset of the chronic respiratory illness that is already an indication for both influenza vaccine and pneumococcal polysaccharide vaccine.

Cindy Whitney (CDC) commented that it was interesting as this outbreak was unfolding that secondary bacterial infections were not being observed in the places they were being looked for. That is surprising, given the older data that suggest that when examining an autopsy series it is always there. It is being found in the severely ill or dead when there are good specimens.

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13-Valent Pneumococcal Conjugate Vaccine (PCV13): Disease Burden Estimates & Options for Catch-Up Immunization

Pekka Nuorti, MD, DSc
Respiratory Diseases Branch
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Dr. Nuorti began by reviewing the ACIP recommendations for use of pneumococcal conjugate vaccine. In 2000, the 7-valent pneumococcal conjugate vaccine (PCV 7) was introduced. It was initially recommended for all children <2 years of age, and children 2-4 years of age with certain underlying medical conditions and immunocompromising conditions. At that time, there was also a recommendation to consider the vaccine for children 2-4 years of age, with priority for those 24 to 35 months of age in the Alaska Native, American Indian, and African American populations, as well as those attending day care based on higher rates of disease in those groups.

In 2007, the recommendation was revised to include all children less than 5 years of age. Today's discussion is about the recommendation for the 13-valent vaccine (PCV13) that will replace PCV7 in the future. PCV13 contains 6 additional serotypes, including 19A. It is currently under FDA licensure review for a pediatric indication against invasive disease and otitis media in children less than 5 years of age. It is expected to be licensed during the 4th quarter of 2009. Timing might allow use of this vaccine during the upcoming influenza season.

During this presentation, Dr. Nuorti provided an overview of the estimated potentially vaccine-preventable burden of invasive pneumococcal disease (IPD) caused by serotypes included in the new vaccine in the vaccine target group of children under 5 years of age as well as in adults due to the potential for indirect effects. In addition, Dr. Nuorti discussed the options that the workgroup has considered regarding a PCV13 catch-up immunization program for older children who have received all of their PCV7 doses.

With respect to the baseline rates of IPD after 8 years of routine PCV7 use, Dr. Nuorti reported on data from the Active Bacterial Core Surveillance (ABCs), which is an active population-based and laboratory-based surveillance system for IPD in a population of about 18.5 million people. During 1998-1999, before PCV7 was introduced, the rate in children less than 5 years of age was about 100 per 100,000. At that time, about 80% of disease was caused by the serotypes that are included in PCV7. After PCV7 was introduced, rate of PCV7 type disease decreased rapidly and these types are currently practically eliminated with a rate of less than 1 per 100,000. However, soon after the vaccine was introduced, non-PCV7 type disease began increasing and resulted in the overall incidence of IPD, leveling at 22 to 25 cases per 100,000 [CDC, Active Bacterial Core surveillance, unpublished].

Taking a closer look at the absolute rate differences, stratified by age and comparing the rate in 1998 to the rate in 2007, the rate difference from 1998 to 2007 especially in children less than 2 years of age was quite dramatic at about 120 and about 170 per 1000,000. The current rates are much lower than they were before PCV7 introduction. After 2 years of age, the rates decreased fairly rapidly. Currently, the rates in children under 2 years of age are actually lower than the rates in 2 year olds were in 1998, before the PCV7 was introduced and these children were not originally recommended to receive PCV7.

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The 6 new serotypes included in the conjugate vaccine are 1, 3, 5, 6A, 7F and 19A. Looking at the rate difference in incidence by 1 year age strata, by vaccine serotype group, the same pattern is seen with decreasing rates by age. In addition, PCV6 type diseases constitute fairly similar proportion of the total rate in all of the age groups. However, the expected absolute rate reductions are going to be much less than they were with PCV7 given the current rates of disease [CDC, Active Bacterial Core surveillance, unpublished].

In terms of the proportion of remaining IPD cases by conjugate vaccine serotype in children less than 5, in 2007 there were approximately 5,000 estimated cases in the United States (US). Of the serotypes causing disease, PCV7 types are now less than 2% of the cases. The majority of remaining disease is caused by serotype 19A (42%), followed by 7F (14%), and serotype 3 (5%). There are very few cases of serotype 1 and 5 disease in the US, although these types are important in other parts of the world and could also be important for other pneumococcal syndromes. For example, serotype 1 has been identified in empyema complicating pneumonia. There is also very little serotype 6A in invasive disease in children. Overall, the PCV13 types account for approximately 64% of the remaining cases or about 3,200 annual cases in the US. It is important to note that the three most common serotypes (19A, 7F, and 3) actually account for 98% of the new 6 serotypes.

With regard to overall incidence of IPD by race, the pattern is similar as in overall disease shown before, but there remains about a 2-fold higher risk of disease among black children compared with white children, although the baseline rates are much lower than they were before PCV7 introduction. Another important group to consider, particularly for catch-up vaccination, are older children who have chronic illnesses or are immunocompromising conditions (e.g., sickle cell disease; HIV). In 2000, PCV7 was recommended for older children 24-59 months of age with these conditions [MMWR 2000;49(RR-9)]. In terms of the proportion of serotypes causing disease among children who have underlying medical conditions compared to healthy children, differences were observed. Based on a combination of two years of data and 30 identified cases with underlying medical conditions (about 10% of all cases in this age group), there were differences in serotypes causing disease. One of the more important differences was that the PCV13 types accounted for 43% of the isolates among children with chronic illnesses compared with about 70% among healthy children, despite small numbers this was a statistically significant difference. In addition, since these children are currently recommended to receive 23-valent polysaccharide vaccine after their conjugate vaccine series at age 2, the 11 additional serotypes included in the polysaccharide vaccine in addition to the PCV13 types accounted for 13% of the disease. Many other serotypes that are not in any vaccine were also causing disease in this group of children who are at very high risk of disease.

Invasive disease in adults is going to be very important because of the potential indirect effects. Adult disease has become even more important due to the changes in the epidemiology that have been brought about by PCV7. Children under 5 years of age account for about 5,000 IPD cases per year or about 12% of the remaining disease burden. However, of the estimated 42,000 annual cases of invasive disease in the US, in 2007, 85% occurred in adults. The trends in PCV7 type disease in adults are similar to those in children; PCV7 type disease has declined dramatically and demonstrated the indirect vaccine effects in unvaccinated groups. Decreases in vaccine type disease have resulted in reductions in overall rates of IPD among adults by about 23% to 49%, depending on the age group. With regard to the proportion of cases that were caused by serotypes in different vaccine formulations, there is still some PCV7 type disease left in adult age groups. PCV13 types caused approximately 43% to 51% of the disease in adults in 2007. It appears that there is a slightly decreasing trend in serotype coverage with increasing age. Adults 65 and older represent the highest risk groups and have

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the highest rates of disease. The proportion of remaining invasive cases by PCV serotype and the serotype distribution in adults is quite different from children. About 7% are due to PCV7 type disease, 14% 19A, 8% 7F, 10% serotype 3, very few serotype 1 and 5 disease, and some serotype 6A disease. These are the same serotypes that are causing disease in children, but PCV 13 type disease accounts now for about 43% of the remaining cases, while the 4 serotypes 19A, 7F, 3, and 6A account for 99% of the new serotype disease [CDC, Active Bacterial Core surveillance, unpublished].

In summary, the serotypes included in PCV13 cause almost two thirds of the remaining IPD in children less than 5 years of age; however, it is important to note that the baseline rates are now much lower than before PCV7 introduction and therefore, the expected absolute rate reductions are smaller. Three serotypes account for 98% of the new serotype type disease and although the rates are lower, racial differences continue. Children 24-59 months with chronic conditions are a small but important group because they are likely to remain at increased risk of disease although the data are limited. The data are limited to numerator data, given that there is not good denominator information from which to calculate rates in most of these groups. The IPD serotype distribution in adults is different from children.

Regarding the possible PCV13 catch-up immunization strategies, typically catch-up refers to catching up children who have missed doses. When PCV7 was introduced, this pertained to unvaccinated children who were recommended for catch-up vaccinations. For PCV13, catch-up refers to one additional PCV13 dose for children who have been fully vaccinated with PCV7. The goals of this strategy would be to provide direct protection against the 6 new serotypes for the children who will receive the catch-up dose, as well as potentially accelerating the indirect effects in unvaccinated groups. The rationale for indirect effects is that children aged >12 months may be important for transmission of *S. pneumoniae,* and reduction in nasopharyngeal carriage of certain PCV6 types.

The topics that the working group has considered for a universal catch-up program include safety information for the 5th conjugate vaccine dose, immunogenicity of one dose for the 6 new serotypes in older children, and the incremental public health impact and cost-effectiveness compared with routine immunization of birth cohorts. In terms of programmatic issues, realizing that there is going to be a considerable amount of vaccination underway in the fall, this means yet another vaccine to add to the crowded schedule. With that in mind, some possible options for a PCV13 catch-up program for older children include the following:

1. All children aged 16-59 months

   OR

2. All children aged 16-35 months AND children 36-59 months with high risk conditions

   OR

3. All children aged 16-23 months AND children 24-59 months with high risk conditions

   OR

4. Children aged 16-59 months with high risk conditions only

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These are not in the order of preference, but instead represent the order of decreasing size of the target group. PCV13 can be substituted for PCV7 at any point in the schedule. One dose of PCV13 in children 12 months and older induces a response that is non-inferior to the 3-dose primary infant series, as well as functional antibody response. The safety profile of 1-2 doses of PCV13 after 4 PCV7 doses is comparable to a 4 dose series. Currently, no data are available on reduction in carriage of PCV6 serotypes after single PCV13 dose in older children (serotypes 1,5 and 7F are rarely carried). There is no information on the duration of protection of a single PCV13 dose. Data are needed with regard to whether one PCV13 dose will also be sufficient for children 24-59 months with underlying medical conditions.

In conclusion, transition from routine infant PCV7 vaccination to PCV13 has the potential to substantially reduce remaining IPD. A PCV13 catch-up program would provide direct protection for children receiving the vaccine and might enhance the indirect effects in unvaccinated groups. Rapid PCV13 introduction, including a catch-up program during the 4th quarter of 2009 might have the potential benefit of reducing pneumococcal infections complicating influenza. Dr. Nuorti requested that the committee consider the following questions:

- Which groups of children should be targeted for PCV13 catch-up immunization?
  - universal for all children up to certain age
  - children with underlying medical conditions
  - racial/ethnic populations with increased rates

- If universal PCV13 catch-up program is recommended, what age groups should be included?

Discussion

Dr. Meissner requested further information regarding the duration of protection among children who received 4 doses of PCV7 with respect to the fact that these children are now 8 to 9 years of age and may have a decline in antibodies.

Dr. Paradiso responded that Wyeth has data from a follow-up study conducted in South Africa. These data are from an efficacy trial 5 years out comparing children who had vaccination and those who had no vaccination. Everybody waned over that time. There was a higher antibody level in the children who had been vaccinated. Importantly, when these children were re-vaccinated after 5 years, they boosted the response better than the group that had not been vaccinated. These are the best data currently available. Wyeth is planning to start a study in Northern California to assess the original population who are now 10 to 12 years out to determine their antibodies and what the priming state is.

Dr. Schuchat added that antibodies can be interesting, but there is really no disease occurring in the 5- to 17-year age group. This was a very low risk group pre-immunization introduction, and it is not a group that has experienced an increase. This was not included in the information Dr. Nuorti presented because the scale would have to be changed so much to include them.

Amy Groom (I HS) Although the data are limited and sample sizes are fairly small for the American Indian / Alaskan Native populations, Dr Kate O'Brien presented information during the February ACIP meeting regarding the serotypes causing disease in the American Indian / Alaskan Native populations that are contained in PCV13. She wondered whether there was a similar breakdown for this population as there was for black and white populations. She thought

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such data would be helpful in forming a discussion regarding recommendations and whether the groups wished to consider something for racial / ethnic groups.

Dr. Nuorti replied that while a discussion on this topic was not prepared for this meeting, it is on the list of data the group intends to review and present. It is known that the distribution of serotypes for Alaska Natives and American Indians differs somewhat from the general population. Alaska has already introduced the 13-valent vaccine as an investigational study in some areas because of their problem with replacement disease. The data on these populations will have to be examined to determine the serotype coverage in these groups.

Patricia Whitley-Williams (NMA) wondered whether children with hemoglobinopathies were included in the incidence by race of IPD.

Dr. Nuorti responded that children are included. The number of children with underlying conditions, such as sickle cell disease, was very low in the surveillance data.

Investigational 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

Peter R. Paradiso, MD
Wyeth-Lederle Vaccines and Pediatrics

Dr. Paradiso pointed out that the data just presented was unique in the world. Wyeth has introduced this vaccine in national programs in 35 countries, and no country has an ABCs surveillance system or a group that can examine the data like this. Therefore, it is important to continue to support these programs at the CDC, because it helps in evaluating the impact of vaccines. He also reminded everyone that in the 2000 ACIP recommendations, to deal in part with the racial disparities and to some extent economic disparities in the population, even though the recommendation in 2-5 year olds was permissive, the VFC covered children up to 5 years of age. Those children who were at highest risk, either because or race of economic condition, had the vaccine available to them.

During this presentation, Dr. Paradiso discussed the transition from PCV7 to PCV13, shared some safety and immunogenicity data on that transition, and discussed the new serotype catch-up program. He reminded everyone that the serotypes common to both PCV7 to PCV13 include 4, 6B, 9V, 14, 18C, 19F, and 23F. PCV13 contains the additional serotypes 1, 3, 5, 6A, 7F, and 19A. In the transition from PCV7 to PCV13, the following represent the possible combinations of where children are expected to be at the time 13-valent vaccine is introduced:

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Transition from PCV7 to PCV13

Infant			≥ 12 months	
2 mo	4 mo	6mo		
7v	13v	13v	13v	--
7v	7v	13v	13v	--
7v	7v	7v	13v	--
7v	7v	7v	7v	13v

Wyeth Vaccines 3

Because 7 of the serotypes, the chemistry, and the quantity are common in both products, the label will indicate that transition to the 13-valent product can be substituted at any point in the immunization schedule regardless of whether a child has received 1, 2, 3, or 4 doses of the 7-valent vaccine.

Referring to a French transition study, “Mix and Match at Toddler Dose 7v/13v vs 13v/13v,” Dr. Paradiso explained that in the second year of life, the antibody response was examined specifically with regard to the 6 new serotypes. In this study, children received either 3 doses of Prevnar® in the first year of life (in the French immunization program, that is at 2, 3, and 4 months of age) with a booster dose in the second year of either the same vaccine or the 13-valent vaccine. A second group received all 4 doses of 7-valent vaccine. At the 12-month age period for the 7 common serotypes, the response is non-inferior between the groups. That is the evidence that using the 13-valent for the 7 types results in the same response as the 7-valent.

Assessment of the immune response of 1 dose of the 13-valent for the 6 new serotypes has been done in two ways. The first was to compare it after 3 doses in infants, which is the criterion used for catch-up programs with Prevnar®. Another is to examine functional antibody with 1 dose in toddlers compared to 4 doses in the regimen. With respect to the IgG antibody response to the 6 new serotypes post dose 3 in infants versus post dose 1 in toddlers, antibody responses following a toddler dose of PCV13 are non-inferior to that achieved after infant series with 13vPnC. That is, one dose in toddlers for all of the 6 serotypes induces a response that is as good or better by geometric mean concentration (GMCs) of antibody than 3 doses in infants. In the original 7 types, several of the serotypes were less with one dose in 12 month olds, with 6B and 23F being the two most important of those. That was the reason for 2 doses in 12-24 months. It appears that the 6 new serotypes fit into a category of good response in the toddler age group. In terms of the OPA antibody response to the 6 new serotypes in a 4-dose series versus 1 dose in toddlers used to show functionality of antibody, there was a nice functional response in toddlers following one dose that matches the total antibody response. Thus, these data are encouraging with respect to the immunogenicity of the vaccine in the over 12 month age group and form the basis for Wyeth’s application and Transition Request with the FDA. Wyeth is currently engaged in discussions with FDA regarding dosing regimens based on these data.

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There are limited safety data from an on-going study that is examining safety in children who have received 3 or 4 doses of PCV7 vaccine and a subsequent 1 or 2 doses of 13-valent vaccine. Although this is a safety and immunogenicity study, only safety data were available at this point. I'll show you 2 groups that are in this study. Of the children 15 months to 2 years of age (n=123), 37 received 3 doses of 7-valent vaccine, 86 had 4 doses of the 7-valent vaccine, and all subsequently received a dose of 13-valent vaccine. The second group included 2 to 5 year olds (n=180) who received either 3 or 4 prior doses of Prevnar®, and then received a dose of 13-valent vaccine.

Prompted symptoms were examined within 1 to 7 days following vaccination for local and systemic adverse events, as well as adverse event reporting to include:

- Local injection site reactions (redness, swelling, tenderness)
- Temperature nightly and when fever is suspected; report highest daily temperature
- Decreased appetite, irritability, increased sleep, decreased sleep, and hives
- Antipyretic use for treatment or prevention of symptoms
- Data collected via electronic diary

Nothing remarkable was observed from a safety prospective when comparing these data to the safety data following doses 1 through 4 in the infant population. That is, the 13-valent vaccine given as a 5th dose of conjugate vaccine in these children did not raise any safety concerns.

The most surprising impact of Prevnar® since the introduction in the vaccine regards the herd effect. While essentially identical for all age groups, Dr. Paradiso reported on those 65 years of age and older. The data from 2007 reflect a 100% herd effect, with the herd effect growing over time since the introduction of the vaccine. In fact, herd immunity continued to increase after a point in time when the vast majority of children, infants, were receiving Prevnar® and a high percentage of those children received this product as infants. It is believed that this is the result of the carriage in the 2 to 5 year old age group being reduced. While 2 to 5 year olds carry approximately half as much pneumococcus in their noses as the youngest children, there were more of them. The importance of the 2 to 5 year old age cohort and reduction of carriage in that group probably is important in inducing the herd effect. The rapidity with which children are vaccinated probably impacts the rapidity with which herd impact is achieved. Wyeth has attempted to model a catch-up program in the context of direct and indirect effects, with the idea that the curve can be sped up somewhat by vaccinating a larger cohort of children [% herd effect based on CDC's ABC Surveillance: M. Moore, personal communication].

Wyeth has attempted to model the herd effect that is likely to be observed with the 6 new serotypes based upon what occurred with the 7 types of PCV7, taking a conservative approach. Projected indirect effects are based on the carriage potential and the immune response to the 6 new serotypes, assuming the following [Wyeth data on file]:

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- No herd protection against serotypes 1 and 5 [these types are not typically carried]
- Serotypes 3 and 19A will have similar effect as 19F—a reasonable assumption based on their characteristics and the antibody response
- Serotype 6A will have similar effect as 6B—while their herd effect may not be as impressive as the rest, there was certainly a significant herd effect, which is intermediate between the very good herd effect of 6B and the not so good herd effect of 19F
- 7F is a low colonizer but induces a good immune response and will have intermediate effect (midpoint of 6B and 19F) (this is a conservative approach)

As reflected in the data presented by Dr. Nuorti, there has been a dramatic reduction in all serotypes, so it is important with this assessment not to make assumptions that will be as dramatic as that, but that reflect that a significant herd effect is anticipated.

Also important to think about in terms of direct and indirect effects of this vaccine is that in interpandemic periods, approximately 50% of influenza hospitalizations are complicated by bacterial pneumonia. On average, 25% of influenza deaths are due to secondary bacterial pneumonia. During the 1957 and 1968 pandemics, 70% of patients with fatal or life-threatening pneumonia had a bacterial etiology. The synergism of influenza and *S. pneumoniae* accounts for significant excess mortality [Scadding JG. *Quart J Med* 1937;6:425-65; Stuart-Harris CH. *J Hyg* 1949;47:434-8; Tyrell DAJ *Quart J Med* 1952;21:291-306; Simonsen L. *Vaccine* 1999;17:S3-10; Hers JFP. *Lancet* 1958;2:1141-3; Linsey M. *JAMA* 1970;214:1825-32].

In summary, the 13-valent vaccine provides coverage for 6 new serotypes. There is a significant burden in children 1 to 5 years of age and some increase in certain racial groups. There is significant potential for indirect effects against the 6 new serotypes that can perhaps be accelerated with a catch-up program.

Public Health and Economic Impact of the 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

David Strutton, PhD, MPH
Wyeth Research, Collegeville, PA
Adjunct Assistant Professor, Johns Hopkins School of Public Health, Baltimore, MD

Dr. Strutton explained that the goals of the research upon which he was reporting were to evaluate the potential public health and economic impact of PCV13 versus current vaccination with PCV7, and versus no vaccination in the US (results of the no vaccination comparison were not discussed in detail during this presentation); and assess the impact of the PCV13 new serotype catch-up program. These analyses were examined from three perspectives: 1) payer perspective (medical costs only); 2) societal perspective (as defined by USPHS Panel on Cost-Effectiveness in Health and Medicine); and 3) societal + productivity perspective (includes productivity losses). The vast majority of data shared by Dr. Strutton during this presentation pertained to the societal perspective.

The primary vaccination strategy examined was for PCV13's standard administration schedule, which is the same that has been used with PCV7 over the past 9 years (e.g., doses at 2, 4, and

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6 months, followed by a booster between 12 and 15 months). Three comparative strategies were examined:

Primary Vaccination Strategy: PCV13

- Vaccinate infants with PCV13 at age 2, 4, 6, and age 12-15 months

Comparators:

- PCV7 vaccination (status quo for the past 9 years)
  - Vaccinate infants with PCV7
    - at age 2, 4, 6, and 12-15 months
- PCV13 with new serotype catch-up program
  - 1 dose of PCV13 for all children aged 1- to <5 who have completed their PCV7 vaccination series at the time of PCV13 introduction
- No vaccination (to give some estimates that would be comparable to what has been done with Prevnar® in the past; results not discussed during this presentation)

The costs and benefits were assessed over a 10-year time horizon to allow sufficient time for the full indirect benefits of the PCV13 vaccination program to be realized, and the long-term consequences of events occurring during the 10-year study period are projected to a lifetime horizon. A 3% discounted rate was used. A decision-analytic Markov (state-transition) model was used to evaluate the following: cases avoided, deaths averted, costs (savings) and cost per child vaccinated, cost per quality adjusted life-year (QALY) gained, and cost per life-year (LY) saved.

In terms of the methods used, for PCV13 versus PCV7 and PCV13 with new serotype catch-up versus PCV13, the incremental economic impact of vaccinating children against 6 additional serotypes of *S. pneumonia* was assessed. The assumption was made that the 2007 serotype distribution of *S. pneumoniae* for IPD was also representative of the serotype distribution of pneumonia and AOM [Supported by data on serotype distribution of AOM and parapneumonic empyema; Bender et al., 2009; Casey et al., presented at ICAAC 2008; Byington et al., 2006]. Also assumed were that the benefits of PCV7 persist at the 2007 level. For the PCV13 with new serotype catch-up versus PCV13, the assumption was made that if there was a full catch-up program of children 15 to 59 months of age with one additional dose of PCV13, there would be a 1-year acceleration in the accumulation of herd effects that was observed with PCV7.

The model inputs for incidence were taken from the published literature in addition to unpublished ABC data, including the following:

- IPD incidence based on unpublished ABC data and published literature [2007 unpublished ABC data, provided by Matt Moore, MD; Hsu et al, 2009]
- Mortality and long-term sequelae from published literature [Lieu et al, 2000; Shepard et al, 2007; Tsai et al, 2008; National vital statistics reports, 2004]
- Hospitalized and non-hospitalized pneumonia incidence estimated from NAMCS and NHAMCS and published literature [National ambulatory medical care survey (NAMCS) and National hospital ambulatory medical care survey (NHAMCS). Grijalva et al, 2007; Grijalva et al, 2009]
- AOM incidence based on published literature [Ray et al 2006].

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Assumptions about accumulation of indirect effects were indirect effects estimated at 7 years post introduction, assuming 100% of indirect effects evident at year 7. A base-case, catch-up program is assumed to accelerate herd effects by 1 year. The percent of full indirect protection realized each year after launch, based on PCV7 data, is as follows:

Year	Base case**	Catch-up
1	12%	33%
2	33%	58%
3	58%	72%
4	72%	85%
5	85%	92%
6	92%	**100%**
7 +	**100%**	100%

The center column shows accumulation of indirect effects observed in older folks in the US during the pre / post time period since the introduction of Prevnar® over the 7 year period to 2007. The last column shows what the ramp up would look like if there was a 1-year acceleration in that accumulation of indirect effects.

The model inputs for estimated effectiveness of PCV13 included the following:

- Direct Effectiveness in Children <5 years
  - IPD, pneumonia, and AOM based on clinical trial data for PCV7, adjusted to reflect serotype coverage of PCV13 [2007 unpublished ABC data, provided by Matt Moore, MD; Hansen et al, 2006; Black SB et al 2000, and Black SB et al, 2002]
  - Direct vaccine protection assumed to last for 2 years and waning efficacy (91% of full efficacy) for the following 3 years [Madhi et al., 2009; Madhi et al., 2007; Black et al., 2007].

- Indirect Effects:
  - IPD reductions estimated from ABC data, as previously discussed [2007 unpublished ABC data, provided by Matt Moore, MD; Hansen et al, 2006; Black SB et al 2000, and Black SB et al, 2002].
  - In < 5 yr olds, pneumonia and AOM adapted from ecologic and clinical trial data on PCV7, adjusted to reflect differences in serotype coverage for PCV7 and PCV13 [Black et al., 2002 and Zhou et al, 2007; NAMCS and NHAMCS; Black et al, 2000 and Zhou et al, 2008; Grijalva et al, 2007; unpublished analysis by Klugman et al, 2009].
  - In > 5 yr olds, pneumonia adapted from ecologic data on PCV7, adjusted to reflect differences in serotype coverage for PCV7 and PCV13 [Madhi et al., 2009; Madhi et al., 2007; Black et al., 2007].

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Economic inputs included the following, with all dollars shown being 2008 figures:

- Costs of clinical events from published sources [Ray et al, 2006; Ray et al, in preparation; Mag Mutual, 2007].
- Base-case price of PCV13 was assumed to be $100 (range from $73.05 to $110)
- Price of PCV7 is $73.05 [Personal Communication, Wyeth Research].
- QALY decrements estimated from Melegaro and Edmunds [Melegaro and Edmunds, 2004].

With regard to the base case results estimated over a 10-year period, estimating the incremental public health impact that is expected to be observed to PCV13 versus PCV7, PCV13 would prevent an additional 110,358 cases of invasive disease; 913,836 cases of hospitalized pneumonia; 1.95 million cases of non-hospitalized pneumonia; and about 20 millions of AOM. The impact of the new serotype catch up program from 15 to 59 months over the 10-year period compared to the PCV13 program without a catch up program is estimated to eliminate an additional 12,975 cases of invasive disease; 118,534 cases of hospitalized pneumonia; 302,287 cases of non-hospitalized pneumonia; and about 2.9 million cases of AOM [New serotype catch-up program includes vaccination of all children previously vaccinated with PCV7 in the first year after introduction of PCV13 with one dose of PCV13; assumes a one-year acceleration in the indirect effects]. The model predicts that PCV13 would save $8.4 billion in medical costs and $12.6 billion from the societal perspective over a 10-year period. This would translate into a cost savings of approximately $320 per child vaccinated from a societal perspective. From a parental perspective, the estimate is about $213 per child vaccinated in medial cost savings. The results of the sensitivity analyses conducted on the base case analyses of PCV13 versus PCV7 suggest that there would be a cost-effectiveness estimate of $23,461 per QALY gained and $71,569 per QL saved. This is a cost savings scenario, so there is a greater return of investment from the cases of disease avoided than the investment in the vaccination program. Indirect protection for invasive disease would still result in a cost saving scenario. Indirect protection against invasive disease and pneumonia would have a greater cost savings, as would indirect protection in children less than 5 years of age.

Pertaining to the direct benefits of a catch-up program over a 10-year period in terms of additional cases avoided: 2,451 cases of IPD; 29,061 cases of hospitalized pneumonia; 115,828 cases of non-hospitalized pneumonia; and 1.8 million cases of AOM would be avoided in children 15 to 59 months of age. For 15 to 35 month old children 1,249 cases of IPD; 9,300 cases of hospitalized pneumonia; 40,115 cases of non-hospitalized pneumonia; and 674,754 cases of AOM would be avoided. For 15 to 23 month old children, 487 cases of IPD; 3,890 cases of hospitalized pneumonia; 11,570 cases of non-hospitalized pneumonia; and 237,601 cases of AOM would be avoided. Obviously, fewer children would be vaccinated in each of these scenarios, so there would be fewer direct benefits to them. In terms of PCV13 + Catch-up versus PCV13 and the base case costs for over 10 years, the model predicts that the new serotype catch-up program would save $255 million in medical costs and $949 million from the societal perspective. From a parental perspective, a new serotype catch-up program would save about $19 per child vaccinated.

Regarding the sensitivity analyses on the various catch-up scenarios examined, for children 15 to 59 months of age, an estimation of a 1-year acceleration in the herd effect was assumed for the base case. The same sensitivity analyses range was estimated for the other 2 catch-up scenarios, but since fewer children would be vaccinated and less carriage overall would be reduced or eliminated, less acceleration in the herd effect would be anticipated. With the 12-month acceleration scenario, the data suggested that there would be cost savings of about $72 per child vaccinated. Assuming that all children through 59 months of age had no effect on the

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acceleration of the indirect effects for the rest of the population, the cost-effectiveness estimate would be about $39,000 per QALY. Thus, it would still be considered-cost effective if only incorporating the direct benefits of vaccination for those children participating in the catch-up program, in that this program would become cost saving somewhere between 0 and 6 months of an acceleration in the indirect effect. If the carriage is reduced in all of the birth cohorts through 59 months, and if the herd effect is accelerated somewhere between 0 and 6 months, it would become a cost saving scenario.

In the catch-up scenario for children 15 to 35 months of age, assuming a 12-month acceleration in the indirect effects, there would still be cost saving. What is not known is whether realistically there would still be a 12-month acceleration. It is likely that there would be somewhat less acceleration since there would be fewer children vaccinated and less elimination of carriage. The price estimate of $140 per dose for PVC13 was intended to provide the cost implication of 2 doses for 12 to 23 month old children. In children 15 to 35 months of age, if there was a catch-up program and zero acceleration of herd effect, the cost for quality adjusted life year is estimated at $3,000. Therefore, this scenario is still highly cost-effective, approaching cost savings even with no catch-up program. In terms of a catch-up program for 15 to 23 month olds, even with zero acceleration of indirect effects, this would be a cost saving scenario because there is less of an investment in that catch-up program.

Wyeth conducted a number of other sensitivity analyses. In terms of vaccine price under the base case effectiveness assumptions, PCV13 would be cost saving at all prices over the range examined. Threshold analyses were also done. Under the base case assumptions, the threshold analysis showed that about $200 per dose is the price at which PCV13 would become cost neutral, or where there would no longer be cost saving. However, it would still be right at the threshold between highly cost effective and cost saving. From a payer prospective, the threshold at which PCV13 would become cost neutral would be about $166 per dose.

There are a number of limitations with respect to these studies. As these analyses are conducted, they are synthesized from a variety of sources. There is uncertainty around the potential indirect effects of PCV13. All estimates for the impact of PCV13 were estimated from the PCV7 experience. The impact of emerging serotype disease with PCV13 was not specifically estimated. This was, to some degree, inherently included in some of the estimates used because the indirect effects on invasive disease estimated were from PCV7, which included some replacement disease and all of the ecologic data used. The impact of the 23-valent polysaccharide vaccine (PPV23) was not considered in the model. Wyeth attempted to address the limitations in the model in the various sensitivity analyses conducted.

In summary, Wyeth estimated that over a 10-year period, PCV13 would avoid about 110,000 cases of invasive disease; about 900,000 cases of hospitalized pneumonia; and about 2 million cases of non-hospitalized pneumonia compared to PCV7 over that same time period. A new serotype catch-up program from 15 to 59 months would avoid an additional 12,000 cases of invasive disease; 420,000 cases of pneumonia; and about 3 million cases of AOM, assuming the 1-year acceleration in the herd effect. The model predicts that PCV13 would save about $12.6 billion compared to PCV7, and an additional $950 million with implementation of the new serotype catch-up program. PCV13 would remain cost saving versus PCV7 at any price of PCV13 up to $200 dollars per dose from a societal perspective, or $166 per dose from a payer prospective. A serotype catch-up program will be cost-saving if there is acceleration in the indirect effect characteristics observed for PCV7 of at least 6 months. It is really somewhere between 0 and 6 months where the cost savings are realized. It appears that indirect effects

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would play an integral role in the impact of PCV13. Even when these effects are reduced or eliminated, PCV13 is still a favorable intervention from an economic standpoint.

Discussion

Dr. Pickering noted that CDC instituted the review of all economic analyses presentations recently, which Wyeth's underwent. He wondered whether there were any major changes or issues that Wyeth had to address as a result of that review.

Dr. Strutton replied that the review was an asset to the evaluation and Wyeth received very good feedback. A major suggestion was to evaluate the other catch-up scenarios. Wyeth was assessing a base case of 15 to 59 months of age initially. In addition, the CDC health economist offered good insight on some of the utility adjustments Wyeth was using for the cost per QALY.

Dr. Marcy inquired as to whether there would be any data on the durability of immunity from a single booster dose against the 6 serotypes.

Dr. Paradiso responded that there would not be from these studies. There will be response and comparative response to what was observed with Prevnar®. In the current package, there are not any data on durability of that response.

Assuming that Wyeth would ramp down the production of PCV7 once PCV13 is licensed and available, Dr. Sawyer requested an estimated timeframe during which both products would still be available.

Dr. Paradiso responded that Wyeth initiated production of 13-valent vaccine in the second half of 2008 and is now manufacturing and accumulating vaccine. The goal is to transition rapidly from 7-valent to 13-valent. Based on discussions with the CDC over the last several months, the data presented during this meeting, and preparedness efforts, Wyeth was inspired to accelerate its thinking about introduction from a normal transition and for the catch-up immunization. Supply planning must be done globally, so feedback about direction would be beneficial.

Patricia Whitley-Williams (NMA) requested insight regarding potential financial challenges and supply that may be faced by individual practices.

Dr. Paradiso responded that through the VFC program, which fortunately can actually be implemented quickly, there was no lag in reimbursement with Prevnar®. In the private sector, they must ensure that the same occurs. There are discussions underway to ensure that the transition in reimbursement from the 7-valent to 13-valent occurs as quickly as possible to avoid supply and economic issues in private practices.

Dr. Englund said that as a pediatrician, it occurred to her that these analyses did not include the pain and suffering of hospitalized children. She also stressed the importance of ACIP seriously considering cost-effective analyses.

Dr. Morse inquired as to whether any studies were planned to examine colonization effect or carriage.

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Dr. Paradiso responded that there is an on-going study to assess carriage for the new serotypes of the 13-valent vaccine. Unfortunately, the data from those studies will not be available by the end of the year as they are long-term studies.

An inquiry was posed regarding whether it would be beneficial to think about the impact of an accelerated immunization schedule on the secondary effects of influenza this winter. Perhaps it would help to understand how quickly the target population and the possible catch-up target population could be immunized if the vaccine is approved.

Cindy Whitney (Respiratory Disease Branch) said she had hoped Dr. Paradiso would discuss doses.

Dr. Paradiso responded that over the past few months, they have been trying to accelerate as many doses of 13-valent vaccine scheduled in the pipeline into 2009 and earlier in 2010. Wyeth is currently trying to anticipate how many doses would be required, what the date would likely be, and how many doses would be needed such that they do not face a situation in which a shortage is created for routine immunization. That would be the worst case scenario. There is a cohort of approximately 12 to 15 million children in that group. All of those children could not be immunized in three months anyway, but Wyeth is trying to estimate whether they can safely say there will be no issues. He did not have an answer with regard to the number of doses at this point, but they are working hard to have a better idea as the summer progresses.

Dr. Morse requested that Dr. Nuorti display the list of questions for ACIP members to consider while the analyses were fresh.

Dr. Nuorti responded that they would be happy to receive input via email or other means of communication pertaining to the universal catch-up scenarios, particularly with respect to the upper age limit that seems appropriate to the committee.

Public Comments Day 3

No public comments were offered during the third day of the meeting.

Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the June 24-26, 2009 ACIP Meeting are accurate and complete.

_____
Date

_____
Dale Morse, M.D., M.S. Chair,
Advisory Committee on
Immunization Practices (ACIP)

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List of Attendees

International

Abu-Elyazeed	Remon	Egypt
Ali Hassan	Ahmed	Egypt
Baker	Alexandra	United Kingdom
Bonadonna	Lisa	Italy
Dhankhar	Praveen	India
Dubischar-Kastner	Katrin Luise	Germany
Ebihara	Keiko	Japan
Espinal	Carlos	Colombia
Florez	Jorge	Colombia
Furuya	Yoshikata	Japan
Gowler	Jeremy	Canada
Hajime	Kamiya	Japan
Jiang	Wu	China
Keiko	Ebihara	Japan
Kenji	Okada	Japan
Khromava	Alena	Canada
Langley	Joanne	Canada
LeBlanc	Julia	Canada
Ma	Rui	China
Major	Maria	Canada
Mascarenas	Cesar	Mexico
MONTEYNE	Philippe	Belgium
Neame	Dion	Canada
Okabe	Nobuhiko	Japan
Okada	Kenji	Japan
Omer	Saad	Pakistan
ORIOL	VALERIE	France
Payne	Debra	Canada
Sabourin	Michèle	Canada
Saddier	Patricia	France
Salisbury	David	United Kingdom
Sandhu	Hardeep	India
senouci	kamel	France
Shaikh	Tarteel	Saudi Arabia
Shindman	Judith	Canada
Skowronski	Danuta	Canada
SOREEFAN	BIBI AISHA	Mauritius
Tahir	huda	Sudan
Tan	Litjen (L.J)	Singapore
Tran	Trung	Vietnam
York	Laura	Canada

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United States

Abraham	Katalin	United States
ADLER	JOAN	United States
Ahuja	Ajay	United States
Ambrose	Karita	United States
Ambrose	Christopher	United States
Ault	Kevin	United States
Baker	Carol J	United States
Bandell	Allyn	United States
Batra	Udit	United States
Baxter	Marguerite	United States
Beck	Robert L.	United States
Bernstein	Jessica	United States
Birkhead	Guthrie	United States
Biscardi	Karen	United States
Blalack	Gary	United States
Blazek	Nicole	United States
Bocchini	Joseph	United States
Boyce	Donna	United States
Bozof	Lynn	United States
Bresnitz	Eddy	United States
Brown	Wendy	United States
BRUMLOW	DEWAYNE	United States
Burkholder	Brenton	United States
Burton	Janet	United States
Bush	Kim	United States
Campos-Outcalt	Doug	United States
Cannon	Patricia	United States
Caporizzo	John	United States
Carey	Chris	United States
Carpentier	Sallie	United States
Cary	Donna	United States
Chaney	Mike	United States
Chapman	Louisa	United States
Chilton	Lance	United States
Cieslak	Paul	United States
Cieslak	Ted	United States
Claxton	Isabelle	United States
Clover	Richard	United States
Coelingh	Kathleen	United States
Colwell	Chris	United States
Combs	Kevin	United States
Conner	Penny	United States
Cullison	Mark	United States
Curlin	George	United States
Dalrymple	Donald "Dack"	United States
D"Ambrosio	Cynthia	United States
Daniels	Janina	United States
Davis	Carolyn	United States

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de Caprariis	Pascal	United States
Dinovitz	Richard	United States
Donnelly	John	United States
Donnelly	Colleen	United States
Dougherty	Kelley	United States
Dubin	Gary	United States
Duchin	Jeffrey	United States
Dueno Berrios	Carlos	United States
Duffy	Colleen	United States
Dull	Peter	United States
Dzubin	Shannon	United States
Ehresmann	Kristen	United States
Elward	Alexis	United States
Englund	Janet	United States
Etkind	Paul	United States
Evans	Jim	United States
Farnon	Eileen	United States
Farzan	Nima	United States
Feinberg	Mark	United States
Ferraro	Louis	United States
Fikry	Christopher	United States
Fischer	Marc	United States
Foster	Stephan	United States
Friedland	Leonard	United States
fryhofer	sandra	United States
fryhofer	george	United States
Fye	Jessica	United States
Gaffoglio	Diane	United States
Gall	Stanley A	United States
Gargano	Lisa	United States
Garrett	Hudson	United States
Gaskins	Diana	United States
Geddes	Cathy	United States
Gellin	Bruce	United States
Gershman	Mark	United States
Gershon	Barry	United States
Gibbs	Tom	United States
Gill	Christopher	United States
Goldenthal	Karen	United States
Gordon-Evans	Jill	United States
Greenberg	David	United States
Greenleaf	Peter	United States
Grogg	Stanley	United States
Gurunathan	Sanjay	United States
Hackman	Jeff	United States
Hage	Raymond	United States
Hahn	Christine	United States
Halsey	Neal	United States
Halstrom	Erik	United States
Hannan	Claire	United States

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Haupt	Richard	United States
Heaton	Penny	United States
Hering	David	United States
Hight	Leta	United States
Hight	Brandi	United States
Hilton	Betsy	United States
Hinman	Alan	United States
Hosbach	Philip	United States
Howe	Barbara	United States
Humphrey Franklin	Donelle	United States
JaapK-NL	JaapK-NL	United States
Jackson	Melonie	United States
James	Chuntiel	United States
James	James	United States
Johann-Liang	Rosemary	United States
Johnson	David	United States
Jones	James F.	United States
Judson	Frank	United States
Kahn	Clare	United States
katz	samuel	United States
Keyserling	Harry	United States
Kimberlin	David	United States
Klein	Nicola	United States
Knouse	Mark	United States
Kramer	Jason	United States
Kroft	Charlotte	United States
Krull	Andrea	United States
Kuter	Barbara	United States
Laird	Susan	United States
Landry	Sarah	United States
Lease	Christian	United States
Lee	Lucia	United States
Lee	Grace	United States
Lee Choe	Jane	United States
Leger	Marie-Michele	United States
Lett	Susan	United States
Lewin	Clement	United States
Lewis	Tamara	United States
Lichtner	Jennifer	United States
Lievano	Fabio	United States
Lima	Peter	United States
Lorick	Suchita	United States
Lukus	Lori	United States
Lyons	Russette	United States
Malone	Robert	United States
Mansoura	Monique	United States
Marcy	S(tephan) Michael	United States
Martin	Tyler	United States
Martinez	Lolita	United States
Martone	William	United States

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Mason	Dean	United States
Mazur	Marie	United States
McCubbins	John (Tom)	United States
McGarry	Lisa	United States
McGlynn	Margaret	United States
Mclaughlin	Jeffrey	United States
McLeod-Sordjan	Renee	United States
McLoughlin	Sean	United States
Meissner	Cody	United States
MelissaMB	MelissaMB	United States
Middleman	Amy	United States
Miller	Claudia	United States
Miller	Michael	United States
Milligan	Mark	United States
Mina	Vivian	United States
Moore	Kelly	United States
MOREL	HEATHER	United States
Morse	Dale	United States
Muhammad	Riyadh	United States
Mulach	Barbara	United States
murphy	linda	United States
Murphy	Ann Terri	United States
Myers	Martin	United States
Neloms	Stacey	United States
Newton	Sharon	United States
Nicholsosn	Ouzama	United States
Nott	Billie	United States
Obara	Timothy	United States
Offit	Paul	United States
O''Neill	Kevin	United States
Pahud	Barbara	United States
Paradiso	Peter	United States
Penrod	Deborah	United States
pernicka	steve	United States
Peters	Martin	United States
Peterson	Diane	United States
Pinckney	Lennisha	United States
Plotkin	Stanley	United States
Pugh	Pearl	United States
Quinn	Jane	United States
Randall	Lisa	United States
Ray	Jill	United States
Reeves-Hoche	Mary Kathryn	United States
Rennels	Margaret	United States
Richards	Steve	United States
Richardson	Vesta	United States
Robert	Malone	United States
Robinson	Robin	United States
Ross	David J.	United States
Rousculp	Matthew	United States

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Rubin	Jaime	United States
Sadr-Azodi	Nahad	United States
Saslow	Debbie	United States
Sawyer	Mark	United States
Sawyer	Leigh	United States
Schaffner	William	United States
Schechter	David	United States
Schmader	Kenneth	United States
Schott	Chris	United States
Seifert	Harry	United States
SHAW	BETTY	United States
Shiff	Jeffrey	United States
Shivaprakash	Sathyanarayana	United States
SIEVERT	ALAN	United States
Silsbee	Jeffrey	United States
Silverstein	Leonard	United States
Skjeveland	Eric	United States
Smalley	Hannah	United States
Sobczyk	Elizabeth	United States
Staples	J Erin	United States
Stein	Gary	United States
Stinchfield	Patricia	United States
Stobbe	Michael	United States
Stoddard	Jeffrey	United States
Strikas	Raymond	United States
Strutton	David	United States
Stuerke	Stacy	United States
Subbarao	Italo	United States
Sun	Wellington	United States
Sutton	Jacqueline	United States
Sylvester	Gregg	United States
Temte	Jonathan	United States
Temte	Emily	United States
Thomas	Lonnie	United States
Thomas	Michael	United States
Tsai	Theodore	United States
Turner	James C.	United States
Vakil	Varsha	United States
Van De Velde	Steve	United States
Vaughn	David	United States
Vaupel	Christine	United States
Vitale	Steven	United States
Vogt	Kitty	United States
Wallace	Amy	United States
Walpert	Kirsten	United States
Walters	Jean	United States
Wassil	James	United States
Wenick	Barry	United States
Wexler	Deborah	United States
Whitley-Williams	Patricia	United States

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Wible	Sharon	United States
Wick	Kathy	United States
Wighton	Timothy	United States
Willis	English	United States
Wilson	Paul	United States
Woldemariam	Mahlet	United States
Wyand	Fred	United States
Yamada	Eileen	United States
Yamauchi	Terry	United States
Zacharyczuk	Colleen	United States
Zacholski	Donna	United States

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