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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
February 24-25, 2010
Atlanta, Georgia

Acronyms

AAAAI	American Academy of Allergy, Asthma, and Immunology
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core surveillance system
ACHDNC	Advisory Committee for Heritable Disorders in Newborns and Children
ACHA	American College Health Association
ACP	American College of Physicians
ACS	American Cancer Society
ACIP	Advisory Committee on Immunization Practices
AEs	Adverse Events
AGS	American Geriatrics Society
AHIP	America's Health Insurance Plans
AIN	Anal Intraepithelial Neoplasia
APA	American Pharmacists Association
AMA	American Medical Association
AOM	Acute Otitis Media
ARRA	American Recovery and Reinvestment Act
ATP	According to Protocol
ASTHO	Association of State and Territorial Health Officials
BARDA	Biomedical Advance Research and Development Authority
BLA	Biologics License Application
BOI	Burden of Illness
BRFSS	Behavioral Risk Factor Surveillance System
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CIN	Cervical Intraephithelial Neoplasia
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
COPD	Chronic Obstructive Pulmonary Disease
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DSTDP	Division of Sexually Transmitted Diseases Prevention [of NCHHSTP]
DtaP-IPV	Diphtheria, tetanus, and pertussis with inactivated poliovirus vaccine
DVA	Department of Veterans Affairs
DVD	Division of Viral Diseases (of NCIRD)
DVH	Division of Viral Hepatitis (of NCIRD)
EUA	Emergency Use Authorization
EGL	External Genital Lesion
EIA	enzyme immunoassay
EIP	Emerging Infections Program
EIS	Epidemic Intelligence Service
EMR	Electronic Medical Records
ESSENCE	Electronic Surveillance System for Early Notification of Community-Based Epidemics
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
GBS	Guillain Barré Syndrome
GDP	Gross Domestic Product
GISN	Global Influenza Surveillance Network

GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GSK	GlaxoSmithKline
HCC	Hepatocellular Carcinoma
HCP	Health Care Personnel
HI	Hemagglutination Inhibition
HICPAC	Healthcare Infection Control Practices Advisory Committee
HepA	Hepatitis A
HepB	Hepatitis B
HHS	Department of Health and Human Services
Hib	*Haemophilus influenzae B*
HM	Heterosexual Men
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
ICD-9	International Classification of Diseases, Ninth Revision
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
ILINet	Influenza-Like Illness Surveillance Network
IM	intramuscular
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
IRB	Institutional Review Board
ISD	Immunization Services Division (of NCIRD)
ITT	Intent to Treat
JE	Japanese Encephalitis
JORRP	Juvenile Onset Recurrent Respiratory Papillomatosis
LEEP	Loop Electrosurgical Excision Procedure
LYS	Life Years Saved
MenACYW-CRM	Meningococcal Conjugate Vaccine
MCV4	Quadrivalent Meningococcal Conjugate Vaccine
MMR	Measles, Mumps, Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NCHHSTP	National Center for HIV, Hepatitis, STD, and TB Prevention (of CDC/CCID)
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NHANES	National Health and Nutrition Examination Survey
NHFS	National 2009 H1N1 Flu Survey
NICE	National Institute Clinical Excellence
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIS	National Immunization Survey
NNDSS	National Notifiable Diseases Surveillance System
NORC	National Opinion Research Center
NSFG	National Survey of Family Growth
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan

NVPO	National Vaccine Program Office
NYSDH	New York State Department of Health
OAH	Office of Adolescent Health (NVPO / HHS)
OBS	Observational Study
OD	Office of the Director (of CDC)
PAHO	Pan American Health Organization
PCP	Pneumocystis Jirovecii
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
RDD	Random-Digit-Dialed
RRP	Recurrent Respiratory Papillomatosis
RSV	Respiratory Syncytial Virus Immunoprophylaxis
SAEs	Serious Adverse Events
SAM	Society for Adolescent Health and Medicine
sBLA	Supplemental Biologics License Application
SCID	Severe Combined Immunodeficiency
SEER	Surveillance, Epidemiology, and End Results Program
SES	Socioeconomic Status
Tdap	Tetanus and Reduced Diphtheria Toxoids
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
VSSN	Vaccine Safety Surveillance Network (DoD)
VSRAWG	Vaccine Safety Risk Assessment Working Group
VZV	Varicella-Zoster Virus
WG	Work Group
WHO	World Health Organization

FINAL – February 18, 2010

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

AGENDA ITEM	PURPOSE		PRESIDER/PRESENTER(s)
Wednesday, February 24, 2010			
8:00	**Welcome & Introductions**		Dr. Carol Baker (Chair, ACIP) Dr. Larry Pickering (Executive Secretary, ACIP; CDC)
8:30	**Human Papillomavirus (HPV) Vaccine** ▪ Introduction ▪ Quadrivalent HPV vaccine for adult women Efficacy in women 24 through 45 years of age Epidemiology and natural history Cost effectiveness ▪ Quadrivalent HPV vaccine in males Efficacy in the prevention of anal precancers ▪ Summary and future plans	Information & Discussion Information & Discussion	Dr. Janet Englund (ACIP, WG Chair) Dr. Richard Haupt (Merck) Dr. Eileen Dunne (CDC/NCHHSTP) Dr. Harrell Chesson (CDC/NCHHSTP) Dr. Richard Haupt (Merck) Dr. Lauri Markowitz (CDC/NCHHSTP)
10 :15		*Break*	
10:45	**13-Valent Pneumococcal Conjugate Vaccine (PCV13)** ▪ Introduction ▪ Recommendation for use of PCV13 and immunization schedules ▪ VFC vote ▪ Program implementation - transition from PCV7 to PCV13	Information Discussion Vote VFC Information	Dr. Kathy Neuzil (ACIP, member) Dr. Pekka Nuorti (CDC/NCIRD) Dr. Jeanne Santoli (CDC/ NCIRD) Dr. Jeanne Santoli (CDC/ NCIRD)
12:15		*Lunch*	

1:15	**Hepatitis Vaccines** ▪ Update on Hepatitis Vaccines Work Group ▪ Diabetes and liver disease		Dr. Mark Sawyer (ACIP, WG Chair) Dr. John W.Ward (CDC/NCHHSTP)
1:45	**Influenza Vaccines** ▪ Introduction ▪ 2009-10 Season review ▪ Influenza epidemiology ▪ Virology ▪ 2009 H1N1 Immunization Program Update	Information & Discussion	Dr. Kathy Neuzil (Chair, WG ACIP) Dr. Anthony Fiore (CDC/NCIRD) Dr. Lyn Finelli (CDC/NCIRD) Dr. Nancy Cox (CDC/NCIRD) Dr. Anthony Fiore (CDC/NCIRD) Dr. James Singleton (CDC/NCIRD) Dr. Pascale Wortley (CDC/NCIRD)
3:45		*Break*	
4:00	**Influenza Vaccines** *(cont'd)* ▪ High dose influenza vaccine for persons 65 and older ▪ Work Group discussion ▪ Annual influenza prevention and control recommendations ▪ VFC vote	Information & Discussion Vote VFC	Dr. David Greenberg (sanofi) Dr. Neuzil and Dr. Fiore Dr. Fiore (CDC/NCIRD) Dr. Jeanne Santoli (CDC/NCIRD)
5:50		**Public Comment**	
6:05		**Adjourn**	

Thursday, February 25, 2010

8:00	**Unfinished Business**		Dr. Carol Baker (Chair, ACIP)
8:30	**Agency Updates (CDC, CMS, DOD, DVA, FDA, HRSA, IHS, NIH, NVAC, NVPO)**	Information	ACIP *Ex Officio* Members
8:45	**Update: National Vaccine Plan**	Information	Dr. Ray Strikas (HHS/OS)
8:55	**Meningococcal Vaccine** ▪ Introduction ▪ Cost-effectiveness analysis of infant meningococcal vaccines ▪ Considerations for use of meningococcal vaccines in infants	Information Information & Discussion	Dr. Cody Meissner (ACIP, WG Chair) Dr. Ismael Ortega-Sanchez (CDC/NCIRD) Dr. Amanda Cohn (CDC/NCIRD)
10:10		*Break*	

10:25	**Ongoing Mumps Outbreaks, Northeastern United States, July 2009 - present**	Information	Dr. Kathleen Gallagher (CDC/NCIRD)
10:35	**Rotavirus Vaccines** ▪ Severe Combined Immunodeficiency (SCID) and rotavirus vaccine	Information Discussion	Dr. Catherine Yen (CDC/NCIRD)
10:50	**Vaccine Supply** ▪ Update on vaccine supply	Information Discussion	Dr. Jeanne Santoli (CDC/ NCIRD)
11:05	**Evidence Based Recommendations Work Group** ▪ Introduction ▪ Methodological standards for clinical practice guidelines ▪ Guidelines for grading the quality of evidence ▪ Guidelines for synthesizing and presenting recommendations	Information Information Discussion	Dr. Jonathon Temte (ACIP, WG Chair) Dr. Faruque Ahmed (CDC/NCIRD) Dr. Craig Umscheid (University of Pennsylvania) Dr. Faruque Ahmed (CDC/NCIRD)
12:20	**Public Comment**		
12:35	**Adjourn**		

February 24, 2010

Welcome and Introductions

Dr. Carol Baker
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Baker called the meeting to order, welcoming those present. She then introduced Dr. Pickering who delivered the administrative announcements.

Dr. Pickering welcomed everyone to the February 2010 Advisory Committee on Immunization Practices (ACIP) meeting. He indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web. He also welcomed those who could not attend the meeting in person.

Noting that Natalie Greene would not be in attendance during this meeting due to the birth of her baby, Dr. Pickering recognized several others in the room who were to be present throughout the duration of the ACIP meeting to assist with various meeting functions: Antonette Hill, Committee Management Specialist for ACIP; Tamara Miller; Tanya Lennon; and John Rawlinson. He also recognized that their hard work very much contributes to the success of each meeting. Those with any questions were instructed to see him, any of these individuals, or Dr. Baker. He indicated that boxed lunches would be provided for a charge during the two days of the meeting in the hallway outside of the auditorium, and that coffee and tea would be available in the hallway for the duration of the meeting.

Handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented at this meeting will be posted on the ACIP website, generally within one to two weeks after the meeting concludes, while meeting minutes will be available on the website within 90 days of the termination of the meeting.

Members of the press interested in conducting interviews with various ACIP members were instructed to contact Tom Skinner for assistance in arranging the interviews.

Dr. Pickering welcomed the following international visitors, noting that they were attending the ACIP meeting to observe the process of immunization policy development in the United States:

- Dr. Barbara Jauregui, Technical Officer, Pan American Health Organization (PAHO)
- Dr. Carla Vizotti, EPI Manager, Ministry of Health, Argentina
- Dr. Elizabeth Ferdinand, EPI Manager, Ministry of Health, Barbados
- Dr. Suarez Castaneda Eduardo, Director of Infectious Diseases, Ministry of Health, El Salvador
- Dr. Hassan Foad Moises, Pediatric Hospital of Nicaragua
- Dr. Nobuhiko Okabe, Director, Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan
- Dr. Hajime Kamiya, Medical Officer, National Institute of Infectious Diseases, Tokyo, Japan

Those unable to attend this ACIP meeting for either or both days included the following:

ACIP Members

- Dr. Michael Marcy

Ex Officio Members

- Dr. Bruce Gellin, National Vaccine Program Office (NVPO) attended the first day; Dr. Mark Grabowsky attended on his behalf the second day.

- Dr. Linda Kinsinger from the Department of Veterans Affairs (DVA) was unable to attend either day; Dr. Terri Murphy attended on her behalf the second day.

- Dr. George Curlin has been the ACIP *ex officio* member from the National Institutes for Health (NIH) for 12 years. With his retirement, ACIP lost not only an exceptional person from the committee, but also a friend. Dr. Curlin will be replaced by Dr. Richard Gorman beginning with the June 2010 ACIP meeting.

Liaison Representatives

- Dr. Greg Poland from the American College of Physicians (ACP) was present the first day; Dr. Sandra Fryhofer attended on his behalf the second day.

- Dr. Christine Hahn from the Council of State and Territorial Epidemiologists (CSTE) was unable to attend; Dr. Dale Morse attended on her behalf.

- Dr. James Cheek from the Indian Health Services (IHS) was unable to attend; Dr. John Redd attended on his behalf.

- Ms. Patricia Stinchfield from the National Association of Pediatric Nurse Practitioners (NAPNAP) was unable to attend; Ms. Tammy Tempfer attended on her behalf.

To avoid disruptions during the meeting, those present were instructed to turn off all cell phones or place them in the vibrate mode. 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.

Topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. 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 in order to be considered before a vote is taken. Those who planned to make public comments were instructed to visit the registration desk in the rear of the room 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 see Ms. Hill to verify that their names were listed and to receive any additional information.

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 (COI) waivers. Members who conduct vaccine clinical trials or who serve on data safety monitoring boards (DSMBs) 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.

The following information was shared pertaining to ACIP:

E-mail: acip@cdc.gov Web homepage: www.cdc.gov/vaccines/recs/acip/

Nominations: http://www.cdc.gov/vaccines/recs/acip/req-nominate.htm
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 are due no later than November 15, 2010 for the term beginning July 2011. Interested parties were encouraged to complete an application and submit it by the deadline.

Next ACIP meeting: June 23-24, 2010
Registration Deadlines: Non-U.S. Citizens 6/4/2010 – U.S. Citizens 6/11/2010

Vaccine Safety: www.cdc.gov/vaccinesafety/

Vaccine Abbreviations:
http://www.cdc.gov/vaccines/recs/acip/vac-abbrev.htm

Vaccine Schedules:
http://www.cdc.gov/vaccines/recs/schedules/default.htm

Adult Vaccine Scheduler:
http://www.cdc.gov/vaccines/recs/Scheduler/AdultScheduler.htm
This scheduler was developed by National Center for Immunization and Respiratory Diseases (NCIRD) of CDC and Georgia Tech. This is very similar to the Pediatric Scheduler, which has been published for a couple of years. The Adult Vaccine Scheduler is an interactive, web-based scheduler that can be downloaded to people's computers so that adults can keep track of the vaccines they have received and prognosticate what vaccines they need in the future.

Vaccine Toolkit:
http://www.cdc.gov/vaccines/spec-grps/hcp/conversations.htm
The Vaccine Toolkit was also developed by NCIRD / CDC in conjunction with the American Academy of Family Physicians (AAFP) and the American Academy of Pediatrics (AAP). This is a providers' resource for vaccine conversations with parents.

Dr. Baker requested that Dr. Pickering comment on the timeline from ACIP recommendations to publication in the *Morbidity and Mortality Weekly Report* (*MMWR*), given the number of questions raised regarding this issue. Dr. Pickering responded that they recognize that there has been a delay that has lengthened over the past couple of years between ACIP recommendations and publication of these recommendations. A document was prepared to address this subject, which was currently being reviewed by the NCIRD leadership for comments, followed by which it would be submitted to the ACIP Steering Committee. The three areas this document approaches include: 1) more liberal use of the policy notes in the *MMWR* (e.g., the shortened versions of publications of the recommendations), which would cut the timeframe down to a couple of months following the vote; 2) streamline of the process for publication of the recommendations and reports, which are the longer versions; and 3) more frequent use of electronic publishing. One way this will be done is if there are updates or contraindications to any of the recommendations, they will be published in the *MMWR* and the base document will include notifications of links that include new recommendations and updates.

Dr. Baker welcomed and introduced new ACIP member, Attorney Sara Rosenbaum, to ACIP. Professor Rosenbaum is a Harold and Jane Hirsch Professor of Health Law Policy and Chair of the Department of Health Policy at George Washington University School of Public Health and Health Services in Washington, DC. She is also the Director of the Center for Health Services Research and Policy and the Director of the Hirsch Health Law and Policy Program at George Washington University. Her commitment to strengthening access to care for middle income minority and medically under-served populations has had a transforming effect on the lives of many Americans, particularly children. Her representation of consumers will be of tremendous value to ACIP.

The following conflicts of interest were declared:

Dr. Janet Englund: Research support for clinical trials from MedImmune, sanofi pasteur, and Novartis

Dr. Wendy Keitel: Clinical trial support from Novartis

Dr. Cody Meissner: Payments made to Tufts Medical Center by MedImmune and Wyeth for participation in multi-vent clinical trials for Prevnar® and RSV-related vaccines

The remainder of the ACIP members declared no conflicts.

Director's Remarks

Thomas R. Frieden, MD, MPH
Director, Centers for Disease Control and Prevention
Administrator, Agency for Toxic Substances and Disease Registry

Dr. Frieden thanked the ACIP members and liaisons for their work, pointing out that ACIP is a great example of not only evidence-based public health practice, but also evidence-based public health practice that can make a major difference in peoples' lives. He stressed that the information presented during this meeting illustrated the important results of their work. For example, with H1N1 ACIP made extremely important contributions and played a significant role in making policy based on the best evidence that was available at the time that decisions had to be made. ACIP's recommendations were flexible, recognized local concerns, and were available just in time to contribute to the response. ACIP's recommendations are really a key part of the decision making science base that affects national policy and maximizes the public health impact of vaccination. With the VFC program, a reduction has been observed in health disparities or disparities in access to health care in children that has not been observed in adults. Not only can evidence-based practices improve health generally, but also evidence-based practices tied to effective programs like the VFC program can significantly reduce disparities in health care access and ultimately health outcomes. Dr. Frieden cited pneumococcal vaccination as another great example of just in time intergovernmental work.

CDC has a wonderful relationship with the FDA, and Dr. Frieden expressed his pleasure to be working again with his longtime friend and colleague Dr. Margaret A. Hamburg, Commissioner of Food and Drugs, who is doing a terrific job there. He thought CDC and FDA were illustrating that when two agencies work together well, there really is synergy. Similarly with ACIP's terrific work, he thought there was a synergy in CDC receiving their input for good analyses that change the way children grown up and live and the way doctors practice. He stressed that they must continue to be rigorous in assessing the science of vaccination, as well as the cost-effectiveness, to fully understand what is being recommended and what the implications are. Public health is a best buy and vaccination is a great example of that. As they examine the large number of vaccinations that could be added, they must also be diligent in assessing the costs. That is a decision that must ultimately be shared with society in terms of how much health the public is willing to pay for. Certainly, vaccines are one of the great triumphs of the past century. In closing, Dr. Frieden emphasized his gratitude to ACIP and its liaisons for the work they are doing and for continued significant progress.

Human Papillomavirus (HPV) Vaccine

Introduction

Janet Englund, MD
Chair, ACIP HPV Vaccine Work Group

Dr. Englund reported that there had been new information on HPV vaccine, specifically with regard to the quadrivalent vaccine for females age 27 through 45 years of age and quadrivalent HPV vaccine for males. Quadrivalent HPV Vaccine for women over 26 years of age was first considered by ACIP in 2008. Merck submitted a supplementary application to the FDA in November 2009 for quadrivalent HPV vaccine for women over 26 years of age, for which a FDA decision is expected before June 2010. The HPV Vaccine Work Group is preparing ACIP for a possible vote during the June 2010 ACIP meeting. Work on quadrivalent HPV vaccine in males has also been a topic of discussion among the HPV Vaccine Work Group. In October 2009, the FDA licensed the vaccine for males ages 9 through 26 years for prevention of HPV 6/11-related genital warts. At that time, ACIP made a permissive recommendation for use of vaccine in males. Data are now available on efficacy for prevention of anal intraepithelial neoplasia in males, although these data have not been submitted to the FDA [http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm].

HPV Vaccine Work Group discussions throughout the past several months pertaining to quadrivalent HPV vaccine for females 27 through 45 years of age have focused on HPV epidemiology and natural history, cost-effectiveness analyses, end-of-study efficacy data from the vaccine trial, recommendation options, and new diagnostic tests for HPV that are available clinically. In terms of quadrivalent HPV vaccine in males, discussions have focused on vaccine efficacy for prevention of anal intraepithelial neoplasia and policy issues.

GARDASIL® Update

Richard M. Haupt, MD, MPH
Clinical Research
Infectious Diseases & Vaccines
Merck Research Laboratories

Dr. Haupt presented data from the end-of-study analyses regarding the efficacy of GARDASIL® in adult women 24 through 45 years old (e.g., Protocol 019). He explained that Merck's studies are designed with pre-specified endpoint-driven tests of efficacy hypotheses. The first analyses were conducted in late 2007, data from which were presented during the February 2008 ACIP meeting. During this session, Dr. Haupt presented the end-of-study data, which now includes the completion of nearly 4 years of follow-up for the women who participated in Protocol 019.

With regard to the study design, Protocol 019 was a randomized, placebo-controlled, double-blind study. This was an international, multi-center study with a fixed event design that was 48 months in duration. The study included 3,800 healthy women enrolled from 24 to 45 years of age at time of first vaccination, with a 1:1 stratification by age: 24 to 34 years of age and 35 to 45 years of age. Subjects were randomized (1:1) to receive either 3 intramuscular (IM) injections of quadrivalent HPV vaccine or a placebo at Day 1, Month 2, and Month 6.

The key exclusion criteria for Protocol 19 were a history of a Loop Electrosurgical Excision Procedure (LEEP) or hysterectomy; history of biopsy-diagnosed cervical HPV disease in the past 5 years; and prior history of genital warts, VIN, or VaIN. Different from Merck's studies in younger populations, no limitations were placed on number of lifetime sexual partners. These exclusion criteria were defined to try to identify women who were less likely to have on-going or active disease due to infection with HPV types, particularly vaccine type, at enrollment.

As in all Merck studies, the primary analysis is known as the per-protocol efficacy population. This consists of women are HPV DNA negative and seronegative at baseline, and HPV DNA negative at Month 7 for the relevant HPV type. Case counting began after Month 7. That is, the women completed the vaccine series and were without any protocol violations. There were several pre-specified objectives, including two co-primary endpoints. The first co-primary endpoint was combined incidence of HPV 6/11/16/18-related persistent infection, CIN, AIS, cervical cancer and external genital lesions (EGLs: genital warts, VIN, VaIN, vulvar cancer, vaginal cancer). The second co-primary was combined incidence of HPV 16/18-related persistent infection, CIN, AIS, and cervical cancer and EGLs. The secondary endpoint was combined incidence of HPV 6/11-related persistent infection, CIN, AIS, and cervical cancer and EGLs. The tertiary endpoint was reduction in HPV 6/11/16/18-related abnormal Pap tests. In previous studies of women, Merck designed studies that were powered to assess disease endpoints and to define efficacy against CIN 2/3. Protocol 019 was not designed to be a standalone study to assess disease endpoints. A composite endpoint of persistent infection and disease as a bridge to the efficacy already demonstrated in Merck's studies of young adult women. The majority of the endpoints accrued in Protocol 019 are persistent infection rather than disease endpoints.

Before reporting on the efficacy analyses, Dr. Haupt reviewed some of the natural history data that can be evaluated from Merck's clinical trials. Regarding Day 1 or HPV baseline status for four vaccine types (HPV 6, 11, 16 and / or 18), roughly 8% of study participants had evidence of HPV DNA detection to one or more of these vaccine types. About a third were positive by either DNA or serology to one or more of these vaccine types. Therefore, of the study subjects, 67% were negative by both HPV DNA and serology to all 4 vaccine HPV types at baseline. It was concluded that 90% of subjects would potentially benefit from protection against 3 or 4 vaccine HPV types. Similar to other populations, most individuals who are positive by either DNA or serology to a vaccine type are typically positive to only one type. Many women are still negative to 3 or 4 types.

Analyses were conducted to understand which subject characteristics were associated with the risk of being infected with a vaccine HPV type at study entry. In a cross-sectional analysis at Day 1 of all women who participated in the trial, a subgroup was selected from within three categories (e.g., lifetime number of sexual partners, number of new sexual partners, marital status) who had the lowest risk as the referent population and the odds ratio was calculated against that referent population to reflect the odds of having a prevalent HPV DNA detection at baseline. Not surprisingly, women who had more lifetime sex partners or who had more new lifetime sex partners had higher odd of having prevalent HPV DNA detection. Also observed was that other than being in a first marriage, all of the other relationships statuses defined also increased the odds of having a prevalent HPV infection. In addition, a longitudinal analysis for new incident infections in the placebo arm of subjects HPV DNA negative and seronegative at baseline was conducted. Based on this analysis, the same subject characteristics that predicted prevalent infection predicted the risk of developing a new infection in a woman who is

negative at baseline [Velicer C, Zhu X, Vuocolo S, Liaw KL, Saah A. Prevalence and incidence of HPV genital infection in women. *Sex Transm Dis*. 2009 Nov;36(11):696—703].

In summary, most women who had evidence of past or current vaccine HPV type infection were infected with only one type. Few women had evidence of past or current infection with 3 or 4 vaccine HPV types. Subject characteristics that predicted baseline vaccine HPV type infection were the same characteristics that predicted incident infections, which makes the identification of a risk demographic difficult to identify.

Dr. Haupt then reported on efficacy in the pre-specified population and pre-specified endpoints (e.g., the vaccine type related endpoints). Based on the end-of-study data for the first co-primary endpoint (HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL), there were 10 cases in the GARDASIL® arm and 86 cases in the placebo arm, and the observed efficacy is 88.7% (78, 95 CI). Most of the end points were persistent infection endpoints. Because there was a stratified enrollment, Dr. Haupt also provided data for efficacy based on the stratified age group populations. The efficacy by age strata was also high and statistically significant. For 24 to 34 year-olds, there were 5 cases in the GARDASIL® arm and 56 cases in the placebo arm, with an observed efficacy of 91.3% (78, 97 CI). In the 35 to 45 year-olds, there were 5 cases in the GARDASIL® arm and 30 cases in the placebo arm, and the observed efficacy was 83.8% (58, 95 CI). Given that vaccine efficacy is a calculation based on a relative risk reduction, having lower event rates in the older age group will lower the calculated vaccine efficacy. Vaccine efficacy in the older age strata is numerically lower, although not statistically so based on the confidence intervals. Because there are equal numbers of women in these groups, the 30 events in the placebo arm of the older age group and 56 in the younger age group reflects the lower event rates in the older age strata.

In terms of the co-primary endpoint by disease severity, because the study was powered on the composite endpoint, there are limitations of power particularly for the CIN 2/3 endpoint. Most of the endpoints were persistent infection. There were 9 events of persistent infection, 7 of which were related to type 16 and 2 of which were related to type 6. There was 1 disease event in the GARDASIL® arm, which was a CIN 2 attributed to type 16 in a woman in whom that lesion was also confounded with HPV type 51. There was very high efficacy against CIN (94.1%) and external genital lesions (100%). Regarding the co-primary endpoint by HPV type, there were 2 events of HPV 6 (35 in the placebo arm), 0 events of HPV 11 (4 in the placebo arm), 8 events of HPV 16 (39 in the placebo arm, and 0 cases of HPV 18 (13 in the placebo arm). The observed efficacy was 94.4% (78, 99 CI) for HPV 6, 100% (-52, 100 CI) for HPV 11, 79.9% (56, 92 CI) for HPV 16, and 100% (67, 100) for HPV 18.

For women to have been evaluated in the full analysis set population (e.g., intention-to-treat population), they had to have been enrolled and have received at least one dose of either vaccine or placebo, to have had at least one follow-up visit, and they did not have to complete the vaccine series. Case counting began right after Day 1, so this reflects a lot of prevalent infection or disease at study entry. Even in the intent-to-treat populations, there was close to 50% efficacy (47.2%) against the composite endpoint due to vaccine types which was statistically significant. Assessing that by disease severity, there is significant efficacy for some of the endpoints, but power is limited for the CIN 2/3 endpoint.: persistent infection 49.0% (36, 60 CI), any grade CIN 47.5% (16, 68 CI), CIN 2/3 or worse 22.4% (-43, 58 CI), external genital lesions 8.5% (-127, 63 CI), condyloma 41.8% (-60, 81CI), and for VIN 2/3 or VaIN 2/3 there were too few endpoints for meaningful analysis.

In terms of the co-primary and secondary endpoints across all ages, efficacy for HPV 16/18-related persistent infection, CIN, or EGL was 84.7% (68, 94 CI); and efficacy for HPV 6/11-related persistent infection, CIN, or EGL was 94.8% (80, 99 CI). Regarding co-primary and secondary endpoints by age strata for HPV 16/18-related persistent infection, CIN, or EGL, efficacy was 86.0% (64, 96 CI) in 24 to 34 year-olds and 81.8% (36, 97 CI) in 35 to 45 year-olds. Efficacy for HPV 6/11-related persistent infection, CIN, or EGL was 100% (83, 100 CI) in 24 to 34 year-olds and 86.2% (40, 99 CI) in 35 to 45 year-olds. The same trend is reflected here as well, with high efficacy in both age strata, but numerically lower efficacy in the older age strata driven primarily by the lower event rates observed in that group.

Regarding the tertiary endpoint of the impact of GARDASIL® on incidence of HPV 6/11/16/18-related Pap diagnoses, in the per protocol efficacy population, there was very high efficacy of 97.4% (85, 100 CI). Efficacy was equally high in both age groups in this analysis. There was only one case in the GARDASIL® group, which was HPV 16-related. Of the 38 placebo cases, 12 were HPV 6-related, 4 were HPV 11-related, 21 were HPV 16-related, and 6 were HPV 18-related. In the intention-to-treat population (e.g., full analysis set), observed efficacy overall was 50.1% (24, 68 CI). Efficacy in 24-34 year-olds was 52.6% (21, 72 CI) and in 35-45 year-olds was 42.0% (-25, 74 CI). This intention-to-treat analysis includes subjects with prevalent vaccine HPV type infection. No impact was observed in an intention-to-treat analysis that was irrespective of any HPV type, which assessed the prevention of abnormal Paps of all women who entered the study regardless of causative HPV type, regardless of prevalent versus incident occurrence. This illustrates that a tremendous amount of prevalent infection by non-vaccine types occurred in this population, which were already present at baseline before women were enrolled into the study.

Observed fairly consistently across all populations studied, GARDASIL® is a generally well-tolerated vaccine. The most common adverse event observed is local injection site reactions (e.g., injection site pain, swelling, redness). That by far drives the adverse event profile. Serious adverse events are uncommonly observed. No vaccine-related serious adverse events were observed in this study population. It is uncommon for women to discontinue from Merck's clinical trials at all, and it is certainly uncommon due to an adverse event. The following table illustrates clinical adverse events:

Clinical Adverse Experience Summary

	Gardasil (N=1890)		Placebo (N=1888)	
	n	%	n	%
Number (%) of subjects:				
With 1 or more AEs	1645	87.0	1535	81.3
With injection-site AEs	1450	76.7	1213	64.2
With systemic AEs	1121	59.3	1135	60.1
With serious AEs	14	0.7	16	0.8
With serious vaccine-related AEs*	0	0.0	0	0.0
Who died†	7	0.4	1	0.1
Discontinued due to an AE	7	0.4	2	0.1
Discontinued due to a serious AE	2	0.1	0	0.0
Discontinued due to a serious vaccine-related AE	0	0.0	0	0.0

*Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
†All deaths in the study were determined by the investigator to be "definitely not" related to the vaccine. Vaccine: hypertensive heart disease, nasopharyngeal cancer, breast cancer, pulmonary tuberculosis, cardiac failure from hyperthyroidism, post-operative PE, pericarditis secondary to SLE. Placebo: Acute lymphoblastic Leukemia

N = number of subjects with follow-up

In summary, women aged 24 to 45 are susceptible to HPV 6/11/16/18 infection and disease. Women aged 24 to 45 are at continued risk for acquiring infection and disease lesions from these HPV types. GARDASIL® is highly efficacious against HPV 6/11/16/18-related persistent infection, CIN or EGL in adult women negative to the relevant HPV type. Efficacy is supported by significant efficacy for the primary endpoint in the intention-to-treat population analyses. GARDASIL® is generally safe and well tolerated in women aged 24 to 45 years old.

HPV Epidemiology in Adult Women 27 Through 45 Years

Eileen Dunne MD, MPH
Division of STD Prevention, CDC

Dr. Dunne presented updated information on the epidemiology of HPV infection, with a focus on women 27 through 45 years of age. HPV epidemiology is one of several considerations for policy decisions for use of HPV vaccine in women 27 through 45 years of age. Other considerations include vaccine efficacy, safety, immunogenicity, programmatic considerations, and cost-effectiveness. To put this policy consideration in perspective, Dr. Dunne reviewed ACIP's current recommendations for use of the HPV vaccine, which is as follows [http://www.cdc.gov/vaccines/recs/provisional/downloads/hpv-vac-dec2009-508.pdf]:

> Routine vaccination is recommended by ACIP with either the bivalent or quadrivalent HPV vaccine for 11 or 12 year old girls. Catch-up vaccination is recommended through age 26 years. Benefit is greatest before sexual debut.

Based on data previously shown to ACIP from the National Survey of Family Growth on the percentage of adolescents who have had vaginal sex, for both females and males there is an increasing prevalence of ever having vaginal sex with increasing age. By age 15 years, 26% of girls have had vaginal sex [Mosher et al. 2005; Vital and Health Statistics: No. 362]. Thus, increasing age presents more opportunities for acquiring HPV infection, which may reduce the opportunities for the full benefit of prophylactic HPV vaccines. HPV prevalence peaks in the 20s, and tends to decline with age. Smaller secondary peaks in prevalence among older women have been observed in some geographic regions outside the United States (US). A variety of sexual behaviors are risk factors for prevalent and incident HPV infection (e.g., lifetime sex partners, recent sexual partners).

Some of the best data on incident infection in adult women is data from the clinical trials and cohorts outside the US. Based on data regarding incidence from the quadrivalent vaccine clinical trials, which provides information on acquisition of vaccine-type infection during the trial, with increasing age the incidence of infection with HPV 6, 11, 16 or 18 decreased from 7.4 infections per 100 person years in 24 through 29 year olds to 1.9 per 100 person years in the 40 through 45 year olds [Haupt R, Merck presentation to ACIP, Feb 2008]. A study of women attending cervical cancer screening centers in Bogota, Colombia similarly demonstrates decreased incidence of infection with age. In terms of the incidence of infection with HPV 16, 18, 6 or 11 by age in this study, the highest rate of infections occurred among the women in their late teens and early 20s and decreased with age.

When considering incident infection in women over 26 years of age, it is important to note that it is unclear if these are first infections, re-infections, or re-activations from a previous infection acquired earlier. There may be a contribution of each of these. In studies of younger women, especially virgins, incident infection is often implied to be new infection, but this same conclusion cannot be made with older women who may have had more sexual experiences.

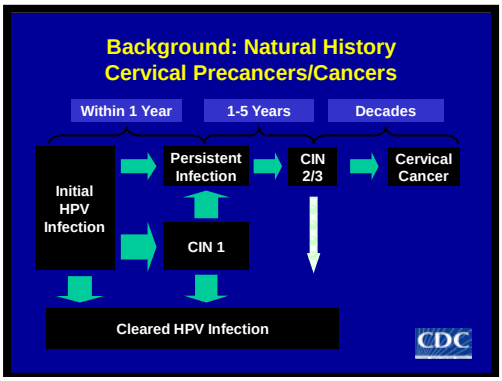
There is evidence that at least a proportion of incident infections in this age group is due to transmission from a partner.

Regarding HPV infection from a partner in adult women, epidemiologic data that suggests HPV infection is transmitted from and between sex partners are from a myriad of studies in younger women, showing that sexual behaviors are risks for incident infection. However, there are fewer studies of adult women over 25 years of age. Sex behavior is clearly linked to incident infection in studies of younger women. Based on the few studies of adult women over 25 years of age, adult women dating online were more likely to have prevalent oncogenic HPV with increasing number of male sex partners, concurrent partnerships, and recent relationship [Winer R, et al. IPV Conference 2009 P-30.18]. Additional data are available from the quadrivalent HPV vaccine clinical trials on risk factors for incident HPV 6, 11, 16 or 18 infection. In terms of the risk factors for incident infection, incident infection HPV 6, 11, 16, or 18 infection is associated with increasing lifetime sex partners, increasing number of new partners, and marital status [Velicer C, Zhu X, Vuocolo S, Liaw KL, Saah A,*Sex Transm Dis*. 2009 Nov;36(11):696—703]. Given that the risk of incident HPV infection is related to sexual behavior, it is important to summarize sexual behavior data from the US. The National Survey of Family Growth found that between 7.1% and 15.1% of adult women, depending on age, had two or more sex partners in the past 12 months.

Despite clear risk factors for incident infection, it is challenging to identify specific groups of adult women who might benefit from vaccination. Data available from the placebo month of the vaccine trial found that although there were clear sexual risk factors for incident infection, these risk factors were the same risk factors for finding baseline prevalent infection. This means that identifying women at risk of incident infection who could possibly benefit from vaccination may also identify women who were more likely to already have been infected who possibly would not benefit from vaccination. In addition, there are programmatic challenges to implementing a "targeted" approach for adult woman, especially using sexual behavior risk factors. For both of these reasons, the opportunity to identify specific groups of adult women who would benefit from vaccination is not feasible.

There are other important considerations about preventing "incident" infection in adult women through vaccination. Questions remain with regard to the natural history of incident infection in women over the age of 25 years. For example, it is not clear whether incident infection in women over 26 years of age is more aggressive than that in younger women. That is, do these infections contribute to more persistent infection or disease? If this is the case, there might be a stronger reason to prevent even few incident infections. One study evaluated incident infections prospectively. This study enrolled women who had low grade abnormalities or normal findings on Pap screening and evaluated women for incident infection. Women with incident infection were followed to find what percentage of these infections persisted and for how long. Different age groups were evaluated, and essentially a similar pattern was found in the women aged 30 years and older compared to younger women. This implies that the natural history of incident HPV infection is not more aggressive in older women than younger women [Mourcourt-Boulch,et al. Int J Cancer 2010]. Another study, a cohort study in Guanacaste, Costa Rica, evaluated development of CIN 2/3, and CIN3 after incident infection and found that older women with incident infection had a similar risk of CIN 2/3 and CIN3 as younger women [Rodriguez AC, et al. J Nat Cancer Inst. 2010].

The following graphic reminds us about the natural history of HPV infection and the development of cervical pre-cancers and cancer, and is a reminder that infection occurs years to decades before development of disease, and that persistent infection is the most important risk factor for development of pre-cancers and cancers:



The peak in diagnoses of CIN 2/3, or cervical pre-cancers, in the US is among women in their late 20s to 30s. infection often occurs years earlier before development of these disease outcomes [Insigna RP, et al. Am J Ob Gyn 2004].

In conclusion, as women age from their mid 20s, HPV prevalence and HPV incidence decrease. The likelihood of having acquired HPV infection increases. Given that disease outcomes (e.g., genital warts, CIN 2/3) peak among women in their mid to late 20s, the potential benefit of vaccinating women in their late 20s to early 40s would be minimal. Questions remain with regard to the natural history of incident infections in adult women. The greatest benefit would be from vaccinating females in early adolescence.

Cost-Effectiveness of Quadrivalent HPV Vaccination of Adult Women

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The routine vaccination of 12-year-old females in the US is a cost-effective use of public health resources. Cost-effective estimates are consistent across a wide range of studies. However, there is more uncertainty and less precision in the cost-effectiveness estimates for HPV vaccination of adult women and HPV vaccination of males. With that in mind, Dr. Chesson focused this presentation on an update of data pertaining to vaccination of adult women that was presented to ACIP in February and June 2008, a review of cost-effectiveness ratios and quality adjusted life years (QALYs) for other vaccines and other health interventions, which was specifically requested by several ACIP members; and a summary of three cost-effectiveness models for adult women in the US: Kim & Goldie (N Engl J Med 2008), Merck (based on Elbasha et al., Emerg Inf Dis 2007); and Chesson et al. (based on Emerg Inf Dis 2008).

Vaccination cost-effectiveness is often expressed in terms of the cost per QALY gained. The cost per QALY gained by adding HPV vaccination to cervical cancer screening can be expressed as follows:

$$\frac{\text{(Vaccine cost + administration cost) – (cost of illness averted by vaccination)}}{\text{Number of QALYs gained by vaccination}}$$

QALYs can be used to measure the health impacts of interventions, such as vaccination. QALYs also take into account reductions in morbidity and mortality by taking into account quality and length of life. One year in perfect health = 1 QALY, Death = 0 QALY, and one year of life in less than perfect health is assigned a value between 0 and 1 QALY depending upon the severity of the health issues.

Currently, there is no consensus on the appropriate cost-per-QALY threshold for determining cost-effectiveness of public health interventions in the US. Likewise, there is no official ACIP threshold for determining the cost-effectiveness of vaccination. In the US, a threshold of $50,000 to $100,000 is often cited. However, this threshold has been described as arbitrary and lacking in empirical or theoretical justification [Grosse (2008). See also Weinstein et al. (2010) for additional incremental QALY threshold interpretation]. Globally, the World Health Organization (WHO) suggests using per-capita Gross Domestic Product (GDP) [Grosse (2008). See also Weinstein et al. (2010) for additional incremental QALY threshold interpretation] in which a cost per QALY of less than per-capita GDP would very cost-effective, and less than 3 times per-capita GDP would still be considered cost-effective. Under this guideline, the US per-capita GDP of approximately $50,000 per person would correspond to a cost-effectiveness threshold of about $50,000 to $150,000. However, the WHO threshold has also been described as lacking a theoretical rationale [Grosse (2008). See also Weinstein et al. (2010) for additional incremental QALY threshold interpretation].

Another way to think about cost-effectiveness thresholds for vaccination is to assess the cost-effectiveness of recommended vaccines. The following chart shows the cost per outcome gained for selected childhood vaccines in the US:

Vaccine	Cost per outcome gained (compared to no vaccine)	Source
DTaP, Hib, MMR, Polio, Varicella	<$0 per QALY (cost-saving) Individually and as a group	Ekwueme (2000), Zhou (2004, 2005, 2008), Cochi (1985), White (1985), Thompson (2006), Preblud (1985)
Influenza (LAIV)	≈ $10,000 per QALY	Prosser (2006)
Hepatitis A	≈ $10,000 to $30,000 per QALY	Das (1999), Rein (2007)
Meningococcal	≈ $120,000 per QALY	Shepard (2005)
Pneumococcal	≈ $10,000 to $105,000 per LYS	Ray (2006, 2009) and Lieu (2000)
Rotavirus	≈ $135,000 to $225,000 per LYS	Cortese (2009) and Widdowson (2007)

These results are shown in terms of cost per QALY except for pneumococcal and rotavirus vaccine, which are shown in terms of cost per life year saved. The first five vaccines (DTaP, Hib, MMR, polio, varicella) have been found to be cost saving whether considered individually or as a group. That is, each one of these vaccines pays for itself in terms of offset medical costs. Other vaccines such as meningococcal have a relatively high cost per QALY at $120,000. Other vaccines such as pneumococcal ($10,000 to $105,000 per LYS) and rotavirus ($135,000 to $225,000 per LYS) have relatively high costs per outcome gained. The meningococcal estimate is for vaccination at age 1 year. This table shows a collection of point estimates; the ranges shown for hepatitis A, pneumococcal, and rotavirus vaccination reflect base case results of more than one study. For each vaccine, the actual range of plausible cost-effectiveness estimates varies (not shown). See source studies for details.

The cost per QALY gained for selected adolescent vaccines in the US, with HPV shown in bold:

Vaccine	Target group	Cost per QALY gained (compared to no vaccination)
Hepatitis B	College freshmen	<$0 (cost-saving) to ≈ $10,000
Hepatitis A	College freshmen	<$0 (cost-saving) to ≈ $15,000
HPV	**12-year-old females**	**≈ $3,000 to $45,000**
Influenza (LAIV)	12- to 17-year olds, high risk	≈ $10,000
Tdap	All 11-year-olds	≈ $25,000
Meningococcal (MCV4)	All 11- to 17-year-olds	≈ $105,000
Influenza (LAIV)	12- to 17-year olds, healthy	≈ $140,000
Meningococcal (MCV4)	All 11-year-olds, routine	≈ $140,000

Source: Ortega-Sanchez et al. *Pediatrics* (2008), except HPV

HPV vaccination compares relatively favorably to the other vaccines. Again, meningococcal has a relatively high cost per QALY gained as does influenza for healthy 12- to 17-year olds. For HPV, lower and upper bound estimates were obtained from Elbasha (2007) and Kim (2008), respectively. This table shows a collection of point estimates; the range shown for HPV reflects base case results of two studies; and the ranges shown for hepatitis A & B reflect base case results from two perspectives. For each vaccine, the actual range of plausible cost-effectiveness estimates varies (not shown). See source studies for details.

Cost per QALY gained for selected health interventions in the US is shown in the following table:

Vaccine	Cost per QALY gained
Chlamydia screening	≈ $3,000 to $40,000
Cervical cancer screening	
Every 2 years vs. never	≈ $25,000
Annual vs. every 2 years	≈ $725,000
Breast cancer screening	
Every 2 years vs. never	≈ $40,000
Annual vs. every 2 years	≈ $65,000 to $160,000

All of these screening activities have the potential to cost less than $40,000 per QALY gained, but the cost-effectiveness of screening depends upon the frequency of screening. For example, cervical cancer screening every two years as compared to never screening costs about $25,000 per QALY gained. However, if the frequency was increased to every year, the cost per QALY is estimated to be $725,000 or greater. Chlamydia screening shown is annual (compared to no screening), for sexually active women aged 15-24 years (Hu 2004, lower bound estimate) and for women aged 15 to 34 years (Gift 2008, upper bound estimate). Cervical cancer screening estimates were extrapolated from Goldhaber (2008) and consistent with other estimates [Tengs 1995; Goldie 2004,2006; Kulasingam 2006; and Kim 2002]. Breast cancer screening (every year vs. every 2 years, and every 2 years vs. every year) was estimated to cost approximately: $40,000 and $160,000, respectively, by Ahern (2009)(extrapolated), for combined mammography and clinical breast exam for ages 40 to 79 years; and $40,000 to $65,000, respectively, by Stout (2006)(extrapolated), for mammography for ages 40 to 80 years, per QALY. Ranges (where given) reflect point estimates from more than one study. For each intervention, the actual range of plausible cost-effectiveness estimates varies (not shown). See the source studies for more details.

While there is a great deal of confidence that HPV vaccine for 12-year old females is fairly cost-effective compared to other vaccines and health interventions, one of the remaining issues regards the cost-effectiveness of vaccinating adult women. Dr. Chesson summarized the three models that address this issue: Kim & Goldie, Merck, and Chesson et al. All three models examined female only vaccination and assumed a lifelong duration of vaccine protection. The Merck model used a $400 cost per vaccine series, while the Kim & Goldie and Chesson et al models used $500. All models examined a wide range of outcomes (e.g., cervical cancer, CIN, genital warts, non-cervical cancers, recurrent respiratory papillomatosis (RRP)); however, not all of these outcomes were included in every scenario examined. The published results by Kim & Goldie did not include the reductions in HPV-associated health outcomes in men that might be achieved by vaccinating women, nor did they assume that CIN would have an impact on quality of life. All models included indirect effects, although the Chesson model used a relatively simple approach to do so. All models examine the addition of HPV to cervical cancer screening,

although the Chesson model did not model cervical cancer screening directly and instead assumed that it was reflected in the rates of cervical cancer observed in the US. All models assumed a relatively similar impact of genital warts on the quality of life, but the duration of this reduction in quality of life was greater in the Merck model.

All of the models assumed that there would be no vaccine protection against HPV types acquired prior to vaccination, and that there would be lifelong natural immunity following clearance of HPV, although the degree of this immunity varied across the models. All models examined a relative long time horizon at 100 years for the Merck and Chesson models and lifetimes of relevant birth cohorts for the Kim & Goldie model. With respect to the results of the Kim & Goldie model when cervical outcomes and genital warts were included, as older age groups were added incrementally the cost per QALY increased as follows: 12 years of age $34,900; 13-18 $81,000; 19-21 $101,300; and 22-26 $133,600. This increase in the cost per QALY as the age at vaccination increases is to be expected because the probability of being previously exposed to the vaccine types increases and incidence of HPV decreases. Although this model did not address the cost effectiveness of vaccinating women over age 26, some information on the cost-effectiveness of vaccinating women over age 26 can be derived from this model. Based on the increasing costs per QALY for the ages included, it is reasonable to assume that the cost per QALY of vaccinating women over age 26 would be at least $133,000. When Kim & Goldie focused on the effect of inclusion of other health conditions on the cost-effectiveness of female vaccination strategies, the cost effectiveness of vaccine appears to be more favorable.

In this model for age 26, the cost per QALY exceeded $100,000 in all of these scenarios except the most optimistic scenario of 100% vaccine efficacy against a wide range of health outcomes.

In another application of their model, Kim et al focused on women 35 to 45 years old. The results were fairly consistent with what would be expected based on their previous study. Compared with current screening, HPV vaccination was less cost-effective than other well-accepted interventions in US.

With regard to the Merck model results of the cost-effectiveness of female vaccination by age when including cervical, vulvar, and vaginal outcomes in women and genital warts in males and females, incremental ages added resulted in the following cost per QALY: 9-26 years of age $7,800; 27-34 $51,900; and 35-44 $142,000. As with the Kim & Goldie model, when more health outcomes were included, the cost per QALY was reduced as shown in the following table:

Incremental cost-effectiveness ratios by HPV disease prevented

Merck model results: Base case cost per QALY estimates

HPV Diseases	Female-only 9–26	+ 27–34 females	+ 35–44 females
Cervical	$17,500	$84,000	$224,000
+ Vulvar and vaginal	$16,000	$77,000	$205,200
+ Genital warts	$7,800	$51,900	$142,000
↑ Evidence of vaccine efficacy in females ↑			
+ Anal	$6,200	$41,600	$113,400
+ Head & neck	$4,300	$31,700	$87,800
+ Penile	$4,200	$30,900	$85,700
+ RRP	$2,300	$28,900	$83,300

QALY: quality-adjusted life year

This chart shows how the cost per QALY gained by vaccination decreases as more health outcomes are included in the analyses. The top row shows the cost per QALY when including only cervical outcomes, while the bottom row shows the cost per QALY when all health outcomes are included. In the most optimistic scenario shown by the bottom row, the cost per QALY was about $28,000 for vaccination 27 to 34 year olds and about $83,000 for vaccinating 35 to 44 year olds. If the analysis is limited to just those outcomes for which there is evidence of vaccine efficacy in females, the cost per QALY in 27 to 34 year olds is about $50,000 and for 35 to 44 year olds is about $142,000.

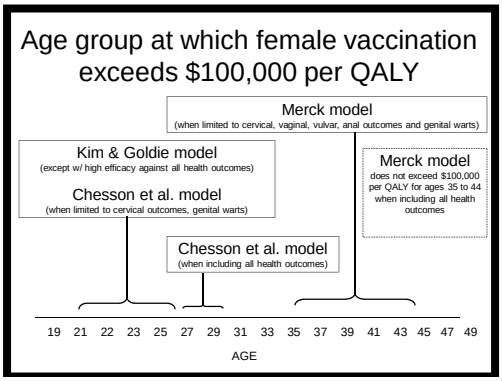
The Chesson model includes results for two scenarios, one in which cervical outcomes and genital warts were included and one in which all outcomes were included. As with the other models, as the age of vaccination increases, the cost per QALY increases as well as shown in the following table:

Chesson et al. model results: Cost-effectiveness of female vaccination by age

Ages vaccinated	Incremental ages added	Cost per QALY	
		Cervical, warts	All outcomes
12	12	$8,000	$3,000
12-18	13-18	$26,000	$17,000
12-21	19-21	$55,000	$38,000
12-26	21-26	$119,000	$85,000
12-29	27-29	$254,000	$179,000
12-34	30-34	$449,000	$305,000

Cost per QALY (quality-adjusted life year) of each strategy is the incremental cost-effectiveness ratio of the strategy compared to the preceding strategy. Cost per QALY of vaccinating 12-year-olds is as compared to no vaccination (screening only). All strategies include cervical cancer screening. Results preliminary.

The following chart summarizes the results of all three models by showing the age group at which female vaccination exceeds an arbitrary threshold of $100,000 per QALY:



In the Kim & Goldie model, the cost per QALY exceeded $100,000 in the early to mid 20s except when they included all health outcomes at 100% vaccine efficacy. In the Chesson model, the cost per QALY exceeded $100,000 in the 22 to 26 age group when focusing only on cervical outcomes and genital warts. When Chesson et al included all health outcomes, the cost per QALY exceeded $100,000 somewhere in the 27 to 29 year age group. In the Merck model, the cost per QALY exceeded $100,000 for ages 35 to 44 when the analysis was limited to cervical, vaginal, vulvar, and anal outcomes and genital warts. However, when all outcomes

were included in the Merck model, the cost per QALY never exceeded $100,000 even at ages 35 to 44.

Regarding factors that contribute to differences in model results, compared to the Kim & Goldie model, the Merck model uses a lower cost per vaccine series, assumes a greater quality of life impact of CIN and genital warts, and includes more health outcomes (outcomes in males; adult-onset RRP). There are also differences in how screening is modeled, which may affect the calculation of the marginal benefits of adding vaccination to screening. The model structures also differ, which may make it difficult to compare how each model simulates the changing dynamics of HPV in the population after the introduction of a vaccine.

The actual change in costs and benefits when expanding the cut-off age of vaccination age from 26 to 44 years were presented for the Merck and Chesson models. As would be expected, when more people are included in a vaccination program, vaccination costs will increase, (approximately 20% in each model). The increase in the net cost of vaccination, however, is relatively more pronounced. This is because the net cost of vaccination includes the cost of the vaccine as well as the medical costs offset by the vaccination. On average, vaccinating a 27 to 44 year old will offset less future medical costs than will vaccinating a 12 to 26 year old, so the net costs increase relatively more rapidly than vaccination costs when expanding vaccination to include 27 to 44 year olds (~70% to 80%). The increase in QALY gained was less than 5% in both models. Thus, expanding vaccination to include 27 to 44 years olds has a notable increase in cost with a relatively smaller increase in health improvements as measured by the gain in QALYs.

In conclusion, routine HPV vaccination of 12-year-old girls is cost-effective. For adult women, vaccination is less cost-effective as age at vaccination increases due to the fact that HPV incidence decreases, and the probability of previous exposure increases. Extending vaccination beyond age 26 years would account for small percentage of total vaccine benefits. The precise age at which vaccine is no longer cost-effective is uncertain. This depends on many factors such as the health outcomes included in the analysis, screening assumptions, other modeling assumptions, et cetera. Results can vary within and across models due to uncertainties in the natural history of HPV that the models must address, other uncertainties such as the cost and impact on quality of life of HPV-related outcomes, and differences in model structure.

Quadrivalent HPV Vaccine Recommendation Options for Adult Women 27-45 Years

Dr. Lauri Markowitz
CDC / NCHHSTP

Dr. Markowitz reported that in 2008 when the HPV Vaccine Work Group first considered adult women and again more recently, the group has considered a variety of options for women in this age group including a permissive recommendation only; a targeted catch-up recommendation, which may be risk-based; and extending catch-up recommendations to females in all or part of this age group.

Some of the key points presented during this session today, and which were considered by the work group when reviewing options, are that HPV vaccine is prophylactic and would have the greatest impact and be most cost-effective when administered before exposure to HPV. Infections do occur in females over the age of 26, but incidence decreases with increasing age. It is difficult to target by behavioral risk factors. Risk factors for prevalent infection and past

exposure are similar to those associated with incident infection. Models show decreasing cost-effectiveness with age at vaccination for adult women, although the age at which vaccine is not cost-effective differs by model and within models.

If the vaccine is licensed by the Food and Drug Administration (FDA) for use in women over 26 years of age, it is unclear what the indications will be. There were few CIN 2/3 cases in the trial and there were no cases of VIN / VaIN 2/3, which is part of the indication for 9 to 26 year olds. As noted earlier, there is very high efficacy against the combined endpoint, but few CIN 2/3 endpoints, which was the primary outcome in the pivotal trial, or VIN / VaIN 2/3.

Based on this information, the quadrivalent HPV vaccine recommendation to be proposed by the ACIP HPV Work Group for women 27-45 years during the June 2010 ACIP meeting will be a permissive recommendation. The rationale for this is that there would be a relatively small impact of vaccination in adult women, the models show potential for high cost per QALY in this age range, and that the main focus of the vaccination program should be adolescents. The ACIP HPV Vaccine Work Group plans are to further review of data on adult women, prepare for a vote during the June 2010 ACIP meeting in the event that the vaccine is licensed for this age group by FDA before that time, and to draft a "Policy Note" for an *MMWR* (publication pending ACIP vote), which would state the efficacy observed in this age group; that vaccine may be given to women age 27-45 years but that there is no extension of the catch-up recommendation; and that cervical cancer screening should be the primary focus of cervical cancer prevention in this age group.

Discussion

Regarding larger social questions pertaining to vaccination, Dr. Rosenbaum inquired about the extent that something like HPV becomes understood as routine for all women beginning prior to sexual activity and through their adult years, and whether there was any energy at the crucial pre-puberty ages by having the vaccine understood as something people should receive universally. That is, she would be inclined to worry less about the cost implication in older ages if there was a rollover effect on the younger populations (e.g., understanding that this is routine).

Dr. Markowitz responded that the HPV Vaccine Work Group's feeling was that ACIP should emphasize that the focus of the HPV immunization program is on adolescents. If anything, having an extended recommendation would likely dilute that emphasis. Thus, she thought the focus should be on targeting the vaccine to adolescents before sexual activity.

Dr. Temte pointed out that there is good evidence that the decision by mothers to immunize their daughters is dependent upon two things: their knowledge of HPV causing cervical cancer and their own behavior regarding Pap smears. This also fits into ACIP's duty to enhance coverage for HPV in the younger age group. HPV, and especially cervical cancer, are highly disparate illness that tends to affect minority communities, the poor, and lower educated individuals. He thought this was where ACIP's focus should be.

Regarding Dr. Haupt's presentation showing that the number of lesions in 27 to 45 year old women is not changed overall by the vaccine (e.g., those who have received the vaccine do not have more lesions overall for all HPV types than those who are in the control group), Dr. Chilton said that this implied to him that there was some replacement of 16 and 18 by other viruses. He wondered whether this was also Dr. Haupt's interpretation.

Dr. Haupt replied that it was not. His interpretation was that they were assessing a study population of about 3,800 women, which is a relatively small sample size to examine intent-to-treat analyses across all HPV types. In terms of non-vaccines types, Merck observed an imbalance in the number of cases due to non-vaccine types. However, this reflects an imbalance of the same non-vaccine types that occur at baseline. These women were not randomized across those non-vaccine types, so there is an imbalance by type-specific non-vaccine type at baseline which then contribute to the development of disease endpoints by those same non-vaccine later.

It seemed to Dr. Cieslak that when considering the cohort of women 27 and older, they were really addressing all women rather than any subgroups. He wondered if there was enough information to determine whether certain subgroups of these women may be more likely to benefit from the vaccine (e.g., women who present at STD clinics; women who are less likely to obtain regular Pap smears), while others would be less likely to benefit (e.g., married women in stable relationships).

Dr. Dunne responded that that the findings from the clinical trial suggest that sexual behavior factors that make incident infection likely also make prevalent infection likely. However, there would be a number of challenges in terms of a venue-based or Pap screening findings-based approach. At this time, it is unknown whether there would be a benefit to focusing on certain subgroups.

Noting that Dr. Haupt did not discuss a booster dose in his presentation, Dr. Meissner noted that there is some evidence that there is loss of antibody a number of years after administration of GARDASIL®, particularly Type 18. He requested that Dr. Haupt comment on the issue of equating loss of antibody to susceptibility to infection, and whether the cost of booster doses should be factored in.

Dr. Haupt responded that they have observed loss of seropositivity in women who they have followed for a while. There continues to be virtually 100% efficacy in women who become seronegative. At this point, it does not appear that the loss of antibody is associated with loss of protection. Particularly for type 18, they are measuring a very specific neutralizing antibody against one known neutralizing epitope. They know it is not the immunodominant epitope, and it is very likely that the amount of antibody women need for protection is substantially lower than what is being measured. The data thus far suggest that no booster is going to be required, and using immunogenicity as a measure of that is probably not the right approach.

In terms of long-term immunologic memory, Dr. Judson inquired as to whether at this point this seemed analogous to hepatitis B.

Dr. Haupt responded that this was a fair comparison. Much like hepatitis B, HPV vaccine is a subunit protein vaccine with a prime boost immunological response, so it behaves similarly. It is important to remember that there is evidence from 5 years of GARDASIL® and about 9.5 years from the monovalent HPV 16 study in which 100% efficacy has been observed against infection and disease. Some of those women are seronegative as well. Long-term surveillance projects are in place that will continue to assess this. An important study in the Scandinavian countries will come out in 2010, which will continue to address long-term protection.

Dr. Sumaya said he was agreeable to the potential language to be used by the work group for the recommendation. He has sometimes had difficulty with the disconnect of expanding to other groups in which vaccine may not have major impact, while the principal age group that will have the greatest impact is often left with deficiencies in implementation. He supported the focus of the potential recommendation on immunizing the younger age group, and wondered whether the work group had discussed any specific steps that might be taken to increase the impact in that age group.

Dr. Markowitz replied that they would need to work on this in conjunction with the Immunization Services Division (ISD) of NCIRD. Everyone realizes that uptake needs to be increased in the target age group.

Dr. Baker stressed the importance of focusing on the age group before sexual debut because, especially for the medically underinsured or uninsured, this is the age at which there is the greatest likelihood of capturing them while they are still socially engaged in school and other venues. There is a great deal of emphasis in many states on the medical home for underinsured and uninsured individuals.

Dr. Rodewald (ISD / NCIRD / CDC) added that the National Vaccine Advisory Committee (NVAC) has had a major focus on improving vaccination of adolescents. For the three adolescent vaccines that are currently front and center in terms of the best programmatic way to improve coverage, a key issue is making the vaccine and financing available. This has been done quite well for the HPV vaccine. Also important is to measure coverage at the state level. For the first time ever, there has been coverage measurement at the state level for the population. They should now be able to see what the performance is and what needs to be improved. This is a much longer conversation, but there is a considerable amount of interest in making sure that this vaccine and the other adolescent vaccines help to establish a platform for vaccination.

Dr. Baker inquired as to what the state level coverage is for the Vaccines for Children (VFC) program.

Dr. Rodewald (ISD / NCIRD / CDC) replied that very quickly after ACIP passed the VFC resolution and the contract was in place, within less than two months all states were ordering HPV vaccine using the VFC program. This has been somewhat slow on the Section 317 side

Dr. Sawyer said that he was always sobered by the difference in outcome in the intent-to-treat population compared to the per protocol population. He inquired as to what vaccine efficacy was used in the summary numbers provided for the models Dr. Chesson presented on, and / or how they responded in sensitivity analyses to lower efficacy more like what is observed in the intent-to-treat group.

Dr. Chesson replied that the Merck model used the efficacies observed in the according to protocol population because the model can actually know who has been exposed and who has not, takes into account what happens after exposure, and assumes that there will be no protection against an HPV vaccine type for vaccination after exposure to that HPV type. The Kim & Goldie model used a range of efficacies from 75% to 100%. Those have not been updated yet, but they still capture the range of probable vaccine efficacies. The Chesson model used vaccine efficacies that were similar to Merck's.

Dr. Sawyer inquired as to whether he was right that at least the Merck data reported during this session showed an intent-to-treat efficacy of about 50%.

Dr. Chesson responded that this would be taken that into account because the models would apply no vaccine efficacy for those who were exposed to the HPV types already. In effect, the models should reflect that same finding.

Regarding the cost per outcome gained for selected childhood vaccines and the use of two different units (e.g., QALY and LYS), Dr. Turner (ACHA) wondered what would happen to the figures for which LYS was used if they were converted to QALYs, in terms of whether they would be higher or lower and what the order of magnitude would be.

Dr. Chesson responded that while it was difficult to determine for sure, most of the time when cost-effectiveness is expressed in terms of cost per QALY rather than cost per LYS, , the cost-effectiveness ratio is lower. For example, when influenza vaccine is expressed in terms of cost per LYS, it can be much higher than it is in terms of cost per QALY because of the substantial reductions in non-fatal outcomes. It is difficult to speculate regarding the difference in cost per life year and cost per QALY for a given vaccine. The percentage of the benefits that pertain to mortality and the percentage that pertain to morbidity would have to be taken into account. The potential is there for it to be an order of magnitude difference for some vaccines, but not necessarily.

Dr. Neuzil added that for PCV13 vaccine that is more expensive in an older age group, QALYs are in the $25,000 range or lower.

Dr. Schaffner (NFID) very much favored the emphasis on pre-adolescent and adolescent immunization, but was still interested in adult women. In terms of behavioral characteristics, he wondered how much was really known about incident infection in women by socioeconomic status (SES) and perhaps race / ethnicity, and whether it is possible that there are subsets of the population defined in those ways who have higher risk of incident infections.

Dr. Markowitz responded that there are national data from the National Health and Nutrition Examination Survey (NHANES) on prevalence of different HPV type infections by SES and race / ethnicity, but there are not any good incidence data in this age group. It is difficult to conduct these studies. Some of the best data there are have come from the placebo arm of the vaccine trial. The work group has been reluctant to assess / target specific risk groups, so she expressed interest in knowing whether ACIP would like for the work group to pursue this direction.

Given that these vaccines never would have been developed if there was not a belief that they would prevent cervical cancer, Dr. Judson wondered whether there was a more direct way to answer this question merely by assessing rates of cervical cancer by race / ethnicity that can be assumed as proxies for SES.

Dr. Markowitz replied that there are data on rates that cervical cancer, and part of that is due to differences in screening. The risk of infection is different from the risk of cervical cancer. These data can be provided to the full ACIP. However, the work group has not gone down the path of a risk-based recommendation.

As the Chair of the work group, Dr. Englund emphasized that the group had discussed multiple scenarios with multiple experts, particularly some of the adolescent experts on the committee, about the use of target- or risk-based use of this vaccine. The work group felt that it would be a major disservice to the use of this vaccine in the adolescent population if it became stigmatized to be used for certain risk-based socioeconomic persons when they are potentially more at risk because of the inequalities in health care delivery systems and screening. The majority of the work group members believe that a targeted strategy is not suitable. However, she agreed that if the full ACIP was interested in further consideration of this issue, the work group could further assess it.

Dr. Baker noted that the ACIP had a history of observing how ineffective risk-based recommendations are, even if there is lack of stigma in risk-based recommendations.

Dr. Salisbury (DOH UK) reported that at the time they were making decisions about the age groups to consider for inclusion in their program, cost effectiveness was a very important component of that consideration. According to the criteria they used, it was not going to be cost-effective to vaccinate beyond the age of 18. They have revisited this a number of times, and the situations remains the same. The point is that those considerations were being taken forward a couple of years ago. Since then, the girls within the catch-up program up to 18 years of age are now moving through into the over 18 cohort. That reduces any possible cost-effectiveness of having a recommendation for those over 18 as each of those who is highly protected moves into that group. This is not a static consideration. They break down their coverage data by locality. When they assess the immunization coverage now observed in the 12 year old girls, some of the highest reports (e.g., 98% third dose coverage) come from the most deprived and most multi-ethnic parts of the country. Dr. Salisbury believes that it is delivery of the program that is following forth rather than targeting, which creates new inequalities.

Dr. Schuchat pointed out that an important difference between the UK program and the US is the role of schools as a site for vaccination.

Dr. Rosenbaum said that rather than thinking about this incrementally in terms of risk groups and sub-risk groups, she was mindful of the cost issues and was also very focused on how the strength of messaging around the universality of this vaccine for women beginning early in their lives and proceeding up through life could serve as a boost to the earliest vaccinations. The benefits are profound in the earliest vaccinations, and as the consumer representative, she wished that her daughter had had the benefit of this vaccine at a time when she would have truly benefited. She expressed her hope that as they deliberated, they would give consideration to what position on specific cohorts would get them to the point where the American public could understand that this is something that really must happen for women generally.

Dr. Neuzil responded that this spoke to the fact that there is a lot that is not understood about vaccine acceptance. This arises frequently with influenza vaccine when they try to understand why coverage rates have plateaued and they cannot get beyond certain levels She made a more general plea that this is an understudied area, and that it would help ACIP in many of their deliberations to better understand what does affect consumer opinion and uptake of vaccines.

Representing college health which people believe to be a highly insured, affluent, and fairly well-educated population, Dr. Turner (ACHA) reported that as of last fall, only 39% of women they surveyed had even received one dose of HPV vaccine. They are pretty discouraged by this.

Some of their focus groups have suggested that cost is an issue, but beyond that he did not have any ideas about why there was not more success in getting these women vaccinated.

Dr. Chilton said it sounded as though some of the discussion they had had in the last few minutes had laid the low immunization rate of teenagers at the feet of the teenagers themselves or their families. He expressed his hope that it was clear to most people that much of the lack of good immunization rates in this country as a whole, and not just regarding this vaccine, was really at the discretion of providers in that providers are not doing a very good job of getting vaccines into adolescents. Vaccines must be promoted not only to the public, but also to providers.

Dr. Baker added that in certain, probably at risk, communities there was also a knowledge problem in terms of parents not reaching out to acquire the vaccines that their adolescents should receive.

GARDASIL® Update: Efficacy Against Intra-Anal Infections and Disease

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Dr. Haupt reported on the end-of-study results for Protocol 20, which assessed GARDASIL® efficacy against intra-anal infections and disease. Given that HPV-related cancers affect a significant number of US men each year, Merck was pleasantly surprised by the results of this exploratory study against intra-anal endpoints.

Estimates were calculated using 2007 data from the American Cancer Society (ACS) on the annual incidence (N=12,383) and mortality (N=2,595) from anal cancer, penile cancer, oral cavity cancer, oropharyngeal cancer, and laryngeal cancer [Based on American Cancer Society. *Cancer Facts and Figures 2008*]. The fraction of these cases attributable to HPV was then calculated using published estimates of HPV prevalence in the relevant cancers [1. Based on American Cancer Society. *Cancer Facts and Figures 2008*. 2. Daling JR et al. *Cancer*. 2004;101:270–280. 3. Ryan DP et al. *N Engl J Med*. 2000;342:792–800. 4. Kreimer AR et al. *Cancer Epidemiol Biomarkers Prev*. 2005;14:467–475]. There are cancers caused by HPV in men as well. When added together, they are similar in terms of total incidence to cervical cancer in women.

Up to 90% of anal cancers, the rate of which has been steadily increasing in men, are HPV-related. In the US, the annual incidence of anal cancer in males is approximately 2,020 cases [American Cancer Society. *Cancer Facts and Figures 2008*]. Approximately 80% to 90% of these cases are HPV-related [International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. 2007;90]. In one study of patients in the United States, 88% of anal cancers were positive for HPV. HPV 16 was the most common HPV type detected among men and women, found in 73% of tumors. HPV 18 was the next most common type identified, found in 7% of tumors [Daling JR et al. *Cancer*. 2004;101:270–280]. Evidence indicates that the incidence of anal cancer is increasing, particularly among men [Partridge JM et al. *Lancet Infect Dis*. 2006;6:21–31]. An analysis of data from the Surveillance, Epidemiology, and End Results (SEER) Program from 1973 to 2000 found that anal cancer incidence was lower for males (1.06/100,000) than for females

(1.39/100,000) between 1973 and 1979, but it was similar for males (2.04/100,000) and females (2.06/100,000) between 1994 and 2000. Other estimates have suggested that the incidence of anal cancer in US men has increased almost 3-fold in 3 decades. However, the incidence of anal cancer in men who have sex with men, even before the HIV epidemic, was considerably higher (35/100,000). This is roughly equivalent to the incidence of cervical cancer in women in the US prior to routine cervical cancer screening.

Protocol 20 was a randomized, double-blind, placebo-controlled, international, multi-center study. Subjects received 3 doses of GARDASIL® or placebo at 0, 2, and 6 months. Follow-up was designed to be 36 months for each subject. Enrolled subjects included heterosexual men (HM) ages 16 to 23 (N=3463) and men having sex with men (MSM) ages 16 to 26 (N=602). Subjects were seen every 6 months over the course of the 3-year follow-up period. Swabs were obtained for HPV DNA testing (e.g., penile, scrotal, and perineal / perianal swabs were obtained from all subjects, and intra-anal from MSM only); and anal Pap smears were done for cytology in MSM only. Any disease lesion that was determined by the investigators that could potentially be HPV-related was biopsied, so all of these endpoints are based on biopsies with adjudication by the Consensus Pathology Panel and HPV testing. All of the external genital endpoints come from both populations of heterosexual and MSM, while the intra-anal biopsies were done in MSM only.

The primary objective of Protocol 20 was to demonstrate the safety and tolerability of GARDASIL® in young men. There were two efficacy objectives. The primary efficacy objective was to demonstrate reduction in primary-combined incidence of HPV 6/11/16/18-related external genital lesions (e.g., external genital warts, as well as penile, perineal / perianal intraepithial neoplasia) in heterosexual and MSM subjects. The second efficacy objective was efficacy against anal intraepithelial neoplasia (AIN) in MSM only. The secondary efficacy endpoints evaluated 6/11/16/18 persistent infection (6-month definition) and any-time HPV 6/11/16/18 DNA detection. The immunogenicity endpoint evaluated vaccine-induced serum anti-HPV 6/11/16/18 responses.

In terms of the baseline status of HPV types across the entire study set, by serology about 7.6% of the men were seropositive to one or more of the four vaccine types, 12.2% were HPV DNA positive, and 17.3% were positive by either PCR or serology, which means that approximately 83% of the men studied were negative for all four types. As observed with the adult women, most men infected with a vaccine type were infected with only one type. Dr. Haupt also examined this data stratified by the two different sexual orientation groups. There was a lifetime sexual partner exclusion criteria for this study, so men had to have had 5 or fewer lifetime sex partners. That was true for the MSM subgroup as well. One of the reasons that the age range went to 26 in the MSM was because there were difficulties enrolling MSM with that few a number of lifetime sex partners. Despite that their baseline positivity by PCR and serology is substantially higher than the MSM, which reflects two things. First, there was additional swab with the intra-anal swab that was done in the MSM, so there was greater opportunity to capture HPV DNA. Second, even though these men may have reported fewer lifetime sex partners, there is no limit to how many lifetime sexual partners their partners had. Of the 602 MSM who were positive to one or more HPV 6/11/16/18, 22.8% were positive by serology, 30.5% by PCR, and 39.1% by PCR or serology.

In previous presentations which represented the first EGL analyses, there were case counts of 3 (vaccine) and 31 (placebo) with an efficacy of about 90%. At the end-of-study there are still 3 GARDASIL® cases and 32 cases in the placebo arm, for a highly statistically significant efficacy for external genital lesions. Most of these endpoints are external genital warts, with 3 GARDASIL® cases and 28 placebo arm cases, for an efficacy of 89.3% (65, 98 CI). The additional case that occurred in this study against external genital lesions was a PIN 2/3 in the placebo arm that occurred in one of the MSM subjects. At the end-of-study there are now 4 endpoints of PIN where there were 3 previously.

Procedures were performed in addition to genital procedures for evaluation of anal endpoints in the MSM substudy. Rectal examinations were conducted at Day 1 and Months 7, 12, 18, 24, 30, and 36. High resolution anoscopy was performed if an abnormality was noted in the rectal examination or a subject had an abnormal anal Pap test, and a mandatory high resolution anoscopy was done on all subjects at the close of the study. It was recommended by their Data Safety Monitoring Board (DSMB) to end the study early based on the early high efficacy and safety demonstrated. Thus, completion of the study was accelerated so that they could begin vaccinating placebo recipients and a high resolution anoscopy was done in all subjects at the close of the study. In order to be an endpoint, subjects had to have a consensus diagnosis made by the Pathology Panel of AIN1, AIN2, AIN3, anal cancer and detection of HPV 6/11/16 or 18 DNA by Thinsection PCR in an adjacent section in the same tissue block. Pathology Panel consensus diagnosis of condyloma acuminatum in an intra-anal biopsy specimen are grouped under AIN1 (acuminate and non-acuminate), which was advised by Merck's Scientific Advisory Committee.

Dr. Haupt reminded everyone that in October 2009, he cautioned everyone that he may not be able to present anal disease endpoints. Given the number of case counts, he was concerned that they may not reach the number needed to show efficacy. In fact, there were 29 endpoints, which was quite remarkable for the MSM per protocol efficacy population. There were 5 GARDASIL® HPV 6/11/16/18-related AIN endpoints and 24 placebo cases, with an observed efficacy of 77.5% (40, 93 CI). This study was powered for any grade AIN, but was not powered for AIN 2/3. Thus, they were very surprised to have 16 endpoints for AIN 2/3 (3 GARDASIL® and 13 placebo), reflecting 74.9% observed efficacy (9, 95 CI). Stratification of AIN 1 was very good in terms of identifying condyloma, with 100% observed efficacy due to intra-anal condyloma, which are typically HPV 6 /11.

Two of Merck's analyses support this efficacy against AIN 2/3. The high risk types associated with AIN 2/3 were assessed for the 3 GARDASIL® and 13 placebo subjects. For overall HPV 16/18-related AIN 2/3, there was 1 GARDASIL® case and there were 8 placebo cases for 86.6% efficacy (0.013, 100 CI). For HPV 16 there was 1 GARDASIL® case for 82.8% efficacy (-41, 100 CI), and for HPV 18 there were no GARDASIL® cases and there were 2 placebo cases for 100% efficacy (-501, 100 CI). By lesion type, for AIN 2 there were no GARDASIL® cases and 6 placebo cases for 100% efficacy (9, 100 CI). For AIN 3 there was 1 GARDASIL® case and 4 placebo cases for 73.0% efficacy (-173, 100 CI). There were no cases of anal cancer in either group. The one case of HPV 16-related was an AIN 3 that was a co-infected lesion with Type 39. The subject had persistent infection with Type 39 from Day 1 throughout the entire study period until this lesion was identified. This was the only time that Type 16 was actually found in that subject. The other compelling analysis for the potential of GARDASIL® for preventing intra-anal disease is the efficacy against persistent infection. There was very high efficacy for the vaccine types of 94.9% (80, 99 CI), with 2 cases in the GARDASIL® group and 39 in the placebo group.

End-of-study safety data are consistent with previous data. No new vaccine-related severe adverse events (SAEs) were observed. There were 25 SAEs in 21 subjects, none of which were vaccine-related. The proportion of subjects reporting new medical conditions was comparable between the vaccine and placebo groups (28% versus 30% respectively). The most common conditions included upper respiratory infections and pharyngitis. The proportion of subjects reporting conditions potentially consistent with autoimmune phenomena was comparable between vaccine and placebo groups (0.7% versus 1.1% respectively).

The conclusions are that GARDASIL® has high efficacy against 6/11/16/18-related intra-anal persistent infection, AIN, and AIN 2/3, as well as 16/18-related AIN 2/3. High efficacy against HPV vaccine type persistent infection and disease (including high-grade) is now demonstrated at another anogenital site (CIN, VIN, VaIN, AIN, genital warts). High efficacy is observed in both keratinized and mucosal epithelial surfaces in both women and men, which provides a strong picture of the overall benefit of GARDASIL® against vaccine type HPV-related infections and diseases.

Quadrivalent HPV Vaccine For Males: Future Considerations

Lauri Markowitz, MD
NCHHSTP / CDC

Dr. Markowitz reminded everyone that in October 2009, the FDA licensed the quadrivalent vaccine for males 9 through 26 years of age for prevention of HPV types 6/11-related genital warts [http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm]. During the October 2009 ACIP meeting, after considering various options, ACIP made a permissive recommendation for use in males. Data are now available on some additional endpoints in terms of efficacy for prevention of anal intraepithelial neoplasia in males.

With regard to the projected timeline for review of the new data, submission of the AIN sBLA by Merck to FDA is expected in 2010, and the FDA review will take approximately 6 to 10 months. The data were presented during this session to update ACIP, but there is no projected timeline yet for when there would be a possible vote.

In terms of the current status of the recommendations and availability of quadrivalent HPV vaccine for males, there is a permissive ACIP recommendation and HPV vaccine for males was also included in the VFC program. Merck has also included HPV vaccine for males in their Vaccine Patient Assistance Program, which provides vaccines free of charge to males 19 to 26 years of age who are uninsured and meet the program criteria. The specific wording of the October 2009 ACIP recommendation and VFC resolution are as follows:

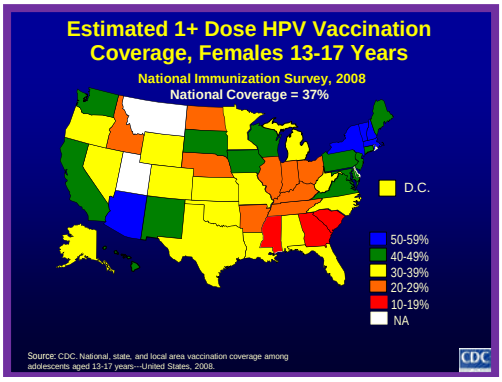
ACIP Recommendation
The 3-dose series of quadrivalent HPV vaccine may be given to males aged 9 through 26 years of age to reduce their likelihood of acquiring genital warts. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact.

Vaccines for Children (VFC)
Quadrivalent HPV vaccine for males approved to be included in VFC enabling VFC providers to provide VFC HPV vaccine to eligible males, age 9 through 18 years of age.

Further information may be found at the following urls:
http://www.cdc.gov/vaccines/recs/provisional/default.htm#acip
http://www.cdc.gov/vaccines/programs/vfc/downloads/resolutions/1009hpv-508.pdf

When considering a recommendation for males during the October 2009 ACIP meeting, the work group and the full ACIP reviewed a variety of data including vaccine efficacy and immunogenicity available at that time, epidemiology and burden of disease, programmatic issues, and cost-effectiveness. The cost-effectiveness of HPV vaccine in males depends upon a variety of assumptions in models. The models show that male vaccination is most cost-effective when coverage among females is low, when all potential health outcomes are included, and when vaccine efficacy is high in males. Results from one efficacy model (Kim & Goldie) were shown. In this model, vaccine efficacy was assumed to be 100% in females in the Kim & Goldie model and vaccine coverage was assumed to be 75% in males and females. In this model, efficacy for prevention of outcomes in males was 75%, which is similar to the results from the efficacy trial in males that were presented during this session. Of note, some cost-effectiveness analyses to date, including the Kim & Goldie model, have included prevention of anal cancers as well as other HPV-associated cancers for which there are not yet data. While male vaccination did not appear cost effective in Kim & Goldie analysis, using coverage estimates that reflect current coverage in the US would result in more favorable cost-effectiveness analyses for male vaccination.

Because of the importance of coverage in these models of male vaccination, and also because questions had arisen during the course of this ACIP session, Dr. Markowitz presented some data on current coverage in adolescent girls in the US. These were data pertaining to vaccine initiation (e.g., 1 or more doses, not complete coverage) from the National Immunization Survey (NIS) in 2007 and 2008 showing coverage in 13 to 17 year old adolescent females. Coverage increased between these two years from 25% in 2007 to 37% in 2008. Coverage with 3 doses was lower at about 18%, although this is probably an underestimate because not everyone in this survey had an opportunity to complete their series. The following map reflects the considerable variation in vaccine initiation by state from 55% in some states in the Northeast to the lowest coverage of just 16% in some states in the South:



In terms of the ACIP HPV Vaccine Work Group's plans to address the new data for quadrivalent vaccine in males, vaccine trial data in males will be further reviewed. The cost-effectiveness analyses will be refined with the vaccine trial data endpoints and different coverage assumptions. The work group will also review the epidemiology and develop cost-effectiveness models for HPV vaccine in MSM, and will consider the feasibility of reaching MSM when they

would most benefit from vaccination. Further consideration and discussion of these issues will occur during the June 2010 and subsequent ACIP meetings.

Discussion

Dr. Keitel inquired as to whether subjects in the MSM group were screened for HIV infection before enrollment, and if so whether the investigators monitored incident HIV infections and whether there was any association between the acquisition of the two types of viruses. That is, was acquisition of HIV associated with more advanced lesions.

Dr. Haupt responded that men had HIV assessment at enrollment, as well as yearly serology or more frequent serology depending upon potential risks. He clarified that the data shown were in the per protocol efficacy population, so any subject who became HIV positive at any point during the clinical trial would have been considered a protocol violator, so there are no HIV positive subjects included in those analyses. While there were HIV seroconversions, no association with the vaccination was observed. There are not enough cases to show anything significant or robust in an analysis of whether acquisition of HIV was associated with more advanced lesions. None of the subjects represented in his data shown during this session would have been HIV positive.

Dr. Keitel indicated that she was having difficulty understanding the difference in all of the denominators in the different categories of lesions in the MSM group.

Dr. Haupt replied that all of the denominators are based on type analysis, so the denominators change depending upon which type a subject had. A subject can be in a per protocol efficacy analysis for a specific type because he was naïve or negative to that type, so he could qualify for one per protocol analysis but they may not for another. Someone could have an AIN 1 or AIN 2, so the numbers in the rows do not always add up to the composite number because subjects could have more than one disease lesion.

Dr. Temte inquired as to whether anything was known about the uptake in males in the October 2009 ACIP vote.

Dr. Markowitz responded that while there are no data at this time, there will be data about this because these questions were added to the NIS and other surveys.

Dr. Haupt said that his understanding was that insurance coverage for boys was actually quite high. In addition to the VFC coverage, a majority of health plans appear to be covering the vaccine for boys in the indicated age group.

Dr. Turner (ACHA) added that on the ACHA national survey, even before the ACIP recommendation last fall, 15% of males reported that they had received one or more doses of HPV vaccine. They will conduct the survey again in 2010 to determine whether that has increased. They were surprised because they made no specific effort to vaccinate males.

13-Valent Pneumococcal Conjugate Vaccine (PCV13)

Introduction

Dr. Kathy Neuzil
ACIP Member

Dr. Neuzil thanked the very hardworking members of the Pneumococcal Work Group. She also reminded everyone that they had engaged in significant discussion pertaining to PCV13 during the June and October 2010 ACIP meetings. Thus, they were very pleased to have the licensure and to be able to vote during this meeting.

Proposed Recommendation and Immunization Schedules

Pekka Nuorti, MD, DSc
Respiratory Diseases Branch
Centers for Disease Control and Prevention

Dr. Nuorti reminded everyone that PCV13 (Prevnar 13®) contains the seven PCV7 serotypes (e.g., 4, 6B, 9V, 14, 18C, 19F, 23F) and the additional serotypes 1, 3, 5, 6A, 7F, 19A. Prevnar 13® was licensed by the FDA in February 2010 and was approved for use in children 6 weeks through 5 years (71 months) of age for prevention of invasive pneumococcal disease (IPD) caused by the 13 serotypes, and prevention of otitis media caused by PCV7 serotypes. The latter is because there is no efficacy data for the other serotypes.

The PCV13 information previously presented to the ACIP members in June 2009 included immunogenicity and safety (Wyeth); estimated vaccine-preventable IPD burden and options for catch-up immunization; and the economic and public health impact of a routine program and supplemental immunization (Wyeth). In October 2009, PCV13 information was presented on immunogenicity and safety with regard to transition and supplemental immunization (Wyeth); cost-effectiveness for routine and supplemental vaccination (CDC); and draft recommendations and immunization schedules. PCV13 is recommended for all children ages 2 through 59 months of age; and children 60 through 71 months who have underlying medical conditions that increase their risk of pneumococcal disease or complications.

The recommendation was divided into 5 distinct parts, and the votes were structured in the same manner, as follows:

1. Routine recommendation
    - Infants and children who have not previously received PCV7 or PCV13
2. Transition recommendation
    - Children incompletely vaccinated with PCV7 or PCV13
3. Supplemental PCV13 dose recommendation (referred to previously as “catch-up” but changed by the work group to “supplemental” because these children have not actually missed doses)
    - Children completely vaccinated with PCV7
4. High risk children ≥6 years of age (new since the October 2009 meeting)
5. PPSV23 after PCV13
    - Children ≥2 years with underlying medical conditions

Regarding the routine recommendation, for children ≤59 months who have not previously received PCV7 or PCV13,,the proposed recommendation and immunization schedules for PCV13 vaccination are the same as currently recommended for PCV7 [1. *MMWR* 2008;57: 343-4; 2. MMWR 2000;49 (RR-9)]. PCV13 replaces PCV7 for all doses. For routine infant immunization, PCV13 is recommended as a 4-dose series at 2, 4, 6, and 12 through 15 months. The following table (Table 2) reflects the recommended routine schedule for PCV13 for unvaccinated infants and children by age at the time of their first dose of vaccine. This table is identical to the PCV7 schedule:

Table 2. Recommended routine immunization schedule for 13-valent pneumococcal conjugate vaccine (PCV13) among infants and children who have not received previous doses of PCV7 or PCV13 by age at the time of first vaccination

Age at first dose (mos)	Primary PCV13 series*	PCV13 booster dose**
2-6	3 doses	1 dose at 12 through15 months
7-11	2 doses	1 dose at 12 through15 months
12-23	2 doses	--
24-59 Healthy children	1 dose	--
24-71 Children with certain chronic diseases or immunocompromising conditions**	2 doses	--

* Minimum interval between doses is 8 weeks except for children vaccinated at age <12 months for whom minimum interval between doses is 4 weeks. Minimum age for administration of first dose is 6 weeks.
** Given at least 8 weeks after the previous dose
*** For complete list of conditions, see Table 3.

Considerations for the transition recommendation from PCV7 to PCV13 are that they have shared serotypes and similar vaccine formulations, and comparable safety profiles and immune responses [PCV13 – package insert, February 2010]. A schedule of 3 PCV7 doses followed by 1 PCV13 dose vs. 4 PCV13 doses may result in lower IgG antibody levels for 6 additional serotypes; however, the functional OPA responses are comparable for these groups after the 4th dose[2] [Paradiso P, Pfizer. ACIP October 2009]. The product insert for PCV13 states that the clinical relevance for this is unknown. Program implementation and logistic considerations include interchangeability of vaccine doses. Table 3 summarizes the recommendations for children who previously received doses of PCV7 or PCV13. The primary point is that children who have received one or more doses of PCV7 should complete their immunization series with PCV13:

Table 3. Transition from PCV7 to PCV13 among infants and children according to number of previous PCV7 doses received

Primary infant series			Booster dose	Supplemental PCV13 dose
2 mos	4 mos	6 mos	≥12 mos*	14-59 mos**
PCV7	PCV13	PCV13	PCV13	–
PCV7	PCV7	PCV13	PCV13	–
PCV7	PCV7	PCV7	PCV13	–
PCV7	PCV7	PCV7	PCV7	PCV13

*No additional PCV13 doses are indicated for children 12 through 23 months who have received 2 or 3 doses of PCV7 before age 12 months and at least 1 dose of PCV13 at age 12 months or older.
** For children with underlying medical conditions, a supplemental PCV13 dose is recommended through 71 months of age.

Table 9a is intended to provide the detailed schedules for providers for the number of doses and dosing intervals by the age of the child at examination, and the vaccination history of either PCV7 or PCV13:

Table 9a. Recommended schedules for administering doses of PCV13 to children <24 months of age by PCV vaccination history and age

Age at examination (mos)	Vaccination history: total number of PCV7 and/or PCV13 doses received previously*	Recommended PCV13 Regimen†
2–6 mos	0 doses	3 doses, 8 weeks apart; fourth dose at age 12–15 mos
	1 dose	2 doses, 8 weeks apart; fourth dose at age 12–15 mos
	2 doses	1 dose, 8 weeks after the most recent dose; fourth dose at age 12-15 mos
7–11 mos	0 doses	2 doses, 8 weeks apart; third dose at 12–15 mos
	1 or 2 doses before age 7 mo	1 dose at age 7–11 mos, with a second dose at 12–15 mos (≥ 8 weeks later)
12–23 mos	0 doses	2 doses, ≥ 8 weeks apart
	1 dose before age 12 mo	2 doses, ≥ 8 weeks apart
	1 dose at ≥12 mo	1 dose, ≥ 8 weeks after the most recent dose§
	2 or 3 doses before age 12 mo	1 dose, ≥ 8 weeks after the most recent dose§
	4 doses of PCV7 or other age-appropriate complete PCV7 schedule	1 supplemental dose, ≥ 8 weeks after the most recent dose¶

The proposed recommendation for children ≥24 months who are incompletely vaccinated with PCV7 or PCV13 is that healthy children 24 through 59 months with any incomplete PCV schedule (PCV7 or PCV13) should received a single dose of PCV13. Children 24 through 71 months with underlying medical conditions who have received an incomplete schedule of <3 doses of PCV (PCV7 or PCV13), 2 doses of PCV13 are recommended. If 3 doses of PCV have been received (PCV7 or PCV13), a single dose of PCV13 is recommended.

In terms of the supplemental recommendation for children who have been completely vaccinated, a supplemental PCV13 dose appears to be safe. The data suggest that the local and systemic adverse reactions after one supplemental dose are similar to those after a 4-dose PCV13 series. Based on the available data, the additional dose is no more reactogenic than a 4-dose series. In addition, one dose of PCV13 elicits antibodies against 6 additional serotypes in children ≥12 months [1. PCV13 package insert, February 2010; 2. Paradiso, P Pfizer. ACIP June and October 2009]. Two independent cost-effectiveness analyses have been presented to the committee, the first of which was presented during the June 2009 ACIP meeting. In that analysis, the supplemental dose was found to be cost saving under the assumption that it would accelerate the indirect effects by 6 months or more. Even if the indirect effects in this Wyeth study were removed, the supplemental dose was still found to be cost-effective [Strutton D, Pfizer. ACIP June 2009]. The second cost-effectiveness study was conducted by CDC and was presented to the committee during the October 2009 ACIP meeting. Although the methods and some of the assumptions of that analysis were different from the Wyeth analysis, the conclusions were largely consistent. The CDC analysis found that the supplemental dose was not cost saving when indirect effects were not considered, but it was found to be reasonable with about $28,000 per discounted QALY saved in a cohort model that did not take into account the indirect effects. This analysis was conducted with a base case scenario with an approximate vaccine price of about $100 average between the public and private sectors [Messonnier M, CDC, ACIP October 2009]. In terms of the potentially preventable disease burden that was also discussed during the October 2009 ACIP meeting, it is true that the rates of invasive disease are quite low in that age group and they decrease rapidly; however, there is a substantial burden of pneumococcal pneumonia, otitis media, and antibiotic-resistant disease in that age group, particularly of serotype 19A. There have been multiple reports on multi-drug resistant 19A disease causing meningitis or severe invasive disease. The supplemental recommendation that the work group is proposing is not only based on the invasive disease

rates, but also other potentially preventable pneumococcal syndromes. It was felt that this approach would be programmatically feasible with a limited implementation time period of one year. This proposal does not include active recall of children. Instead, this vaccine should be given during the next routine medical visit.

The proposed recommendation for the supplemental dose is that children 14 through 59 months of age who have been completely vaccinated with PCV7 who have received 4 doses of PCV7 or other age-appropriate, complete PCV7 schedules are recommended to receive a single supplemental dose of PCV13. For children who have underlying medical conditions, the supplemental dose is recommended through 71 months of age. This includes children who have previously received PPSV23. The reason for the somewhat awkward age of 14 months has to do with the minimum interval between doses, which is at least last 8 weeks after the last PCV7 dose, at the next medical visit. Age 14 months is the first opportunity to receive supplemental PCV13 according to the schedule. Tables 9a and 9b shown earlier reflect this information, and the footnotes for Table 9 are as follows:

Footnotes, Table 9:
1) Minimum interval between doses is 8 weeks except for children vaccinated at age <1 year, for whom minimum interval between doses is 4 weeks.
2) No additional PCV13 doses are indicated for children 12 through 23 months of age who have received 2 or 3 doses of PCV7 before age 12 months and at least 1 dose of PCV13 at age 12 months or older.
3) For children with underlying medical conditions, PCV13 is indicated through 71 months of age.

* A single supplemental dose of PCV13 given at least 8 weeks after the last dose of PCV7 is recommended for all children 14 through 59 months of age who have received 4 doses of PCV7 or other age-appropriate, complete PCV7 schedule (fully vaccinated with PCV7). For children who have underlying medical conditions, a supplemental dose is recommended through 71 months of age.

The need for a statement about children ≥6 years of age who have a high risk condition was also raised during the October 2009 ACIP meeting. While the work group discussed this at length between that meeting and this, Dr. Nuorti emphasized that PCV13 is not licensed for this indication, so this would be an off-label recommendation. PCV7 is licensed by the FDA up to age 9 years. The current ACIP recommendations for PCV7 are as follows [MMWR 2000;49 (RR-9); ACIP, June 2008]:

- Administering PCV7 to older children [≥5 years] with high risk conditions is not contraindicated.
- For HIV infected children aged 5-17 years on HAART who have not been previously immunized with PCV7, practitioners may consider administering 2 doses of PCV7 followed by PPSV23.

Current AAP / COID recommendation for PCV7 [AAP COID Red Book, 28th edition, 2009] are as follows:

- Administration of a single dose of PCV7 to children of any age who are at high risk of IPD, is not contraindicated

While studies of PCV13 among healthy children ≥6 years and children with HIV infection and SCD are currently underway to evaluate safety and the optimal number of doses, there are no data available at this point. The proposed wording for high risk children ≥6 years of age is as follows:

- Vaccination with a single dose of PCV13 may be appropriate for children 6 through 18 years of age who are at increased risk for IPD because of sickle cell disease, HIV-infection, or other immunocompromising condition, regardless of whether they have previously received PCV7 or PPSV23.

- Routine use of PCV13 is not recommended for healthy children ≥5 years of age.

Limited safety data are available for PPSV23 after PCV7. There are some immunogenicity data showing that this induces a nice booster response to those serotypes that are shared with the vaccine. No safety or immunogenicity data available for PPSV23 given after (or before) PCV13, and the clinical effectiveness of this sequence is unknown. CDC surveillance data suggest that the opportunity to provide additional serotype coverage with PPSV23 when PCV13 is implemented may become limited since the serotypes in PPSV23 that are not in PCV13 caused about 16% of the IPD cases in children 24 through 59 months with medical conditions over a three-year period [CDC, Active Bacterial Core surveillance 2006-2008, unpublished]. PCV13 types cause about 45%. With that information , the proposed recommendation is that in addition to PCV13, children with underlying medical conditions should receive PPSV23 at age ≥2 years. The recommended doses of PCV13 should be completed before PPSV23 is given. However, children who have previously received PPSV23 should also receive the recommended PCV13 doses. Table 11 reflects the schedule for vaccination with PPSV23 after PCV13 for children ≥2 years of age with underlying medical conditions:

Table 11. Schedule for vaccination with PPSV23 after PCV13 for children ≥2 years of age with underlying medical conditions

Group	Schedule for PPSV23	Revaccination with PPSV23
Children who are immunocompromised, have sickle cell disease, or functional or anatomic asplenia	1 dose of PPSV23 administered at age ≥2 yrs and ≥ 8 weeks after last indicated dose of PCV13	1 dose 5 years after the first dose of PPSV23
Immunocompetent children with chronic illness	1 dose of PPSV23 administered at age ≥2 yrs and ≥ 8 weeks after last indicated dose of PCV13	Not recommended

Table 1 defines the underlying medical conditions that are indications for pneumococcal vaccination among the children to whom the recommendation applies:

Table 1. Underlying medical conditions that are indications for pneumococcal vaccination among children

Immunocompetent persons	Chronic heart disease*
	Chronic lung disease**
	Diabetes mellitus
	Cerebrospinal fluid leaks
	Cochlear implant
Functional or anatomic asplenia	Sickle cell disease (SCD) and other sickle cell hemoglobinopathies Congenital or acquired asplenia, or splenic dysfunction
Immunocompromised persons	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with immunosuppressive chemotherapy, or radiation therapy including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid organ transplantation
	Congenital immunodeficiency***
* Particularly cyanotic congenital heart disease and cardiac failure ** Including asthma if treated with high-dose oral corticosteroid therapy	
*** Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease)	

Discussion

Dr. Englund noted that for children with underlying conditions, Table 9a indicates that those who have had 4 doses of PCV7 should receive 1 supplemental dose, while the proposed recommendation stated that children 24 through 71 months with underlying medical conditions who received 3 doses of PCV (PCV7 or PCV13) should receive a single dose of PCV13.

Dr. Nuorti responded that this was for children who were incompletely vaccinated with PCV7 versus the supplemental dose, which is for children who have completed their vaccinations.

Dr. Englund said she wanted this to be absolutely clear because she was sent there from her Transplant Unit to determine whether they could give the extra dose of PCV13.

Dr. Nuorti responded that the recommendation for children 24 months and older who are incompletely vaccinated is similar to what has been previously recommended for PCV7.

Dr. Chilton pointed out that this year, practitioners have had to deal with the discrepancy between 9 and 10 years of age for a second dose of influenza vaccine. He wondered whether it was really necessary to have a difference between 5 and 6 years of age for children with no underlying conditions versus those who do have underlying conditions. There did not seem to be a natural break point in either of those ages.

Dr. Nuorti responded that this point was discussed by the work group. The reason the decision was made to break the recommendation down in this way was because that is how PCV7 is recommended. PCV7 is not recommended for healthy children 5 years and older. The work group felt that since the vaccine is approved through 5 years of age, it should at least be recommended for those children who are at increased risk. The other consideration was that it was the work group's understanding that the manufacturers intends to apply for an expanded indication for the vaccine once all of the data are in such that the upper age limit would be 18 years. At that point, it would be easier to extend the high risk recommendation up to age 18 years.

Dr. Baker wondered whether there were any data on the duration of protection (functional or immunoantibody) for high risk children who have been vaccinated appropriately with PCV7 and at 2 or more years have received PPSV23.

Dr. Nuorti responded that he was unaware of any data that have assessed this specific situation. Limited immunogenicity data are available for PCV7, and it is difficult to study now.

Dr. Baker wondered whether such data would become available as they moved forward.

Dr. Nuorti deferred to the manufacturer to discuss the types of studies they have planned.

Dr. Whitney added that there are really no data pertaining to duration of protection with PCV7. There was a study regarding PCV9 in South Africa that examined direction of protection among healthy children and children with HIV. Those children received a 3-dose primary series without a booster. The healthy children had significant protection 4 years later, but the HIV children did not. Given that this was without a booster, it is difficult to compare to the US schedule.

Dr. Paradiso added that when the South African children were given a dose of vaccine at 4 years of age, the induced response was higher in the children who had received the 3 doses in infancy than those who had not. That was true for HIV positive children as well, although by the time the HIV positive children reach 5 years of age, they had similar antibodies to the unvaccinated children.

In terms of the supplemental dose, Dr. Neuzil reported that the work group spent a significant amount of time discussing the issues and were quite persuaded by the cost data. The amount of $28,000 per QALY was congruous with some of the other outcomes gained for other selected childhood vaccines. The HPV models discussed earlier by Dr. Chesson, for example, all included indirect effects. For PCV13, the figure was $28,000 with no indirect effects included. These data were presented to the full ACIP in more detail in October 2009. The work group also felt that high risk children should receive that dose at an early age. It would be nice to say "high risk children $\geq$5" but because of the licensure language, between 5 and 6 years of age, the work group is stating that it is recommended. For over the age of 6, since it is not yet licensed, the group is suggesting that it "may be given." The discrepancy in age does not really pertain to healthy versus high risk children. It is because of the age of licensure currently.

Ms. Rosenbaum requested that someone explain to her the range of possible votes that could be cast.

Dr. Nuorti responded that the work group prepared five separate votes, and that if the committee wanted to package some of those, it would be fine.

Ms. Rosenbaum clarified that she did not mean the specific votes. She assumed that for any topics upon which ACIP voted, there would be possible votes that could be taken. For example: a recommendation without any limitation, a permissive recommendation, et cetera. She requested that someone walk her through the possible range of voting could be.

Dr. Pickering replied that the possible range was that a recommendation would be made for general use for the population for that age group, as licensed by the FDA.

Ms. Rosenbaum inquired as to whether ACIP always voted for routine use as opposed to permissive use, and requested further information between these two types of votes.

Dr. Pickering explained that votes vary based upon what work groups propose. Work groups make proposals about what they feel the recommendations should be. Sometimes there are options, in which case they will state the options in order of preference. There are cases in which there is permissive use, which means that the vaccine can be given to an individual who requests the vaccine or to a person for whom the physician feels the vaccine is needed after discussion with that person.. It is considered by some to be a weaker recommendation.

Dr. Gellin indicated that they are in a transition period, which allows them to take a step back to think about where they have been and where they are going. He expressed gratitude to the FDA for giving them a just-in-time indication, which is for a 3 + 1 schedule. He also acknowledged that throughout the world, not everyone has a 3 + 1 schedule. In Europe, it is about split. It is complicated because of the schedule that has been licensed, but he wondered whether there had been any discussion regarding 2 + 1 versus 3 + 1 and what this country gets for what it buys, particularly in light of Dr. Frieden's comments.

Dr. Neuzil responded that the work group has discussed this, but not extensively. There is some difficulty within the committee when dealing with the US's package insert and country experience of 3 + 1. It is not that the work group is not willing to consider other countries, but it difficult because they do not know what plans the manufacturer has for further studies of the schedule and perhaps requesting a license change. Moving forward, she thought that if there was interest, they could systematically review the schedules of other countries. However, the position in the past has been that they would be stepping fairly far from US licensure, which makes the work group members somewhat uncomfortable.

Dr. Whitney responded that they reviewed this extensively for PCV7 as some of the data began to show that a 2 + 1 schedule had been used effectively in other situations. Until there is licensure in this country suggesting that this is okay for providers, the work group is hesitant to recommend a primary schedule that is off label. This is complicated and it was raised with the National Vaccine Advisory Committee (NVAC), where it also did not receive much traction.

Dr. Baker added that providers have been accustomed to using this schedule for nearly a decade with PCV7. To re-educate them would be quite a major task.

VOTE 1

For Vote 1, ACIP members voted on the routine vaccination for infants 2 through 6 months of age and catch-up vaccination for unvaccinated children 7 months of age and older, the exact wording for which is as follows:

Infants 2 through 6 months of age:

- *The primary infant series consists of 3 doses of PCV13. Infants receiving their first dose at age ≤6 months should receive 3 doses of PCV13 at intervals of approximately 8 weeks (the minimum interval is 4 weeks).*

- *Minimum age for administration of first dose is 6 weeks.*

- *The fourth (booster) dose is recommended at age 12 through 15 months and should be given at least 8 weeks after the third dose (Table 8).*

Unvaccinated children 7 months of age and older–catch-up:

- *Infants 7 through 11 months of age*
  Three doses are recommended. The first 2 doses should be given with an interval of at least 4 weeks between doses. The third dose should be give at age 12 through 15 months, at least 8 weeks after the second PCV13 dose.

- *Children 12 through 23 months of age*
  Two doses are recommended, with an interval of at least 8 weeks between doses.

- *Children 24 months of age and older*
  Unvaccinated healthy children 24 through 59 months of age should receive a single dose of PCV13. Unvaccinated children 24 through 71 months of age with underlying medical conditions (Table 2) should receive 2 doses of PCV13 with an interval of at least 8 weeks between doses (Tables 8 and 9).

Vote 1 Motion: Routine and Catch-Up Recommendations

Dr. Sawyer made a motion to approve the routine and catch-up recommendations as stated. Ms. Ehresmann seconded the motion. The motion carried with 13 affirmative votes, 1 abstention, and 0 negative votes.

VOTE 2

For Vote 2, ACIP members voted on the transition recommendation for children incompletely vaccinated with PCV7 or PCV13, the exact wording for which is as follows:

Children <24 months incompletely vaccinated with PCV7 or PCV13

- *Infants and children <24 months of age who have received one or more doses of PCV7 should complete the 4-dose immunization series with PCV13 (Tables 9 and 10).*

- *For children 12 through 23 months of age who have received 3 doses of PCV7 before age 12 months, 1 dose of PCV13 is recommended given at least 8 weeks after the last dose of PCV7 (Tables 9 and 10).*

Children ≥24 months incompletely vaccinated with PCV7 or PCV13

- *A single dose of PCV13 is recommended for all healthy children 24 through 59 months of age with any incomplete PCV schedule (PCV7 or PCV13).*

- *For children 24 through 71 months of age with underlying medical conditions who have received any incomplete schedule of <3 doses of PCV (PCV7 or PCV13), 2 doses of PCV13 are recommended (Table 9).*

- *For children with underlying medical conditions who have received 3 doses of PCV (PCV7 or PCV13), a single dose of PCV13 is recommended through 71 months of age.*

- *The minimum interval between doses is 8 weeks.*

Discussion

Dr. Nuorti noted that "4-dose" should be removed so that the first bullet would read: *Infants and children <24 months of age who have received one or more doses of PCV7 should complete the immunization series with PCV13 (Tables 9 and 10).*

To better harmonize, Dr. Lett inquired as to whether it would be acceptable to state "children with underlying medical conditions through 9 years of age?" This is included in the original label.

Dr. Nuorti responded that based on the work group discussions, there was hesitancy to recommend beyond the label. Vote 4 addresses the older high risk children, so that would be a separate permissive statement.

Dr. Cieslak was not clear what the second bullet added to the first.

Dr. Nuorti explained that it was to emphasize that children who had received the full infant series with PCV7 could receive a booster dose of PCV13. This could be removed because it is covered in the first bullet.

For physicians who have a refrigerator full of PCV7 vaccine, Dr. Temte inquired as to whether there were plans to institute a buy-back or exchange program.

Dr. Garrett (Pfizer) responded that Pfizer plans to take returns of Prevnar® and will amend the return policy to accept in-date Prevnar® as well as partial packages through the end of 2010.

Dr. Judson inquired as to whether he was correct in understanding that there is no evidence showing that 3 + 1 is superior to 2 + 1.

Dr. Whitney responded that for PCV7 there is a fair amount of data. There are some subtle differences with a couple of the serotypes in that there is not quite as good protection in between the primary series and the booster dose. Some breakthrough cases have been observed early on until herd immunity occurs, which seems to protect most children. While there are subtle differences, they are very similar in terms of the impact studies that have been conducted and the quality of those.

Dr. Richardson (NACCHO) reported that Mexico uses a 2 + 1 schedule. They do not have serologic evidence thus far, but preliminary data show a significant decrease in mortality from pneumonias and bacterial meningitis as of 2007, which is when the vaccine was introduced. She will forward these data to Dr. Whitney.

Vote 2 Motion: Transition Recommendation

Dr. Sawyer made a motion to approve the transition recommendations as written, with the removal of "4-dose" and removal of the second bullet for Children <24 months incompletely vaccinated with PCV7 or PCV13. Dr. Keitel seconded the motion. The motion carried with 13 affirmative votes, 1 abstention, and 0 negative votes.

VOTE 3

For Vote 3, ACIP members voted on the supplemental PCV13 dose recommendation for children completely vaccinated with PCV7, the wording for which is as follows:

Children >14 months of age who are completely vaccinated with PCV7

- *A single supplemental dose of PCV13 is recommended for all children 14 through 59 months of age who have received 4 doses of PCV7 or other age-appropriate, complete PCV7 schedule (fully vaccinated with PCV7).*

- *For children who have underlying medical conditions, a single supplemental PCV13 dose is recommended through 71 months of age. This includes children who have previously received PPSV23.*

- *PCV13 should be given at least 8 weeks after the last dose of PCV7 or PPSV23. This will constitute the final dose of PCV for these children (Tables 9 and 10).*

Discussion

Dr. Meissner indicated that he and Dr. Neuzil had been discussing the issue of cost of the vaccine because this will be an additional dose to what is currently being done. He requested comments on this.

Dr. Garrett (Pfizer) responded that the private market price would be $108 plus .75 cents for Federal Excise tax. The VFC contract is not yet completed, given that it is awaiting a vote. The expected price of the VFC price with the private price will bring the average weighted price just under the $100 that was used in all of the economic studies.

Ms. Ehresmann pointed out that this is really a time-limited recommendation in that it is a catch-up for children, so even if there is a cost factor it will not be on-going throughout the duration of using this product.

Dr. Baker clarified that this would be true for healthy children, and that in the future they would likely be considering those with underlying risk factors in terms of age limits when more data become available.

In view of recurring or intermittent shortages or lack of availability of vaccine, Dr. Keitel inquired as to whether it would be beneficial to include verbiage in the background materials indicating that there are data available that suggest that the 2 + 1 schedule can be implemented.

Dr. Nuorti replied that there would later be an implementation presentation, and he requested that the manufacturer to comment on the current supply situation in terms of the availability of PCV13.

Dr. Baker indicated that the scenario of children not being fully vaccinated exists in practice.

Dr. Garrett (Pfizer) responded that currently there are 8.3 million doses of product already filled for the US market. They are in the process of final packaging now that the final labeling is approved. Pfizer expects to begin shipping these doses the week of March 15, 2010. That represents approximately 6 months of supply for the US market based on Prevnar® usage. There are over 20 million doses already filled for global demand, so Pfizer is ahead of supplies

normally anticipated for a launch supply-wise. They also anticipate exiting 2010 with a global inventory of filled product of over 6 months of inventory.

To address Dr. Keitel's question, Dr. Pickering reported that there is a very active group which considers vaccine supply and limitations, which meets by teleconference on a weekly basis and is composed of private professional and state organizations, many of which were represented in the room. When a vaccine is known to be in short supply the manufacturers inform this group, at which time plans are made in terms of dosing recommendations for the future depending upon the manufacturers' provision of information about supply. Therefore, this includes a specific recommendation about supply in the statement may be somewhat limiting.

Vote 3 Motion: Supplemental PCV13
Recommendation for Completely Vaccinated Children

Dr. Neuzil made a motion to approve the supplemental PCV13 recommendation for completely vaccinated children as stated. Dr. Chilton seconded the motion. The motion carried with 13 affirmative votes, 1 abstention, and 0 negative votes.

VOTE 4

For Vote 4, ACIP members voted on the recommendation for children 6 through 18 years of age with SCD, HIV, or other immunocompromising condition, the exact wording for which is as follows:

Children 6 through 18 years of age

- *A single dose of PCV13 may be administered for children 6 through 18 years of age who are at increased risk for invasive pneumococcal disease because of sickle cell disease, HIV-infection, or other immunocompromising condition, regardless of whether they have previously received PCV7 or PPSV23.*

Discussion

Dr. Baker inquired as to whether this was a recommendation for permissive use.

Dr. Nuorti responded that this is not an approved indication for the vaccine, so it would be for permissive use.

Ms. Rosenbaum requested that someone explain to her the impact of a permissive use recommendation versus a recommendation on VFC coverage and the standard response by the insurance industry.

Dr. Nuorti replied that this age group is listed under the eligible groups that are included in the proposed VFC recommendation that Dr. Santoli would be showing. In terms of the impact of a permissive recommendation versus a recommendation, in this case it is included in the VFC.

Dr. Santoli added that the ACIP would have the opportunity to decide whether to include a permissive recommendation just like any other recommendation in the VFC resolution. This would be included in the VFC vote.

Dr. Netoskie (AHIP) indicated that generally speaking, routine vaccinations would be covered by practically all insurers. There is more variability with a permissive vaccine; however, something like this would most likely also be covered based on the discrete population for which the permissive vaccine is being indicated.

Dr. Nuorti added that this is fairly small group of children.

Dr. Neuzil commented that sometimes the work group, and certainly it is true in this case, is persuaded by whether there will be more information in the future to help answer questions. For example, ACIP recommends influenza vaccine for pregnant women even though it is not licensed because they do not believe that this indication is likely to change and there is a very strong rationale for that recommendation. In this case, the work group opted to select "may be administered" because this is done for PCV7 and they do believe that this group of high risk children needs the protection. There are on-going studies that will offer further information in the future with respect to what the exact recommendation and perhaps what the exact number of doses should be.

Dr. Ceislak pointed out that the end of the recommendation states "regardless of whether they have previously received PCV7 or PPSV23." A year from now there will be 5-year olds who have received a dose of PCV13, and he wondered whether a dose would be appropriate for them at 6 to 18 years of age.

Dr. Nuorti responded that his interpretation was that if they have received a single dose prior to that, they would not receive another dose.

Dr. Baker agreed that this was her interpretation as well. As Dr. Neuzil emphasized, they would receive additional information to inform future recommendations in high risk children.

As a practicing pediatrician, Dr. Englund found the recommendation to be very helpful. The permissive recommendation is beneficial because there are children whose conditions change. She appreciated the inclusion of "other immunocompromising condition" because there are children who have conditions that were not in the text. However, she expressed concern about Table 2 which stated "underlying medical conditions that are indications for pneumococcal vaccination" because she wanted to insure that they were not limited to those underlying medical conditions (e.g., diseases associated with immunosuppressive chemotherapy because it could be steroids). She like the wording for Vote 4 and commended the work group for making it a broad condition, but wanted that philosophy continued in the text.

Dr. Duchin (NACCHO) encouraged the committee to include language that would educate clinicians about the real intent to immunize children who have underlying risk conditions. "May be administered" might not convey the language discussed here about the importance of vaccinating that group.

Dr. Baker responded that this could be dealt with at the professional society level.

Regarding the wording of the draft statement presented to ACIP members, Dr. Sawyer pointed out that beginning on line 546 referring to the immunization of premature infants, the first statement is that "Premature infants should receive PCV13 at the recommended chronologic age" but then the next sentence is "For infants with prolonged nursery stays, vaccination should begin during discharge planning," which would not necessarily be the chronologic age. The General Recommendations, as they currently stand, suggest that premature infants should be

immunized based on chronologic age. Thus, he wondered why the second sentence was included and whether someone could clarify this.

Dr. Nuorti responded that this point has already been revised to be consistent with the General Recommendations and the sentence about discharge planning has been deleted.

Dr. Pickering complimented the work group for getting this policy note to the members so that they could review it. He requested that any changes or suggestions regarding the wording should be submitted to the work group immediately for incorporation as appropriate so that they could submit it to the *MMWR* as soon as possible.

Ms. Rosenbaum voted affirmatively, with significant reservations about the wording, given the potential spillover effects on financing.

Vote 4 Motion: Children 6 through 18 Years of Age with SCD, HIV, or Other Immunocompromising Condition

Dr. Sawyer made a motion to approve the recommendation for children 6 through 18 years of age with SCD, HIV, or other immunocompromising condition as stated. Ms. Ehresmann seconded the motion. The motion carried with 13 affirmative votes, 1 abstention, and 0 negative votes.

VOTE 5

For Vote 5, ACIP members voted on the recommendation for PPSV23 after PCV13 for children ≥2 years with underlying medical conditions, the exact wording for which is as follows:

Use of PPSV23 among children 2 through 18 years of age at increased risk for IPD

- *In addition to receiving PCV13, children with underlying medical conditions (Table 2) should receive PPSV23 at age 2 years or as soon as possible after the diagnosis of chronic illness is made in children ≥2 years.*
- *Doses of PCV13 should be completed before PPSV23 is given.*
- *However, children who have previously received PPSV23 should also receive recommended PCV13 doses.*
- *Minimum interval: at least 8 weeks after the last dose of PCV13 (Table 11).*

Vote 5 Motion: PPSV23 after PCV13 for Children >2 Years with Underlying Medical Conditions

Dr. Judson made a motion to approve the recommendation for PPSV23 after PCV13 for Children >2 years with underlying medical conditions as stated. Dr. Englund seconded the motion. The motion carried with 13 affirmative votes, 1 abstention, and 0 negative votes.

VFC Vote

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

Dr. Santoli indicated that the PCV component of the VFC Resolution was intended to mirror the vote just made by the ACIP. The pneumococcal resolution has two components: the conjugate component and the polysaccharide component.

For the conjugate component, the current wording for eligible groups is: *Includes all infants and children at least six weeks of age through 59 months old*. The proposed wording extends that to include the following language:

> *All infants and children at least six weeks through 59 months of age and children 60 through 71 months with certain underlying medical conditions listed in the table below. Children 6 through 18 years of age who are at increased risk for invasive pneumococcoal disease because of sickle cell disease, HIV-infection, or other immunocompromising condition.*

The following will be labeled as Table 1 in the VFC Resolution:

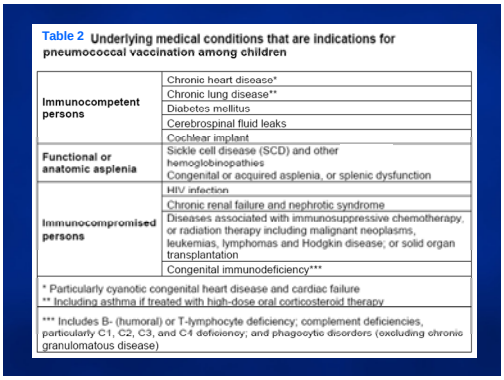


Table 2 Underlying medical conditions that are indications for pneumococcal vaccination among children

Immunocompetent persons	Chronic heart disease*
	Chronic lung disease**
	Diabetes mellitus
	Cerebrospinal fluid leaks
	Cochlear implant
Functional or anatomic asplenia	Sickle cell disease (SCD) and other hemoglobinopathies Congenital or acquired asplenia, or splenic dysfunction
Immunocompromised persons	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with immunosuppressive chemotherapy, or radiation therapy including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid organ transplantation
	Congenital immunodeficiency***

* Particularly cyanotic congenital heart disease and cardiac failure
** Including asthma if treated with high-dose oral corticosteroid therapy

*** Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease)

PCV component of the VFC Resolution will include the following Recommended Schedule and Dosage Intervals, which will be labeled as Table 2 in the VFC resolution and includes the supplemental doses for the age groups where that is appropriate:

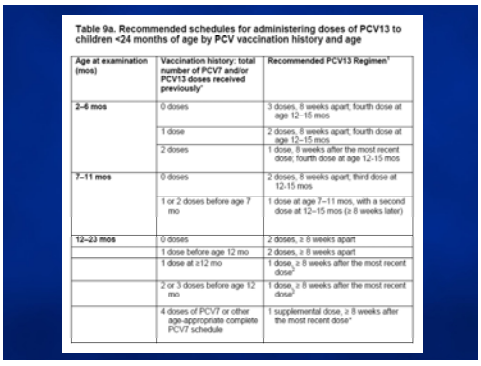


Table 9a. Recommended schedules for administering doses of PCV13 to children <24 months of age by PCV vaccination history and age

Age at examination (mos)	Vaccination history: total number of PCV7 and/or PCV13 doses received previously[1]	Recommended PCV13 Regimen[1]
2–6 mos	0 doses	3 doses, 8 weeks apart; fourth dose at age 12–15 mos
	1 dose	2 doses, 8 weeks apart; fourth dose at age 12–15 mos
	2 doses	1 dose, 8 weeks after the most recent dose; fourth dose at age 12–15 mos
7–11 mos	0 doses	2 doses, 8 weeks apart; third dose at 12-15 mos
	1 or 2 doses before age 7 mo	1 dose at age 7–11 mos, with a second dose at 12–15 mos (≥ 8 weeks later)
12–23 mos	0 doses	2 doses, ≥ 8 weeks apart
	1 dose before age 12 mo	2 doses, ≥ 8 weeks apart
	1 dose at ≥12 mo	1 dose, ≥ 8 weeks after the most recent dose[2]
	2 or 3 doses before age 12 mo	1 dose, ≥ 8 weeks after the most recent dose[2]
	4 doses of PCV7 or other age-appropriate complete PCV7 schedule	1 supplemental dose, ≥ 8 weeks after the most recent dose*

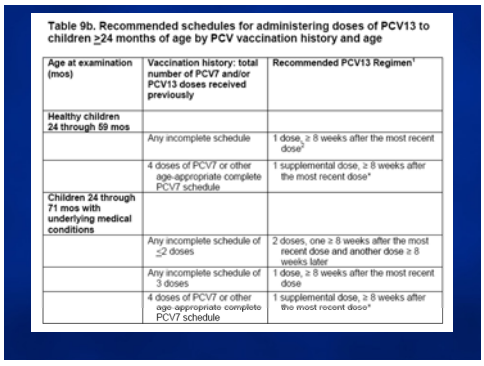


Table 9b. Recommended schedules for administering doses of PCV13 to children ≥24 months of age by PCV vaccination history and age

Age at examination (mos)	Vaccination history: total number of PCV7 and/or PCV13 doses received previously	Recommended PCV13 Regimen[1]
Healthy children 24 through 59 mos		
	Any incomplete schedule	1 dose, ≥ 8 weeks after the most recent dose[2]
	4 doses of PCV7 or other age-appropriate complete PCV7 schedule	1 supplemental dose, ≥ 8 weeks after the most recent dose*
Children 24 through 71 mos with underlying medical conditions		
	Any incomplete schedule of ≤2 doses	2 doses, one ≥ 8 weeks after the most recent dose and another dose ≥ 8 weeks later
	Any incomplete schedule of 3 doses	1 dose, ≥ 8 weeks after the most recent dose
	4 doses of PCV7 or other age-appropriate complete PCV7 schedule	1 supplemental dose, ≥ 8 weeks after the most recent dose*

The footnotes will be as follows for Table 2:

Footnotes, Table 9:
1) Minimum interval between doses is 8 weeks except for children vaccinated at age <1 year, for whom minimum interval between doses is 4 weeks.
2) No additional PCV13 doses are indicated for children 12 through 23 months of age who have received 2 or 3 doses of PCV7 before age 12 months and at least 1 dose of PCV13 at age 12 months or older.
3) For children with underlying medical conditions, PCV13 is indicated through 71 months of age.

* A single supplemental dose of PCV13 given at least 8 weeks after the last dose of PCV7 is recommended for all children 14 through 59 months of age who have received 4 doses of PCV7 or other age-appropriate, complete PCV7 schedule (fully vaccinated with PCV7). For children who have underlying medical conditions, a supplemental dose is recommended through 71 months of age.

The Recommended Schedule and Dosage Intervals will also include the following statement about the permissive use of the vaccine in children 6 through 18 years of age:

> *A single dose of PCV13 may be administered for children 6 through 18 years of age who are at increased risk for invasive pneumococcal disease because of sickle cell disease, HIV-infection, or other immunocompromising condition, regardless of whether they have previously received PCV7 or PPSV23*.

For the recommended dosage, the VFC Resolution will refer to the product package inserts as is done on all VFC Resolutions. The following contraindications and precautions will be included:

> *Vaccination with PCV13 is contraindicated among persons known to have severe allergic reactions (e.g., anaphylaxis) to any component of PCV13 or PCV7, or any diphtheria toxoid-containing vaccine*.

For the PPV23 component of the VFC Resolution, the current wording pertaining to eligible groups is:

> *Children and adolescents aged 2-18 years who have functional or anatomical asplenia, immunocompromising illness or medications, chronic illness (as specified above), who are Alaska Native or American Indian, or who have received a bone marrow transplant*.

The proposed wording is:

> *Children and adolescents 2 through 18 years with certain underlying medical conditions listed in Table 1 above or children 2 through 18 years who are Alaska Native or American Indian*.

For the Recommended Schedule and Dosage Intervals, the following table and footnote that follows it will be labeled as Table 3 in the VFC Resolution:

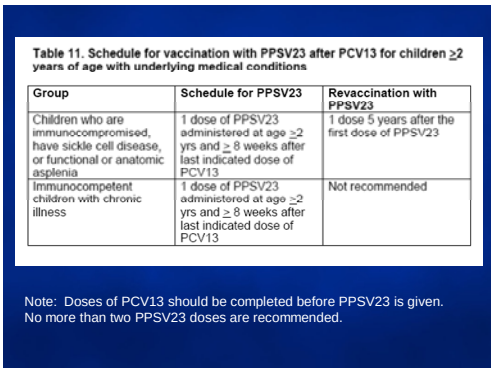


Table 11. Schedule for vaccination with PPSV23 after PCV13 for children ≥2 years of age with underlying medical conditions

Group	Schedule for PPSV23	Revaccination with PPSV23
Children who are immunocompromised, have sickle cell disease, or functional or anatomic asplenia	1 dose of PPSV23 administered at age ≥2 yrs and ≥ 8 weeks after last indicated dose of PCV13	1 dose 5 years after the first dose of PPSV23
Immunocompetent children with chronic illness	1 dose of PPSV23 administered at age ≥2 yrs and ≥ 8 weeks after last indicated dose of PCV13	Not recommended

Note: Doses of PCV13 should be completed before PPSV23 is given. No more than two PPSV23 doses are recommended.

For the recommended dosage, again there will be a referral to the product package inserts. Contraindications and precautions refers to the current statement, given that those are unchanged and can be found at the following site:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4909a1.htm

Where published links can be used, they are. When recommendations are new and are appearing in writing for the first time, the wording and tables are included. When there are published documents, tables are changed to links so that a single source can be referred to.

There is also a statement regarding coverage of PCV7 during the transition period, which reads as follows:

> *Until the transition between seven valent pneumococcal conjugate vaccine (PCV7) and thirteen valent pneumococcal conjugate vaccine (PCV13) is complete and providers have sufficient supplies of thirteen valent pneumococcal conjugate vaccine in their offices to meet demand among VFC eligible children, the VFC program will continue to include seven valent pneumococcal conjugate vaccine and the schedule provided in VFC resolution 2/09-1 should be followed for administration of PCV7 during that time*.

In addition, a statement regarding updates based on published documents is included, which reads as follows:

> *If an ACIP recommendation regarding pneumococcal 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*.

Discussion

Dr. Keitel commented that Table 2 lists underlying medical conditions, but does not include Alaska Natives / Native Americans. While she understood that they could not list everything, she suggested including these groups on the table.

Dr. Santoli responded that the ACIP specifically voted these groups of children in the PPV23 component, which is why they were added to the eligible groups, which is why the wording states “those in the table or those who are Alaska Native / American Indian.” This differed from the recommendation, but was a conscious decision. They would not have been included in the

table of immunocompromising conditions necessarily, but this is the way that the ACIP can state that they want these specific children covered in the VFC program.

Ms. Rosenbaum requested clarification regarding whether, if they say a vaccine "may be appropriate" versus "may be administered" or some other language, the vote they were about to make would make clear that in those situations where the vaccine is appropriate, VFC will fully cover the vaccine. When ACIP members express their views on VFC, she wondered whether the committee would explain the framework for the determination. That is, she assumed that what they would be signaling to the world was that ACIP considers the issue of appropriateness to be an issue of clinical judgment, and in those situation where clinical judgment needs to be exercised, they expect that the vaccine will be readily available. She emphasized that it is very important to say what they mean, even if it takes extra words or a note, because whatever they have to say within the VFC vote will have spillover effects into how insurers understand what ACIP is recommending. Based on the answer from the AHIP representative, if they elaborated on what they meant by saying that something was "clinically appropriate," they would be sending a strong signal to private insurers by how recommendations are dealt with within the VFC.

Dr. Santoli requested that Ms. Rosenbaum submit a specific suggestion.

Dr. Chilton thought the recommendations seemed more complex than necessary, given that under the age of 5 years to 59 months all children receive PCV13. Between 5 and 6 years of age, all children in Dr. Nuorti's Table 2 receive the vaccine, and between 6 and 18 years of age, all of the people in Table 2 minus those who are immunocompetent receive the vaccine. He wondered if there was a way to simplify the recommendation somewhat.

Dr. Santoli inquired as to whether he was talking about the recommendations or the VFC resolution.

Dr. Chilton responded that he meant both.

Dr. Santoli replied that the tricky thing about the resolution was that in two days, this would be the first item published. Due to the components required by law, there must be significantly more information in a resolution than is really needed just to say that it is covered in the program. All of the changes and suggestions about simplifying really need to go into the recommendations. This was simply an opportunity to say "yes" for the VFC resolution, except sometimes there may be some additional groups who should be covered. This is not really a chance to make any changes to the recommendations sections because this is not the final reference document.

Dr. Baker pointed out that they had already voted on the recommendations, which would remain as they stood following the vote.

Dr. Schuchat indicated that the ability to simplify and enhance uptake was an implementation issue that CDC's education and communication staff and their health professional partners could assist with.

Dr. Sumaya thought this tied to the issue that Ms. Rosenbaum raised. While he understood that while they had language such as "may be appropriate" or a permissive recommendation, he thought it would behoove them as an advisory group to understand that first the provider may be making that judgment. In addition, someone has to pay for it. The VFC provides a structure for

that. He thought it would be beneficial to have further information how permissive ACIP language has impacted the private insurance world, such as: How are these recommendations utilized? Who is making the determinations? Are the communities ACIP is targeting being reached?

John Redd (IHS) indicated that IHS supported the verbiage of the VFC resolution as stated.

Given the complexity of the schedule, Dr. Whitley-Williams thought this supported the use of immunization registries. In addition, she pointed out that pediatric providers are caring for an aging group, particularly of HIV-infected patients and youth who are transitioning. While these recommendations address individual through 18 years of age, she thought consideration should be given to that population moving forward so that they could benefit from this as well.

Motion: VFC Resolution

Dr. Judson made a motion to approve the VFC Resolution as stated. Dr. Neuzil seconded the motion. The motion carried with 13 affirmative votes, 1 abstention, and 0 negative votes.

Program Implementation:
Transition from PCV7 to PCV13

Dr. Santoli then reported upon an implementation plan that has been discussed in-house at CDC and with partner groups with regard to PCV13 replacing PCV7 in terms of challenges, plans for educational materials, and evaluation plans for the use of this vaccine.

As commented upon by the manufacturer, PCV13 supply is currently sufficient to vaccinate children according to the routine schedule and to provide the supplemental dose as indicated. When PCV13 is available in the office, unvaccinated and incompletely vaccinated children should receive PCV13 *not* PCV7. That is the spirit of the recommendation and is being crafted for an *MMWR* that will be published sooner than the recommendation. CDC anticipates publishing this *MMWR* in mid-March. If only PCV7 is available in the office, also covered in the planned *MMWR*, unvaccinated and incompletely vaccinated children should receive PCV7 and should complete the series with PCV13 at subsequent visits. Children for whom the supplemental PCV13 dose is recommended should receive it at their next medical visit. Active recall is not recommended.

With respect to some of the logistics of implementation at the practice level, CDC is currently preparing to add this vaccine to its vaccine contracts. Work has been done on the back end to try to facilitate this. Now that there is a vote, they will move forward. The guidance to providers is that they should contact state and local immunization programs to determine when PCV13 available to order. It is anticipated that state programs will be able to begin ordering at the end of March. However, programs have different timeframes by which they make vaccines available to their providers because of changes that they need to make. Thus, the direction is that providers should reach out to their state programs. During the transition period, providers are encouraged to maintain their unused doses of PCV7. In terms of returning unused PCV7, for private supplies, Pfizer is offering a credit for returns of unused PCV7 vaccine. For public supplies, providers should work with their state VFC program.

There are some challenges in making this transition. As often occurs, private supplies of PCV13 will be available before public supplies. However, CDC has done as much work in advance as possible so that the contract does not delay the process of making this vaccine available in the VFC program. The challenge of administering a supplemental dose of PCV13 is somewhat minimized by having that vaccine recommended at the next rather than during an additional medical visit.

In terms of communication and educational materials, the provisional recommendations will be posted online ahead of the official recommendation and will be available at the following site:

http://www.cdc.gov/vaccines/recs/provisional/default.htm

The *MMWR*, with an anticipated March 12, 2010 publication date, will highlight the information discussed during the presentations. A Provider Q & A and Parent Q & A are under development. The plan is to post the Provider Q & A in early March, with the Parent Q & A to follow.

With respect to future evaluation plans, there are two short-term evaluations planned in addition to including this vaccine and its coverage in the National Immunization Survey (NIS). The first is a registry sentinel site for which an immunization information sentinel site analysis will take place 6 months after the transition to assess uptake by provider type, VFC status of the child, and other factors. In addition, a provider survey is being planned that will use sentinel networks of physicians (e.g., pediatricians and family practitioners), which will assess knowledge, attitudes, practices, and barriers related to the transition from PCV7 to PCV13.

At the conclusion of this session, Dr. Pickering noted that Dr. Stanley Plotkin had not been able to attend the last few ACIP meetings. While his presence was truly missed, Dr. Pickering indicated that luckily Dr. Plotkin was present during this meeting and that they looked forward to his insight.

Hepatitis Vaccines

Update on Hepatitis Vaccines Work Group

Mark Sawyer, MD
Chairman, ACIP Hepatitis Vaccines Work Group

Dr. Sawyer reported that the Hepatitis Vaccine Work Group had been meeting to deliberate the term of reference to review data from recent hepatitis B outbreaks among diabetics in institutional care to determine whether vaccination is appropriate. Topics reviewed and discussed by the work group regarding this matter included modes of hepatitis B virus transmission during diabetes care; outbreaks and the morbidity of acute hepatitis B among persons with diabetes; long-term care and infection control; current prevention recommendations; the epidemiology of diabetes and blood glucose monitoring practices; hepatitis B vaccine immunogenicity relative to age, diabetes status, obesity, and specific vaccine type / dose; hepatitis B vaccine coverage estimates among persons with diabetes; diabetes and liver disease; and seroprevalence of hepatitis B virus infection among persons with diabetes versus persons without diabetes.

The Hepatitis Work Group is currently considering three major options to bring forward to the full ACIP. The work group's timeline has been delayed slightly, but the intent is to deliver additional presentations during the June 2010 ACIP meeting, as well as a proposal for consideration. A vote is anticipated in October 2010. The three major options are as follows:

A: Prevent hepatitis B virus infection among persons with diabetes using three approaches
- → Improve infection control practices, uptake of prevention recommendations (HICPAC, ADA, etc)
- → Improve devices used to manage diabetes (FDA, manufacturers)
- → Recommend hepatitis B vaccine at diagnosis of diabetes

B: Obtain additional data needed to establish incident risk of hepatitis B virus infection among persons with diabetes

C: Expand hepatitis B vaccine recommendation to the entire US adult population

Tentative future Hepatitis Work Group topics before bringing the recommendation to the full ACIP include estimates of risk for hepatitis B infection among persons with diabetes; vaccination schedules and dosages; pre / post-vaccination serological testing; "catch-up;" cost-effectiveness analysis; and implementation.

Diabetes and Liver Disease:
Implications for Hepatitis B Vaccination

John W. Ward, MD
Division of Viral Hepatitis (DVH)
National Center for HIV / AIDS, Viral Hepatitis,
STD and TB Prevention (NCHHSTP)
Centers for Disease Control and Prevention

Dr. Ward discussed trends in diabetes; the adult hepatitis B immunization schedule; acute hepatitis B outbreaks among persons with diabetes; and offered an overview of diabetes and liver disease with respect to acute liver failure and chronic liver disease in terms of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and cirrhosis and hepatocellular carcinoma (HCC).

The number of persons living with person in the US has increased over the last several decades, particularly over the last 10 to 15 years. The most recent estimate is that 17.7 million persons are living with diagnosed diabetes in the US. That represents about 7.8% of the US population [CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics from NHIS].. The average age at diagnosis is approximately 50 years, with a large increase in prevalence between the 20 to 39 year old age group (2.6%) and the 40 to 59 year old age group (10.8%), with the prevalence approaching 1 in 4 for persons 60 years of age and older (23.1%) [Cowie et al., Diabetes Care 2009;32:287-94. CDC available at http://www.cdc.gov/diabetes/statistics/prev/national/tprevage.htm].

Monitoring blood glucose is a recommended intervention for self-management of diabetes. This is a 2010 Healthy People objective that is monitored through the Behavioral Risk Factor Surveillance System (BRFSS). The question included on the BRFSS is: About how often do you check your blood for glucose or sugar? The responses to this question indicate that the majority of people with diabetes do self-monitor their blood glucose at least one time per day:

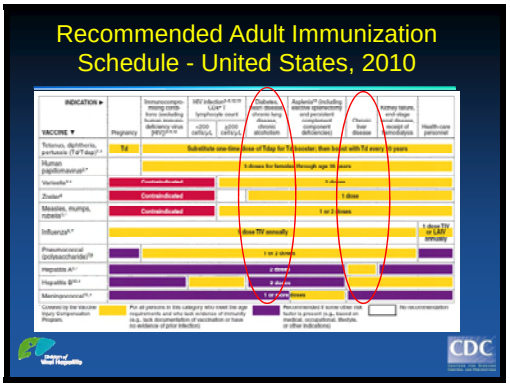
Rates of monitoring blood glucose ≥1 time/day by type of medication

Medication	%	(95% CI)
None	35	(31-39)
Oral medication only	63	(59-66)
Insulin only	91	(88-93)
Insulin and oral medication	84	(80-88)
All persons with diabetes	64	(62-66)

The prevalence of self-monitoring is highest for those who are receiving medication, oral or insulin. Blood glucose monitoring also has implications for risks of blood-borne transmission in settings where good infection control is not practiced by the individual or by the person who may be monitoring glucose for that individual in a setting such as a residential care facility [Adults 18+ yrs. Behavioral Risk Factor Surveillance System *MMWR* 2007;56:1133-1137].

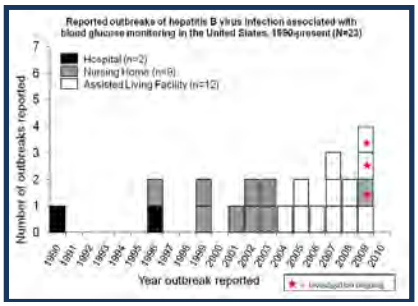
The relationship between hepatitis causing morbidity among persons with diabetes has also been examined. According to a dataset from the National Hospital Discharge Dataset (1987-1991), though quite old and in need of updating, the ratio of the rates for discharge diagnoses in persons without diabetes for hepatitis and cirrhosis was more common than for those without diabetes [Everhart JE. Digestive Diseases and Diabetes (Table 21.3, Figure 21.2) Diabetes in America 2nd edition 1995].

The current US adult immunization schedule, published in January 2010, is as follows:



The yellow bars in the adult schedule indicate vaccine recommendations for particular and specific patient categories. Hepatitis A and B vaccine are recommended for persons with chronic liver disease, which is how this is stated in the 2006 ACIP statement, which was the first time for the hepatitis B recommendations to include a recommendation for vaccination of persons with chronic liver disease. Persons with diabetes are on this schedule and are recommended for the receipt of other vaccines; however, the recommendation does not currently include a recommendation for hepatitis A and B vaccine. The rationale for placing chronic liver disease on the immunization schedule for hepatitis A and B vaccine was that hepatitis A superimposed on chronic hepatitis C (HCV) infection and other chronic liver disease increases the risk of acute liver failure and death; acute hepatitis B (HBV) infection morbidity can be more severe among persons with chronic HCV than without chronic HCV; and chronic infection with both HCV and HBV increases incidence of cirrhosis and liver cancer [Datta D, et al. *Antiviral Ther.* 2000. Keeffe EB. *Am J Med*. 2005, Bell B. Acta Gastroenterol Belgica 2000, Reiss G,*Aliment Pharmacol Ther.* 2004. Sagnelli E. *Hepatology.* 2002, Benvegnu L, *Cancer.* 1994].

With that as a backdrop, the work group felt that it was important, as they consider the rationale for hepatitis B vaccine for persons with diabetes to assess acute hepatitis B virus infection, acute liver disease among persons with diabetes, and the risk for chronic liver disease among persons with diabetes. The following graphic depicts the timeline of outbreaks of hepatitis B virus infection associated with blood glucose monitoring that have been reported to CDC:



Since 2007, about 9 (39%) of the 23 outbreaks that have been identified are recent outbreaks in nursing homes and 21 were in some type of elder care facility. On-going investigations are being conducted for the most recent outbreaks, shown by the red stars in the graphic.

When the 21 outbreaks in persons with diabetes in long term care facilities are examined more closely, 136 / 151 (90%) of the cases reported in these settings were among persons with diabetes who were having their blood glucose monitored, and 15 / 151 (10%) cases among roommates, family members, and staff suggests secondary transmission of infection in long-term care facilities. The median age was 76.5 years (range 42–92) for the outbreaks that included that information (age information was available for 14 of 21 outbreaks) [CDC. In terms of the clinical picture of the cases among the 151 persons with acute hepatitis B (positive for anti-HBc and anti-HBc IgM), 56 (37%) had symptoms, 21 (38%) were hospitalized, and 10 (18%) died from acute hepatitis B (median age 88 years; range 64 to 92) [CDC. Unpublished Data 2009].

For 13 of the outbreaks, a serologic survey was done to identify all cases of acute hepatitis B among residents with and without diabetes (n=1278) [CDC. Unpublished Data 2010]. The following table reflects the comparison of the serologic results for persons with diabetes versus persons with no diabetes:

Hepatitis B	No Diabetes (n=940)	Diabetes (n=338)
Acute Infection	01.0% (9/940)	30.5% (103/338)
Chronic Infection**	0.4% (3/818)	6.3% (19/300)

This shows that the prevalence of both acute and chronic disease was higher for persons with diabetes in these settings where outbreaks were identified and investigated. The 6.3% prevalence of chronic infection suggests a persistence of hepatitis B infection after a transmission that is higher than what is typically observed among adults. It has been reported in the literature that persons with diabetes have an increased likelihood of persistent or chronic hepatitis B infection after transmission The risk for developing chronic hepatitis B in young, healthy adults is < 5% -10%; in persons with diabetes is ~ 45%; in older adults (mean age 74 yrs) is ~ 59%, and in those undergoing hemodialysis is 40% - 45%. [Shepard CW, Epidemiol Rev 2006; Hyams Clin Infect Dis 1995, Polish LB. N Engl J Med 1992, Kondo K . Hepatology 1993]. This study is referenced in the current ACIP statement.

Some investigators have also examined the risk of acute liver failure among persons with diabetes. In a study based on the National VA Medical Record System, patients ages 20+ years with a discharge diagnosis diabetes between 1985 to 1990 were followed up through 2000. Medical records were reviewed for this group to identify ICD-9 codes indicative of acute liver failure and diabetes. A control group was identified and comparisons were made regarding the rate of acute liver failure and its causes. Patients were excluded who had previous liver disease (e.g., HCV, HBV, ETOH, cirrhosis, et cetera). Patients eligible for observation included 173,643 with diabetes (1,494,995 person-years) and 650,620 without diabetes (6,556,350 person-years) [El-Serag HB, Gastroenterology 2002].

In terms of the cumulative risk of acute liver failure by diabetes status in the US from 1985 to 2000, was 0.30% for persons with diabetes (versus the comparison group (no diabetes; 0.19% showing that persons with diabetes were increased risk of acute liver failure and that that risk increased over the observation period [El-Serag HB, Gastroenterology 2002]. In the Cox proportional hazard model (adjusted for demographic, military service, HCV, HBV, other liver disease), diabetes was retained as a risk for acute liver failure, with the strongest risk for acute liver failure being some evidence of underlying liver disease: Diabetes HRR 1.4 (1.3-1.6), Older Age (per decade) HRR 1.9 (1.4-2.5), and Chronic Liver Disease HRR 14.3 (12.5-16.3). The causes were uncertain, although the investigators mentioned that they looked for evidence of hepatitis B as a cause of acute liver failure, but that investigation was not quantified. They went on to speculate that hepatotoxic drugs could have been the culprit because of increased exposure or increased susceptibility [El-Serag HB, Gastroenterology 2002].

It is important to note that diabetes can be a consequence of chronic liver disease as well as a cause of chronic liver disease. Regarding diabetes as a consequence of liver disease, cirrhosis is associated with dysregulation of glycemic control. With on-going fibrosis leading to cirrhosis, glycemic control becomes compromised, and insulin resistance increases, leading to chronic diabetes. At least one report suggests that this occurs in 1 in 5 persons.

Hepatitis C infection also increases the risk for diabetes because of direct biologic activity, host response, or the increasing fibrosis phenomenon [Tolman, Diabetes Care 2007, Mehta SH. Ann Intern Med 2000, White J. Hepatology 2008]. Studies have found that persons with hepatitis C have a 1.7 to 3.8 fold greater risk of diabetes than those without. This must be taken into account when reviewing these studies and trying to determine whether diabetes itself is a risk for progression to chronic liver disease and cancer. The investigations of diabetes and chronic liver disease have found that the association is linked most closely with non-alcoholic fatty liver disease (NAFLD). NAFLD in and of itself is a metabolic disorder with a basis in insulin resistance similar to Type 2 diabetes, leading to an imbalance in lipid metabolism and fatty acid accumulation in the liver. Risks include obesity (central), diabetes, and hypertriglyceridemia.

NAFLD is estimated to affect 40% to 69% of persons with diabetes. At a minimum, about 1 in 10 persons with diabetes in that group will have non-alcoholic steatohepatitis (NASH), and about 10% to 20% may progress to cirrhosis over a 10-year period [Moscatiello, Nut Metab and Cardio Disease 2007; Tolman, Diabetes Care 2007; Lazo, Sem Liver Dis 2008]. NAFLD represents a broad spectrum of fatty liver disorders, ranging from very mild-hepatitis steatosis to the severe outcome of NASH (e.g., inflammation, cell death, fibrosis; cirrhosis; hepatocellular carcinoma) [Moscatiello, Nut Metab and Cardio Disease 2007; Tolman, Diabetes Care 2007].

Dr. Ward presented a few representative studies pertaining to the question of diabetes associated with liver disease, and highlighted those that also included assessment of viral hepatitis B and C. A study of Taiwanese Patients with chronic hepatitis B of 500 adults aged 42 ± 15 years with chronic hepatitis B who were attending a liver clinic followed these subjects for an average of 5.8 years. The study excluded those with a history of alcoholism, IDU, MSM, HIV, et cetera. Of the 500 patients, 71 developed cirrhosis during the study timeframe. Among the 71 cases of cirrhosis, 15 (21%) had diabetes mellitus. That group was then compared to 102 controls without cirrhosis who were age and sex-matched. Factors were examined to determine what increased the risk of developing cirrhosis. One of the risks was diabetes. Thus, in the group of persons with chronic hepatitis B, diabetes was an independent and additional risk for cirrhosis [Huo T-L. J Clin Gastroenterol 2000].

Returning to the national VA medical record study for risk of chronic liver disease and hepatocellular carcinoma (1985 to 2000), the risk of chronic liver disease for persons with diabetes was about twice that for persons without diabetes (18.3 versus 9.6/10,000 patient years), and there was about a 2.75 increase risk for development of liver cancer versus those persons without diabetes. This study also found that over the period of observation this risk increased, demonstrating that it was not just the capture of a person with diabetes about to be diagnosed with cirrhosis, but rather that it was persons with pre-existing diabetes for whom the increased presence of diabetes led to increased risk for progressive liver disease [El-Serag HB Gastroenterology 2004].

An interesting population-based, case-control study of Medicare linked databases examined diabetes and risk for hepatocellular carcinoma (HCC) in the US for the years 1994 through 1999. The study identified 2061 cases with HCC ages > 65+ years and developed a control group of 6183 without HCC. The study looked for potential risk factors (e.g., hepatitis B, hepatitis C, HIV, alcoholic liver disease, and hemochromatosis) and placed those into a model to identify their relative risk . In this study, alcoholic liver disease was by far the risk factor that was most strongly associated with development of HCC: OR 69.6 (44.9-107.9) followed by HCV: OR 24.4 (17.5-34.1), HBV: OR 23.9 (13.7-42.0), Hemochromatosis: OR 8.9 (5.2-15.1), and diabetes: OR 2.9 (2.5-3.3) [Davila JA. Gut 2005].

In 2009, a study was published that examined diabetes and the risk for HCC in Taiwan, which was based on data from 1997 to 2004. This was a community-based cohort among 5929 persons drawn from community recognized to have a high incidence of HCC. Of these, 4115 were seronegative for HBV and HCV; 696 were hepatitis B surface antigen positive (HBsAg +); 982 were anti-hepatitis C positive (HCV+); 134 were co-infected with hepatitis B and C; and 546 had diabetes at baseline. The cohort data were matched with the national cancer registry to assure more complete ascertainment of liver cancer, and found 111 diagnoses of hepatocellular carcinoma. The multivariate Cox hazards model (95% CI) adjusted for demographic factors, health behaviors, BMI, hepatitis status, and diabetes status found that co-infection before the study with hepatitis B and C conferred the greatest risk: HR 25.9 (11.8-57.0; $P < 0.01$) followed by anti-HCV+ before study: HR18.8 (10.3-34.2; $P < 0.01$); HBsAg+ (chronic hepatitis B virus

infection) before study: HR12.6 (6.4-25.0; *P* < 0.01); age ≥ 65 years: HR 3.8 (2.6- 5.6; *P* < 0.01); male gender: HR 3.3 (2.0- 5.0; *P* < 0.01); diabetes before study: HR 2.7 (1.7- 4.3; *P* < 0.01); and BMI ≥ 30: HR 1.7 (1.0- 2.8; *P* <0.05). In this area with a high prevalence of HBV and HCV, diabetes remained an independent risk factor for liver cancer [Wang C-H. Cancer Epidemiol Biomarker Prev 2009].

In summary, it appears that persons with diabetes have multiple possible insults to the liver that they have either already experienced or have the potential to experience (e.g., hepatitis C, hepatitis B, hepatitis A, medication, NASH, and others) that can confer liver disease. This body of work reveals that an estimated 17.7 million persons are diagnosed with diabetes in the US who tend to be older and who are either monitoring blood glucose on their own or have someone monitoring it for them. Outbreaks of hepatitis B virus infection and related morbidity and mortality continue to occur among persons with diabetes. Diabetes can increase the risk for chronic hepatitis B after acute HBV infection, posing on-going health risks for the individual with diabetes and posing a risk for on-going transmission. Diabetes is an independent risk factor for chronic liver disease and hepatocellular carcinoma.

Discussion

Dr. Plotkin expressed his hope that the work group would assess immunization in this group with respect to two factors. The first is the relationship of age to response. There are data showing poorer response with age to hepatitis B. If a vaccine recommendations is going to be made in this group, it will probably have to be similar to the way in which a dialysis patient would be vaccinated with higher doses or with some of the new adjuvanted vaccines that are now in development. The second point regards juvenile diabetics who may have been immunized when they were children. The current doctrine is that people who are vaccinated when young do not need boosters. However, this population should be examined more closely. By examining B-cell memory a determination can be made regarding whether these individuals will need booster immunizations.

Dr. Ward responded that questions pertaining to immunogenicity have been a major focus of the work group's discussions, and they hope to further discuss this issue in more detail when they have more time during the June 2010 meeting. Most of the focus has been on the older diabetic, which is where over 99% of Type 2 diabetes is found. Consideration will have to be given to what can be brought to bear in terms of the immune response for Type 1 diabetes.

Dr. Baker emphasized that the explosion / epidemic of juvenile onset Type 2 diabetes is a log-rhythmic. Pediatric studies should examine both Type 1 and the increasing number of Type 2 diabetic children.

Influenza Vaccines

Introduction

Anthony Fiore, MD, MPH
Medical Officer, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Fiore indicated that this session would consist of presentations regarding the following topics:

- ❑ U.S. epidemiology update (Dr. Lyn Finelli, CDC)
- ❑ Virology and immunology (Dr. Nancy Cox, CDC)
- ❑ Influenza vaccine coverage update (Mr. James Singleton, CDC)
- ❑ 2009 H1N1 vaccine program implementation (Dr. Pascale Wortley, CDC)
- ❑ Higher dose inactivated vaccine for persons ≥65 years (Dr. David Greenberg, Sanofi-Pasteur Vaccines)
- ❑ ACIP influenza workgroup discussions (Dr. Anthony Fiore, CDC)
  - → 2010 influenza vaccine recommendations

Lyn Finelli, DrPH
Epidemiologist / Team Lead, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Finelli reported on data from the US Outpatient Influenza-Like Illness Surveillance Network (ILINet), of about 3000 to 4000 sentinel providers in the US, covering about half of the geographic area of the US. Data from June 27th, the peak of the Spring / Summer pH1N1 wave that occurred during the June ACIP meeting, disease was very focal and only a few areas were two or three standards of deviation above their non-influenza season baseline. In September 12th, the beginning of the Fall pH1N1 wave, disease was largely concentrated in the Southeast where the outbreak began in the Fall and in the West. October 24th, during the last ACIP meeting, the peak of the Fall pH1N1 wave occurred. By February 13th, there was a low level of ILI, with focal outbreaks in a variety of areas scattered across the US.

Based on the traditional ILINet trends time series pertaining to the percentage of visits for influenza-like illness (ILI) from October 1, 2006 through February 13, 2010, in February 2009 there was a peak of influenza that declined. That was followed by a peak in May 2009 that declined again under baseline in June and July 2009. There was a major peak in October 2009 of about 7.8% ILI of all people presenting to the sentinel provider offices. This is the largest peak ever observed in ILI since surveillance began. At the time of this ACIP meeting, ILI was at about 2.1%, which is slightly below the 2.4% baseline. Assessing this regionally, regions 1, 2, and 3 were below their baseline at this time; Region 4, which includes Georgia, was slightly above its baseline though not too critical; Region 7 was slightly above its baseline with nothing dramatic; and Region 9 was somewhat more above its baseline than any other region, and was

being monitored closely because it was somewhat unstable. About half of individual providers were over their baseline in October 2009, while by February 2010 only about 30 to 40 providers were over their baseline rather than half of all providers reporting.

CDC has been following ACHA surveillance of the college population very closely, given that the college age population is one of the primary risk groups. Based on data provided by Jim Turner of ACHA, their peak occurred at about the same time as the ILINet peak. They have had over 91,000 cases reported to their surveillance system, with 169 hospitalizations and 4 deaths in this age group (primarily 18 to 24 year olds). At the time of this ACIP meeting, there was a low level of ILI in the college / university population [Courtesy of Jim Turner and Randol Doyle ACHA. American College Health Association Influenza Like Illnesses (ILI) Surveillance in Colleges and Universities 2009-2010: Weekly College ILI cases reported. Linthicum, MD: American College Health Association; 2010].

Based on data from the BRFSS, overall reports of ILI among adults in households for the first part of February 2010 was 7.6%. This is a fairly dramatic decline from the 10% to 11% observed in October 2009, and it is slightly elevated from about 4% observed at baseline. During the October 2009 ACIP meeting, 49 of 50 states were experiencing widespread ILI; whereas, by the time of the February 2010 ACIP meeting, 3 states had regional ILI activity, 8 states had local activity, most of the remaining states had sporadic activity, and 2 states had no activity. It is very unusual to see the map look like this in mid-February.

CDC has aggregate reporting from 35 health departments for influenza positive, laboratory confirmed hospitalizations and deaths. As of February 13, 2010 there were very low rates of hospitalizations for all age groups over the preceding several weeks. In terms of the overall cases reported, 39% were in the 0 to 18 age group, 52% in the 19 to 64 age group, and only 9% of those found to be hospitalized in this surveillance system were over 65 years of age. The rates of hospitalization were highest in 0 to 4 year olds, but then decline and nearly flatline for all of the other age groups. There was a slight increase in 5 to 24 year olds, a decline until 49 years old, a slight increase between 49 and 64, and then a decrease over 65 years of age.

From the Emerging Infections Program (EIP) data, which were vital to CDC during the outbreak, Dr. Finelli described data from 4 influenza seasons. 2007-2008 was an influenza A (H3N2)-predominant season, as was 2003-2004 (data only on children). For 5 to 17 year olds, 18 to 49 year olds, and 50 to 60 year olds, H1N1 represents the most severe season that has occurred during surveillance. For those over 65 years old, the H3N2 season in 2007-2008 was far more severe than the 2009 H1N1 pandemic. However, for younger children ages 0 to 4, the 2003-2004 season was much worse than the H1N1 pandemic. In terms of hospitalization rates by age group, for children 0 to 4 years of age, the 2003-2004 influenza season represented much higher hospitalization rates that the current season. However, this season these rates were much higher than most influenza seasons. In the 5 to 17 year old age group, there was a high magnitude of hospitalizations, with worse rates than any other influenza season under surveillance. However, the rates in this age group remained lower than those in the 0 to 4 year old age group. There were also higher hospitalization rates in the 18 to 49 year old and 60 to 64 year old age groups than in any other season under surveillance in this system. For the over 65 year old age group, there were lower rates than the 2005-2006 and 2007-2008 H3N2 seasons, which were much worse for this age group.

Based on the 122 Cities Mortality Reporting System, this influenza exceeded the epidemic threshold in the Fall, and currently was fluctuating at the epidemic threshold. Most of the deaths reported through this system have been in people over 65 years of age, and additional investigation has shown that most reported in recent weeks have been in people with various types of pneumonia that is not influenza-related. From the pediatric mortality data, the take away message is that there have thankfully been many fewer deaths in children less than 18 since January 1, 2010. From the aggregate reporting system from 35 states, the peak number of deaths reported was in the Fall around October 31st. By the time of the February 2010 ACIP meeting, influenza deaths due to laboratory-confirmed influenza were low for all age groups. Rates among 50 to 64 year olds have remained elevated above all others. By age groups, as of February 13th, about 12% of deaths were in the 0 to 18 year old age group, 74% in the 19 to 64 age group, and in the 65+ age group 14%. Note that the proportion of the US population that is over 65 years of age is about 13%. The lowest death rates have been in young children 0 to 4 years of age and 5 to 24 year olds, rates increase with age until 50 to 64 years old, and then decrease again in those 65+ years of age.

The risk groups have not changed since the Spring wave, with children and adolescents remaining at the highest risk for acquisition. Hospitalizations are highest in young children and decline with age, and deaths increase with age up to 50 to 64 year olds, but then decline again in the 65+ age group. The majority of those who die and who are hospitalized with influenza remain those with underlying conditions, including pregnancy. Based on EIP data, about 30% of people admitted with influenza have asthma, 23% have diabetes, 20% have cardiovascular disease (CVD), and 14% have chronic pulmonary lung disease (COPD). Neurodevelopmental conditions and neuromuscular disorders are much less prominent than they are in children, and about 9% overall of these cases were pregnant. Note that pregnant women comprise only about 1% of the US population at any time.

Based on the pediatric data, among children who are hospitalized with laboratory-confirmed influenza, the frequency of asthma is very similar in children compared to adults at 33%, 11% have neurodevelopment disorders, 8% have moderate to severe development delay, 6% have seizures, 3% have CP, 5% have chronic lung disease excluding asthma (mostly BPD), 5% have hemoglobinopathy (majority sickle cell), 1% have diabetes, and 1% are pregnant. From the Influenza Associated Pediatric Mortality Surveillance System, among pediatric H1N1 deaths, 65% of children had an underlying condition. Neurological and developmental disorders are extremely common among children who died from 2009 pandemic influenza (42%), with moderate to severe developmental delay being most common at 31%, other neurologic disorders (including CP) 31%, seizure disorders 22%, and other neurologic disorders 2%. Chronic pulmonary disease (excluding asthma) has a frequency of 20% among children who have died from influenza, and cardiac disease has a frequency of 13%. Different from the cardiac disease in adults, this cardiac disease is almost all congenital. These diseases and disorders are not mutually exclusive. Many children have several conditions simultaneously such as CP, seizures, and developmental delay.

With respect to race / ethnicity, data were presented in October 2009. However, during the February 2010 meeting, Dr. Finelli was able to present more robust numbers. The following table reflects the findings from the self-reported ILI during the month preceding interview by adults and ILI related health care-seeking behavior by race and ethnicity from the September through December 2009 BRFSS data:

Race and Ethnicity	% Reporting ILI (weighted) (95% CI)		% Reporting Seeking Health Care for ILI (weighted) (95% CI)	
White, non-Hispanic	8	(7.6, 8.4)	41	(38.6, 43.4)
Black, non-Hispanic	8	(6.7, 9.6)	48	(38.0, 57.5)
Hispanic	7	(6.0,8.2)	36	(29.1, 43.5)
American Indian/Alaska Native	16	(11.6, 22.3)	37	(22.6, 54.3)
Total	8	(7.8, 8.5)	41	(38.3, 42.9)

As shown in the above table, ILI reporting is about equal for White, non-Hispanic and Black non-Hispanic groups, but appears to be about double for American Indian / Alaska Natives. All races / ethnicities reported about an equal rate of health care seeking behavior.

However, there is a disparity between race / ethnicity in terms of hospitalization as reflected in the age-adjusted and season-specific pH1N1 influenza-related hospitalization rates (per 100,000) by race /ethnicity from EIP (2009-2010) shown as follows:

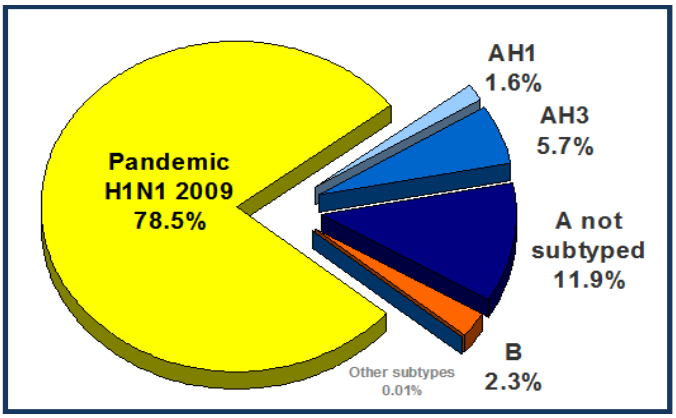
Race/Ethnicity	**Influenza Season**	
	2009	**2009-10**
White, non-Hispanic	3.0	16.3
Black, non-Hispanic	10.9	29.7
Hispanic	8.2	30.7
Asian/Pacific Islander	8.1	12.5
American Indian/Alaska Native	4.1	32.7

In conclusion, H1N1 was widespread over most of the US but incidence has declined in recent weeks. ILINet rates were higher in October 2009 than they have been in any influenza season since surveillance began. According to BRFSS data, 10% of adults and >20% children reported ILI in October 2009. Hospitalizations are highest in the youngest children and decline with age, while excess hospitalizations are highest in the 5-17 year old age group. Deaths are lowest in the youngest children and increase with age, but only up to 50-64 year old age group. Deaths decline in the 65+ age group. The majority of those hospitalized during the 2009 H1N1 pandemic have underlying medical conditions. Asthma is common among those hospitalized. Neurologic disorders are common among children dying from influenza. Pregnant women are at higher risk for severe outcome. Racial ethnic disparities in severe outcomes persist and are under investigation.

Nancy J. Cox, Ph.D.
Director, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Cox reported on the updated global influenza virology and recommendations for the vaccine composition for next season, including a summary of both the WHO's vaccine recommendations and those of FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC), which met on February 22, 2010.

Percentage of influenza viruses reported to the Global Influenza Surveillance Network (GISN) by Types / Subtypes (From 1st September 2009 to 30th January 2010) are reflected in the following pie chart:



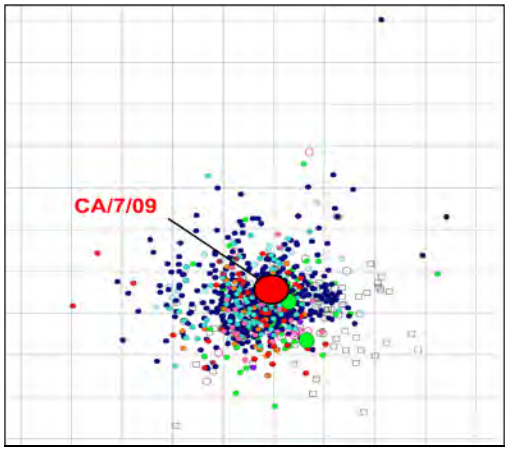
Clearly, pandemic H1N1 viruses predominated globally. Seasonal H1N1 viruses circulated in very low numbers globally. H3N2 viruses circulated in greater numbers than seasonal H1N1 and actually caused some significant disease in some locations. There was a group of viruses that were not sub-typed, but were reported to this network as influenza A. Some of those were not able to be sub-typed using PCR and others were simply run through a rapid influenza diagnostic test. Influenza B viruses also circulated globally, though at a rather low level, but there was an interesting resurgence of influenza B in China during the last month or so. CDC was inundated by samples beginning in May 2009. The majority of those samples were the pandemic H1N1 virus. Thus, there were numerous samples and very rich data to examine.

A major accomplishment of the Global Influenza Surveillance Network is that CDC has been able to fill in many of the gaps in surveillance, particularly in Central America, some countries in South America, and most countries in Africa, which have been able to detect and report to WHO pandemic A(H1N1) occurrence.

In terms of a global summary, pandemic A(H1N1) 2009 viruses pose a public health risk in the coming 2010-2011 Northern Hemisphere influenza season. Currently circulating pandemic A(H1N1) 2009 viruses remain similar to the WHO-recommended vaccine virus. The recommendation was that A/California/7/2009-like virus remains suitable for use in influenza virus vaccines for the Northern Hemisphere for the 2010-2011 influenza season.

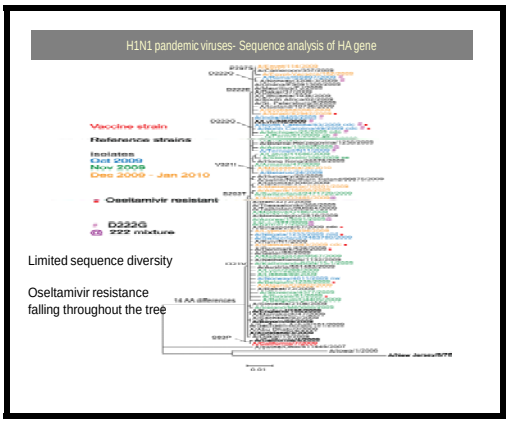
Almost all 2009 H1N1 viruses characterized globally were antigenically and genetically similar to the A/California/07/2009 vaccine virus. Only a few viruses (7 analyzed by CDC's WHO Collaborating Center) have ≥ 8-fold reduced titers to the A/California/07/2009 vaccine virus. Since September 1, 2009 WHO Collaborating Centers have characterized > 8,000 virus isolates and clinical specimens. Very little genetic variation has been detected, complete genomes have been sequenced for over a hundred viruses, and there is no evidence of reassortment. Almost all 2009 H1N1 viruses are resistant to M2 blockers. All 2009 H1N1 viruses are sensitive to zanamivir and most are sensitive to oseltamivir. A total of approximately 100 oseltamivir-resistant viruses have been reported to WHO. Most patients with resistant viruses have taken oseltamivir in the recent past or are taking it at the time the oseltamivir-resistant virus is isolated.

Antigenic cartography, done using data from the hemagglutination inhibition (HI) assay, shows little change in antigenicity as reflected in the following graphic:



The vast majority of H1N1 viruses were antigenically homologous to the A/California/07/2009 vaccine virus. A minority of viruses (<1%) had reduced titers against serum to A/CA/7/09 vaccine virus. Examination of clinical samples from the "low reactor group" indicated that isolation substrate (eggs and cell line) affected the antigenicity of the virus isolates, and the mutations that confer low reactivity are not present in the original clinical sample. No molecular markers for increased virulence were detected.

The following is an amino acid tree, which reflects only those changes that confer amino acid changes in the hemagglutin gene. There are just a few amino acid changes and much more homogeneity then would normally be observed for seasonal influenza viruses.



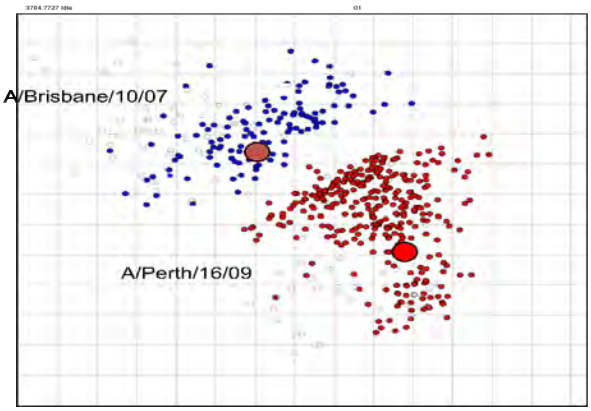
While there have been some amino acid changes among some viruses compared to the vaccine virus, this particular amino acid change does not confer any change in antigenicity. There was also a lot of discussion in the media and among scientists about changes at an amino acid designated 222, which is near the receptor binding pocket of the hemagglutin. The question regarded whether this change really conferred a difference in virulence. The particular change that was being discussed is neither necessary nor sufficient for severe disease.

With regard to seasonal A(H1N1) viruses globally, seasonal A(H1N1) viruses show little evidence of circulation, and are most likely pose a low risk for the Northern Hemisphere 2010-2011 influenza season in the view of WHO and FDA experts. Therefore, WHO and FDA did not recommend a seasonal A(H1N1) virus as a component for vaccines for the Northern Hemisphere 2010-2011.

Influenza A(H3N2) have continued to circulate globally, but at remarkably reduced levels compared with previous years. H3N2 viruses likely pose a risk in the coming 2010-2011 Northern Hemisphere influenza season due to evolution of a new variant. Antigenic, genetic, and drug resistance assays were carried out, and the majority of viruses tested were resistant to M2 blockers and all were sensitive to neuraminidase inhibitor drus. The H3N2 viruses analyzed are antigenically closely related to the vaccine virus recommended by WHO in September 2009 for the Southern Hemisphere 2010 season: A/Perth/16/2009. This emerged after the vaccine recommendations were made in February 2010. In a few countries in Africa, H3N2 viruses were isolated and were causing significant outbreaks. In the early part of the influenza season, H3N2 viruses predominated in China. Thus, it is believed that these viruses will not disappear.

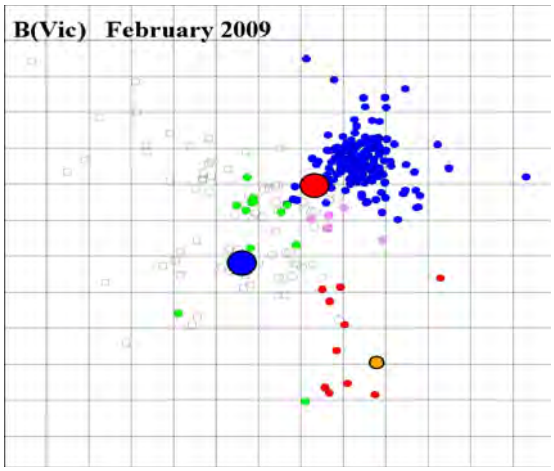
Based on the antigenic cartography of A(H3N2), they are clustering around the A/Perth/16/09 virus, which is the recommended strain for the Southern Hemisphere, and have swarmed Southeast away from the A/Brisbane/10/07 vaccine virus that was previously recommended.

This is reflected in the following graphic:



Influenza B viruses of both the B/Victoria and B/Yamagata lineages continued to circulate at low levels globally. As noted, there was a resurgence of influenza B activity reported by China with B/Victoria lineage viruses predominating in January and February 2010. Influenza B viruses likely pose a continuing risk in the coming 2010-2011 Northern Hemisphere influenza season. Antigenic, genetic, and drug resistance assays have been carried out, and there appears to be no resistance to NIs. The WHO and FDA recommendation is for the B/Victoria lineage only and to retain B/Brisbane/60/2008.

B Victoria antigenic cartography is illustrated as follows:



In summary, the WHO recommendations for the 2010-11 Northern Hemisphere influenza season are as follows:

It is recommended that vaccines for use in the 2010-10 influenza season contain the following:

– an A/California/7/2009 (H1N1)-like virus
– an A/Perth/16/2009 (H3N2)-like virus
– a B/Brisbane/60/2008-like virus

Discussion

Dr. Schaffner (NFID) inquired as to whether Dr. Cox could speculate about why in January and February there had not been more conventional seasonal Influenza A or B viral activities in the US, particularly since pandemic H1N1 seemed to have "given up the field."

Dr. Cox replied that everyone is somewhat puzzled by this, particularly since a resurgence of influenza B has been observed in China during the same period. At this point, there is no explanation. It is a matter of watching and waiting to see what will happen since influenza is difficult to predict.

Dr. Temte inquired as to whether there was an estimate of the existing immunity for H1N1 either by infection or vaccine, especially considering the age group of the spreaders.

Dr. Cox responded that while there are on-going seroprevalence studies in the US, there are no data ready to report. The UK has reported seroprevalence data, which indicate that about 30% of the population has been infected. As more data are accumulated, CDC will publish it as soon as possible. Seroprevalence data should be coming out from some European countries and China as well.

Dr. Keitel requested a follow-up from Dr. Finelli on obesity as a risk factor.

Dr. Finelli replied that there has been some follow-up and inclusion of more cases in the study that Morgan et al conducted in the Fall on adults. The analysis could not be done on children. Using H1N1 cases who were both hospitalized and died, and comparing people who were hospitalized and died of H1N1 without underlying conditions to those in NHANES without underlying conditions, there is about a 4-fold increase in hospitalization and death in people who are morbidity obese (BMI ≥40). It is hoped that these data will be finalized and published soon.

Dr. Meissner noted that while current influenza surveillance data shows that activity had decreased, mortality due to pneumonia and influenza were still high between the seasonal and epidemic thresholds, which seemed contradictory. He thought influenza was the major cause of death.

Dr. Finelli responded that the deaths in the 122 cities were the proportion of deaths attributed to pneumonia or influenza among of all deaths. CDC also receives data on whether deaths are attributed to pneumonia only or influenza only. At this time of year, normally there is some proportion of influenza deaths and pneumonia deaths. Typically, about half are due to influenza, or there is slightly more pneumonia, especially in the elderly and influenza. Those deaths were all pneumonia in almost all people over 65 years of age. Even though these are 7.7% of pneumonia / influenza deaths over all, very few influenza deaths were reported. That is typical of every season. In influenza seasons that are H3N2 or B predominant, a large proportion of the deaths are from influenza. In seasons that are seasonal H1N1 predominant, the proportion of deaths from influenza are reduced among the elderly, and the total number of deaths is less.

Dr. Schuchat clarified that Dr. Finelli was reporting on the excess deaths, and that the vast majority of the excess were considered to be pneumonia deaths, not necessarily influenza related. The vast majority of influenza and pneumonia deaths do not receive a specific etiologic

diagnosis. There was much more laboratory testing being done during the past year than several years ago, but a lot of these are clinical definitions.

Dr. Cieslak noted that based on the numbers circulating, seasonally influenza kills approximately 36,000 people. This season there was a pandemic, and for the most part vaccine was not available before the peak of the pandemic, making the US essentially an unvaccinated population. The number published recently is that 11,000 people died of influenza during this pandemic. While he was aware of where these numbers come from and the different methodologies that generated them, he requested Dr. Finelli's reaction to those numbers.

Dr. Finelli replied that in a season from which those numbers are modeled, there are 8,000 to 9,000 influenza-specific attributable deaths and the remainder of the 36,000 is from underlying all-cause mortality such as CVD, pulmonary disease, et cetera. During this influenza season, there have been more than 11,000 influenza-specific deaths, which exceeds the influenza-specific deaths in a typical season. If CVD and pulmonary disease were added, there would likely be more than 36,000. However, those data are not yet available to analyze.

Dr. Neuzil said she was intrigued by the impact of H3N2 in 2003 for 0 to 4 year olds compared to this season. If memory of deaths from 2003 was correct, there were 153 total while during this season there were 71 just in 0 to 4 year olds. She wondered whether Dr. Finelli thought that was a function of 2003 being the first year that the deaths were reportable and now a better job was being done, or whether there was some discrepancy between the deaths and hospitalization rates in the two years. She emphasized that this was a record number of pediatric deaths, which should be noted.

Dr. Finelli responded that she thought they had more deaths during the current season, with a higher proportion of deaths in school age children over 5 years of age than in 2003. That may add to the excess deaths, although she did not know the exact number in each of the age groups. She also thought a better job was being done of testing and reporting during this season, so there may be some deaths that are just a function of that. There is no question that older children had the highest attack rates and were at the highest risk for acquisition, so there are more deaths in that age group.

Dr. Turner (ACHA) reported that ACHA released data that morning that shows that for the first time in 10 weeks, their flat curve and increased. The rate has been running about 2.7 since early December, but was up to 4.2 per 10,000. Interestingly, the cases are highest in the Southeast and somewhat in the Midwest as well.

Dr. Finelli indicated that she would review these data, particularly in the state-specific data. Regional spread has been observed more in the Southeastern states, especially in Alabama, Georgia, and Tennessee.

Regarding the comparative death issue from seasonal influenza to the pandemic numbers, Dr. Schuchat pointed out that there are numerous ways to measure these. The key issue is age. With seasonal influenza, regardless of whether primary to influenza or secondary to respiratory or circulatory collapse, 90% of the deaths are occurring in people 65 and older. Therefore, of the 36,000 number being reported, 32,000 are in those over 65 years of age. Based on modeling that has been done, CDC is estimating that the deaths in children are probably 5-fold higher at least compared to what would be observed with seasonal influenza. Deaths in people 65 years of age and older are about one-fifth of what is usually observed. There is complexity in a summary number, even when apples are compared to apples, because this was a very bad

year for people under 65 and a wonderfully good year (relatively) for people 65 and over. However, the strains are still circulating and vaccination remains a good idea for seniors and others.

Dr. Kimberlin (AAP) requested that someone comment on Peramivir's susceptibility to pandemic H1N1, seasonal H3N2, and seasonal B viruses.

Dr. Cox replied that the overwhelming number of viruses are sensitive to Peramivir.

Dr. Sumaya inquired as to whether the data on racial / ethnic stratification of hospitalizations and deaths were in adults only or included children. Deaths were disproportionately higher in various racial / ethnic minorities. He wondered what the denominator was: Were these percentages of the group that was hospitalized and died, or population-specific numbers of the racial ethnic groups.

Dr. Finelli responded that the data she showed included all ages. The denominator of patients upon which the rates were calculated was approximately 7,000 patients (3,000 children and 4,000 adults). The racial / ethnic distribution was the denominator.

With regard to infant and child morbidity and mortality, Dr. Katz (IDSA) pointed out that there were some reports of myocarditis detected in infants who died. He wondered whether there were any data to suggest whether this was an isolated event, or if there was a different tropism that H1N1 has demonstrated for organ specificity.

Dr. Finelli replied that she conducted some analyses for an IDSA talk in which she assessed myocarditis, and remembered that it was very infrequent. However, she did not have any data on the underlying pathology.

Dr. Temte requested that someone comment on the contribution of schools, school-aged children, and the school year in the termination of the first wave and the resurgence of the second wave.

Dr. Finelli indicated that CDC has been very attentive to those data in school age children. She did not believe that by chance alone termination / resurgence occurred. There was a fair amount of transmission in schools that abated when schools adjourned in May and June. H1N1 continued to smolder, and there were a number of camp outbreaks in the summer. In the fall, there were widespread outbreaks in many places with the commencement of the school year. Some analyses are being completed by some of CDC's colleagues to assess this issue and offer more insight into community transmission from school outbreaks.

Dr. Baker commented that because schools begin / end at different times in different regions, an analysis by region may make that association even more robust.

Dr. Meissner asked whether there were any results pertaining to Peramivir, which was made available under an Emergency Use Authorization (EUA).

Dr. Schuchat replied that the Peramivir intravenous formulation has been made available under an EUA. CDC runs that program, providing the medication to doctors who order it. There is mandatory adverse event monitoring and surveys are being conducted through which some follow-up data can be obtained. However, she did not want people's expectations to be raised about the completeness and ability of those data to offer effectiveness information. They are

not really suitable for that, so CDC is working with FDA on ways to better determine the efficacy of medications made available under EUAs in the future.

Dr. Whitley-Williams inquired as to whether there were any morbidity and mortality data for the youngest age group, those too young to be vaccinated (0 to 4 years of age), in terms of how many cases occurred in infants less than 6 months of age. This age group is always lumped in with the less than age 4 group, but she thought it was important to acquire PK data, particularly in the youngest children. She also wondered about the mortality data by race / ethnicity.

Dr. Finelli responded that CDC does have these data for a proportion of children less than 6 months of age for both those who were hospitalized and those who died. However, because she did not have those data with her, she preferred not to speculate. In terms of the mortality data by race / ethnicity, only the BRFSS system and Emerging Infections Hospitalization Program collect these data. CDC does not systematically collect mortality data by race or ethnicity, just by aggregate number by age group.

Dr. Chilton noted that the other drug that was used under an EUA was oseltamivir for children younger than 1 year. He wondered whether that EUA would persist into the next influenza season and / or what might be done for young children who are exposed or infected during the coming season.

Dr. Sun (FDA) said that he preferred to defer that question since it pertained to the drug side of FDA and he was from the biological side. In general, an EUA can last no longer than one year, at which time it must be renewed.

Dr. Schuchat added that the EUA is tied to the emergency declarations. She did not believe they should assume that these would be good for the next season.

Based on the way in which data were presented during this ACIP meeting, Dr. Dekker gained the impression that it was viewed by the experts that there is a vaccine for the upcoming season that contains no seasonal H1, but because there were no strong seasonal candidates, it contains the pandemic H1. He wondered at what point they would begin saying that A/California/07/2009 is just another H1N1 that is competing with all of the rest for the chance to be in a seasonal vaccine.

Dr. Cox responded that this point had almost been reached; however it would be premature to state that the pandemic was completely over. There was an increase in activity in some countries such as Africa, and they had yet to see what would occur in the Southern Hemisphere. It is believed that this will become a seasonal strain and will continue to circulate just as the previous H1N1 did, but certain parts of the world and certain communities were being affected by the pandemic virus for the first time.

H1N1 Vaccination Coverage: Updated Interim Results February 24, 2010

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Dr. Singleton presented an update on vaccination rates with H1N1. These results were based on CDC's National 2009 H1N1 Flu Survey (NHFS) results published in the *MMWR* in January 2010 and interviews conducted by February 13, 2010.

The NHFS has provided CDC with weekly estimates of H1N1 and seasonal coverage, including some behavioral data associated with vaccination. The NHFS is a random-digit-dialed (RDD) telephone survey of about 6,000 households per month, which includes land line and cell phone samples, conducted from October 2009 through June 2010. It is supplemented by a sample of children from the National Immunization Survey (NIS) sampling frame. Information from other surveys and data systems used for surveillance of influenza vaccination this season will be reported later, including state-level estimates using data from the BRFSS.

By February 13, 2010 an estimated 97 million doses of H1N1 vaccine (95% CI 81 million to 112 million) had been administered to 86 million persons. This number of doses administered represents about 78% of doses shipped (95% CI 65% to 90%). An estimated 37 million doses had been administered to 27 million children (95% CI 23 to 31). The proportion of estimated cumulative doses received by persons in the initial target group was over 85%, and had declined to 72% by February 13. By December 19, 2009 39 programs had expanded their H1N1 vaccination effort to the general population. Based on NHFS interviews from December 27 through January 30, 2010 an estimated 166 million persons (95% CI 158 to 174) were in the initial target group, or 56% (95% CI 53% to 58%) of the US civilian, non-institutionalized population aged 6 months or older. In terms of cumulative H1N1 vaccination rate by week, by the second week of February, estimated coverage was 28.8% (95% CI 25.2% to 32.4%) overall. Based on a cumulative total of about 126 million doses distributed by February 13, 2010, less than 42% of the population could have been vaccinated, 28.8% of the total population had been vaccinated, and most of those who definitely intended to get an H1N1 vaccination had done so.

Data were accumulated from December 27 to January 30 to have more stable estimates for different sub-groups. By mid-January, overall about 24% had been vaccinated. Coverage rates in children were higher than in adults (about 1/3 of children compared to about 1/5 of adults). Coverage by mid-January in the initial target group was 30% higher than the overall population. The highest rate was in healthcare practitioners at 39%. Pregnant women were included in initial target group estimate, but there were not enough (n=43) for separate estimate. As reported in the January 15, 2010 *MMWR* article, based on BRFSS December 1-27 preliminary data, estimated H1N1 coverage before mid-December was 38.0% (24.3-51.7) for pregnant women. Complete BRFSS data for January are not yet available to provide an updated estimate for pregnant women. Based on the BRFSS estimated reported in the *MMWR* for coverage before mid-December, coverage was 11.6% (9.9-13.3) for high risk adults aged 25-64, and 22.3% (19.6-25.0) for HCP. NHFS December estimates of coverage by mid-December for these groups were 18.5% (14.5-22.5) for high risk adults aged 25-64 and 30.7% (25.0-36.4) for HCP.

With respect to weekly NHFS estimates of the percent of children aged 6 months through 9 years receiving at least one dose of H1N1 vaccination, confidence intervals are wide, but these data indicate an increasing trend in receipt of a second dose among those with at least one dose. At least one third and possibly up to two thirds of children with at least one dose may have received a second dose. This rate may increase as children initially vaccinated in January have more time to get their second dose. By comparison, from the NIS estimates for children 6-23 months, 2007-08 season, 23.4% were fully vaccinated and 40.7% had at least dose of seasonal vaccination, a ratio of 57%. Children were more likely than adults to get both H1N1 and seasonal vaccination by mid-January, while adults were more likely to get seasonal vaccination only. Overall, 51% of children and 47% of adults had received an influenza vaccination of either type.

Racial and ethnic disparities in H1N1 vaccination coverage were also assessed. As is observed for seasonal influenza vaccination, some racial and ethnic disparities in coverage occurred with H1N1. These differences were significant among adults but not children, and these differences were of lower magnitude than for seasonal vaccination. Significant disparities were also observed by levels of income and education, with higher coverage among persons living above the poverty threshold with annual incomes of over $75,000, and for college graduates. The sample size is not sufficient in NHFS monthly samples to reliably estimate disparities among HR 25-64 or HCP. January BRFSS data are not complete yet to allow update of disparity estimates based on December BRFSS data published in the *MMWR*.

With respect to the limitations of the survey, vaccination status and identification of target groups were based on self- or parental-report. Non-response bias may remain after weighing adjustments. The RDD response rate was relatively low at 34% for the landline sample and 26% for the cellular telephone sample; however, this was on par with telephone studies currently. Survey estimates of coverage are consistent with vaccination patterns observed with SDI data.

In summary, by mid-February, 86 million people had been vaccinated with about 97 million doses. Most doses were administered to the target groups. Coverage was higher in children than adults. An estimated 39% of health care workers were vaccinated. Of children less than 10 years who were vaccinated, as many as 60% had received their second dose. H1N1 vaccine coverage in adults was significantly higher in Whites than Blacks or Hispanics. H1N1 coverage did not differ significantly by race or ethnicity among children.

The next steps are to publish state-level H1N1 and seasonal estimates in the *MMWR*, continue to monitor through June, conduct post-season evaluation using all data sources to determine lessons learned for future seasons, and enhance the influenza vaccination surveillance system for the 2010-11 season.

H1N1 Vaccine: Implementation Update February 24, 2010

Pascale Wortley, MD, MPH
Immunization Services Division
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Dr. Wortley reported that as of a few days prior to this meeting, about 126 million doses of vaccine had been ordered by states. As a comparison, for the VFC program that uses the same system, about 80 million doses of vaccine are distributed each year. Of course, all of that activity continued while the intense H1N1 effort took place over 3.5 months. There were over 70,000 unique "ship-to" sites, although vaccine found its way to a lot more than 70,000 sites because states engaged in a fair amount of redistribution using their own resources. The greatest increase in distribution was up through the first half of December 2009. There was a very marked slowing in the ordering pattern beginning the second half of January 2010.

With respect to some of the challenges encountered, influenza vaccine is not generally handled as a "just-in-time" inventory as occurred during the first period. What normally is a fairly invisible process was under a magnifying lens to the point that even a delayed shipment due to weather conditions did not go unnoticed. Sometimes plans had to change because vaccine did not arrive on time for whatever reason. Managing allocations when demand varied across states also posed challenges. During October, everybody wanted more vaccine than there was and things were very straightforward. By mid-November, changes in patterns started to occur. Demand began to decrease in some parts of the country, while it remained strong in other parts. Also important was not to have a situation in which vaccine sat unused in warehouses, because there was always somewhat of a lag between ordering and shipping.

A system was devised that allowed states to order against their future allocations, and the vaccine that was used was that cushion. Of course, that had to be done very carefully so that a back ordering situation did not occur. That system worked well and allowed for addressing the needs of states that were experiencing their ILI peak later than others and had higher demand for the vaccine. Managing allocations was complex for Dr. Santoli's group. Also challenging was the provision of ancillary supplies. Complaints were received from providers who did not like the supplies they received. Part of the challenge was that in order to have enough supplies, HHS purchased 8 different types of supplies. Given that providers could not select what they were going to receive, they often received products they were not familiar with, which created some challenges that CDC tried to overcome with some training.

The current issue pertains to ramping down of the system. By the end of April, CDC will be reducing the amount of vaccine that is available in the warehouses, but will retain the capacity to use it. All viable vaccine will be stored for use. Most of the vaccine will be expired by the end of June 2010, but there are some sanofi pasteur multi-dose vials that have expiration dates in 2011. Decisions must be made about how that can be used. Because it is unknown what the Spring, Summer, and Fall might hold with regard to influenza activity and vaccine demand, this will be a useful asset upon which to draw if necessary.

With respect to financing, the topic that seemed to have consumed so much of CDC's time over the summer, the NVAC H1N1 vaccine financing recommendations involved all key stakeholders in a consensus on important recommendations. They were able to draw upon work that they had already done for vaccination of children and adolescents. The VFC served as a very good model of a free government vaccine program, and it helped to address a number of the policy issues that had to be dealt with throughout the summer. Most private plans covered H1N1

vaccine administration. At some point later in the summer, a decision was made to allow public health to bill in public clinic settings, though they could not charge cash. The impact of the ability to bill in public clinic settings needs to be evaluated.

Providers who were to receive the H1N1 vaccine had to sign a provider agreement. There were minimal federal requirements, and states could add requirements as well. States were asked on a periodic basis to report to CDC how many provider agreements had been signed, which reached a maximum of about 120,000. That is three times the number of VFC providers of 45,000. The make-up of providers varied across states. CDC is in the process of obtaining better information about that, but suspects that it varied somewhat in relation to how states went about recruiting providers, differences in provider interests, and decisions that states or local areas made in terms of whether vaccine was directed to a variety of types of providers or was more specifically directed to specific providers (e.g., pediatric providers, school vaccination, et cetera). A considerable amount of work was done around October 2009 in terms of registering providers.

In terms of where children and adults were vaccinated, H1N1 vaccine (58.6%) was administered primarily in medical settings (e.g., doctor's office, clinic or health center, hospital, other medical related location) just as seasonal vaccine is (64.5%). Other settings included health departments, pharmacies / drug stores, workplaces, schools, and other non-medical settings. Seasonal influenza vaccine is administered in these settings at 32.6%, and H1N1 at 39%. To some extent, that is a reflection of the large amount of school-based vaccination that occurred this past fall. About 40 of the 54 grantees reported some school vaccination activity. In some, it was a statewide activity that was coordinated at the state level, or it may have been a state and local responsibility, but generally was coordinated state-wide. For another 30 areas, it varied county by county, in that counties were responsible for deciding whether they were going to conduct a school-based program.

There was a wide range in vaccination rates by state among children 6 months to 17 years of age, which is typically observed for seasonal influenza vaccination in children as well. For example, in a recent year for 6 to 23 month olds, seasonal influenza vaccination ranged from about 15% to 50%. A number of factors affect influenza vaccination rates. This season, some of the factors likely included the timeframe during which ILI peaked by state, the population the state was focusing on for vaccination, and whether state-wide school vaccination programs coincided with their ILI peak.

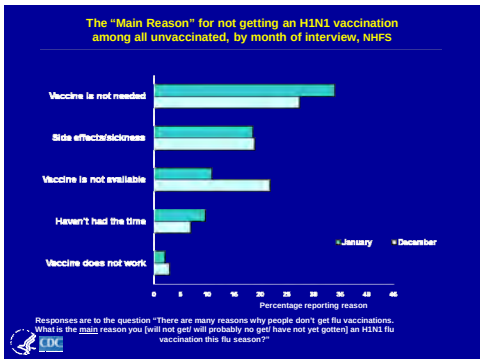
Only a few weeks after states were wrestling with what to do with limited vaccine supply, they had to turn their attention to determining the point at which it was appropriate to open vaccination up to the general public. One state started a couple of weeks before Thanksgiving. The week of Thanksgiving, nothing happened. Then there was an increase over the next three weeks. By Christmas, most states had expanded H1N1 vaccination to the general public. A few states did not expand until the latter part of December or early January.

As noted earlier, the proportion of estimated cumulative doses received by persons in the initial target group was over 85%, and had declined to 72% by February 13. 2010. Based on NHFS interviews from December 27 to January 30, an estimated 166 million persons (95% CI 158 to 174) were in the initial target group, or 56% (95% CI 53% to 58%) of the US civilian, non-institutionalized population aged 6 months or older. For the immunization program veterans who recalled the challenges of vaccine shortages in 2004, the major challenge was starting soon enough that there would still be demand once they expanded the target groups, but not

expanding too soon creating demand that could not be met. Generally, the ACIP recommendations, which were designed for exactly this type of flexibility, worked well.

The purpose of the retail pharmacy initiative that occurred at the end of December was to extend the reach of public health. This was a deviation from the pro rata allocation of vaccine to states. The vaccine was allocated directly to 10 participating retail pharmacies that subsequently distributed doses across their systems as they wished. All but three states participated. A number of states already were directing vaccine to retail pharmacies before this initiative, but the idea was to allow public health to focus on other populations and to send more vaccine out. This was the same principle as the advanced allocation in order to use vaccine that was in the cushion that was sitting unordered. In all, vaccine was distributed to over 10,000 locations. The first direct shipment of vaccine to retailers was sent on December 24, 2009. To date, these pharmacies and clinics have received over 5.4 million doses of 2009 H1N1 vaccine directly from CDC.

The following graphic depicts the reasons stated for not getting vaccinated:



The contract in turquoise and light turquoise are data from January and December. Notably in December is that "vaccine is not needed" and "vaccine is not available" were the two leading reasons. By January, few people were saying vaccine was not available and the focus was that it was not needed. A potential barrier not listed on this graphic was "cost of the vaccine," which fewer than 3% of people reported. An important concern over the summer was that it would be confusing to people that vaccine could be obtained in different places, but they would have to pay for it in some places and not in others. In the end, this did not end up being a barrier at all.

In summary, there were a number of key accomplishments. Public health coordinated distribution of a large amount of vaccine as quickly as it became available. Much experience was gained in large-scale clinics and school-located vaccination. Experience was also gained in managing a scarce resource and addressing vaccine safety and supply concerns. There was a tripling in providers receiving vaccine from public health. New partnerships were forged with health care, community groups, and education which can be built upon in the future.

Key evaluation areas upon which CDC is focusing include approaches to allocation and distribution (state and local), school vaccination best practices, provider involvement best practices, provider perspectives, and billing by public health. Moving forward, consideration must be given to building upon the momentum that was acquired during this past influenza season in terms of partnerships, new capacities that were acquired, and prospective evaluation.

Discussion

It was Dr. Baker's understanding that there has been great reluctance by the AAP to move any kind of vaccines out of the medical home. This season provides some lessons that there can be both school-based immunizations and immunizations in the medical home depending upon the ages of children and other factors. She requested that Dr. Bocchini comment on this, and emphasized that if they were ever going to increase rates, they must diversify their efforts.

Dr. Bocchini (AAP) replied that this subject certainly has been discussed extensively. He thought that the important point was that better vaccine registries must be developed so that the medical home knows what is occurring. Some of the issues in the medical home involve trying to vaccinate all children within a brief period of time for one or two doses of vaccine and making sure that there is adequate supply for that. Planning for patient visits and adequate vaccine supplies placed a great deal of stress and strain on practitioners, but also made them realize that school-based immunization may be a better method on an annual basis for influenza immunization.

Dr. Keitel requested an estimate of how many doses remain in warehouses and what efforts are being undertaken to ensure that those are distributed, particularly given the uncertainty about what will occur in the Fall.

Dr. Wortley responded that there were recently about 28 million doses in the warehouses. CDC is in the process of gradually bringing this number down because by the end of April, they will have half of that. The reason there is so much vaccine in the warehouses is because the ordering has slowed down so much. In terms of distributing these doses, states and local areas are still holding clinics. The demand from providers has slowed down significantly. Most of the states originally were in a mode of pushing vaccine out to providers and then switched to an ordering mode.

Dr. Sawyer noted that clearly, they are still not doing a very good job of immunizing health care workers. In his community, a number of hospitals developed much more aggressive policies for immunization of their workers that had great effect. He inquired as to whether Dr. Singleton could tell them what percent of the healthcare workers surveyed were employed in hospitals as opposed to clinic settings, and whether the survey asked whether there were changes in policy such as a mandatory policy for immunization.

Dr. Singleton responded that while they will be able to examine occupation type later, they do not currently have these data. CDC contracted with RAND and Knowledge Networks, Inc. to conduct internet surveys of healthcare workers and there are some preliminary results; however, these results have not yet been released yet. They should be published in an *MMWR* article by early April. Surveys are conducted monthly that include occupation type and policies that were implemented for this season. Data from the National Epidemiology Center from past seasonal show differences in location. Healthcare workers in hospitals tend to have higher rates than those in long-term care facilities.

Reflecting on Dr. Singleton's comments that there were not differences by race and ethnicity for children receiving vaccine in terms of seasonal and H1N1 but there were for the adults, Ms. Ehresmann hypothesized that the reason for that may be because there is such a strong childhood vaccination program with the VFC. For adults, there were less barriers for H1N1 vaccination than for seasonal vaccination. This supports the fact that the lack of an adult immunization program is quite significant problem.

Dr. Lett shared that Massachusetts is still administering about 60,000 doses a week of H1N1 vaccine. However, they are concerned about using all of the doses available to them and are seeking any possible epidemiologic support they can share with people. For example, spring break may mean that children may be going to Mexico. This could be a reason to have an initiative.

Dr. Baker pointed out that they also need to know whether there is going to be a third wave.

Dr. Fiore responded that CDC is certainly keeping an eye on activity in the US and abroad. There is not a clear hint that something is brewing, but certainly there continues to be activity in the US and other areas. There is always the potential for people to travel to areas where there might be more activity and bring it back to their own community that might not have been hit so hard by the second wave, which could start a new chain of transmission. There are many reasons to continue to promote H1N1 vaccination.

Referring to the two NHFS surveys, Dr. Duchin (NACCHO) noted that the percent vaccinated for adults ages 25 through 64 with high risk health conditions was very different from 11.6% to almost 30%. He wondered what Dr. Singleton's interpretation was of that jump in terms of whether it meant that these people were vaccinated later, and that they were not vaccinated at the time the initial survey was conducted.

Dr. Singleton explained that the number published in the *MMWR* was from the BRFSS from December data, which represented cumulative coverage sometime before mid-December. The number he presented during this session was from the NHFS. There were two different surveys. They were similar in methodology in terms of being telephone surveys, but one major difference was that with data from a month later, they should expect to see an increased uptake. They have compared results from the two surveys using comparable time periods and generally are matching it fairly well, but a few differences are observed. Most of the difference is probably due to it being more up to date with the recent estimates. The NHFS was a little higher than the BRFSS back in December. It was 18% in mid-December and he was showing 29% in mid-January from the same data source.

Dr. Duchin (NACCHO) said that because these are the people at highest risk of death, he thought the timing during which they were immunized was of some significance in the context of informing policy making about how prioritization is done. The timing of immunization for the different subgroups would be useful to know in future reports.

Dr. Singleton replied that they are collecting the month of vaccination, and numerous analyses are being conducted on vaccination timing in different subgroups.

Reflecting on Dr. Sawyer's comments about breaking out where health care providers are vaccinated, Dr. Foster (APA) reported that most of their healthcare professionals were not hesitant to acquire the vaccine. However, they are primarily healthcare professionals versus food service workers, housekeeping staff, et cetera so it would be interesting to understand what is included in the healthcare worker category.

Dr. Singleton responded that the question asked in the surveys is: Do you work in a healthcare facility? This is followed by some examples. Another question asks: Do you provide direct patient care as part of your routine? If someone responded "yes" to either of those questions, they were included. They will be able to assess occupation type later when the data are coded.

Dr. Foster (APA) pointed out that every state is different in terms of the state laws that govern what pharmacists can do. Currently, in all 50 states pharmacists can administer immunizations in some manner. Pharmacists are probably the least threat to pediatrics because they usually do not administer pediatric vaccines in pharmacies. However, states will allow them to vaccinate down to age 12 to 14. It was very difficult for APA this year because they did have a lot of patients present to pharmacies requesting the vaccine. They had to defer people until the season was almost over, and by that point, no one wanted it. Pharmacists have access to many patient records, so they can easily identify those with chronic diseases. Therefore, he advocated that pharmacies be considered to receive vaccine early on because typically in a season, pharmacies administer more vaccines than health departments.

Dr. Sumaya was struck the primary reason for not getting an H1N1 vaccine being "not needed." He thought this needed further investigation, scrutiny, analysis, et cetera.

Ms. Ehresmann pointed out that as they moved forward to build on the successes of this influenza season, it was important to keep in mind that there were some additional funds made available for those efforts. Without those funds, it is not clear how feasible it will be for folks to continue such efforts in the future.

Regarding health care workers, Dr. Morse (CSTE) noted that New York had enacted regulations requiring health care workers to be immunized, but this effort had to be suspended due to a shortage of vaccine. They conducted a brief survey that compared to the previous year when only 43% of healthcare workers were immunized, During this season, it reached approximately 71%. While they need to follow-up on this, it appears to be a successful program that will go forward as a regulation for the coming year. In terms of sustainability, obviously there were a number of good practices developed as a result of the pandemic influenza vaccine campaign. He wondered how that could be translated to seasonal influenza vaccine and what progress was being made to garner funding to support that. It would be a shame to lose the momentum if there is no funding to translate these efforts.

Dr. Wortley responded that clearly, school vaccination requires both operations and vaccine funds for non-VFC children.

Dr. Schuchat added that currently, there are no more resources to support school-associated vaccination, with the exception of the economic stimulus ARRA funds that the states have been programming. There was about a $300 million, two-year program that included substantial funds for vaccine purchase, so the states still have some discretion regarding how to program their remaining vaccine purchase dollars. The operations funds included in that also were at their discretion. This past year, an enormous amount of emergency funds were allocated to support states. Most of the funds that went to the states were for vaccine administration.

Dr. Sun (FDA) said that although there are a lot of successes associated with the response to this pandemic, there might still be a lot of challenges. One of those will be assessment of safety profiles and the effectiveness of these vaccines on their pandemic circumstances. Because in the future there will probably be different vaccines made with more varied technologies, it would be especially important to examine issues of safety and effectiveness, and to be able to track particular manufacturers of vaccines.

Regarding how to promote vaccination, Dr. Plotkin said he had read the paper that states that the transmission of H1N1 was lower than might have been expected. Guinea pig data suggest that this is not the case. He thought that calculating the reproductive number would be important because this is the first time this much vaccination has been given to children, who are the main transmitters of influenza. If they believe that vaccinating children is going to have an impact on an epidemic, he wondered whether there were any data regarding reproductive number which would allow calculations to tell them whether the percentage of children who were vaccinated could have actually had an impact on the epidemic. It may be too optimistic to say that that this is what stopped the transmission at the end of last year, but he though such calculations would be extremely important to determine whether, in fact, vaccination of children is having an impact. He also wondered whether there were any effectiveness data from either American or European experience that would tell them about the effectiveness of the H1N1 vaccine.

Dr. Fiore responded that in terms of the reproductive, certainly CDC is working on this with a number of others throughout the world. Other investigators have done their own calculations of this. However, he did not have a number to provide at this moment. A number of studies are underway to examine vaccine effectiveness. Some preliminary estimates are available, but CDC is hampered by the fact that the pandemic wave in many of the areas where these studies were set up beforehand proceeded the time before there was a lot a vaccination. He thought they would soon have this information and that other countries would also have vaccine effectiveness data available.

Dr. Judson said he thought a study was published just recently that spoke to the issue of transmissibility when there was a primary case within the household, and then assessed spread to other household members. He thought some of that was examined before vaccine was widespread.

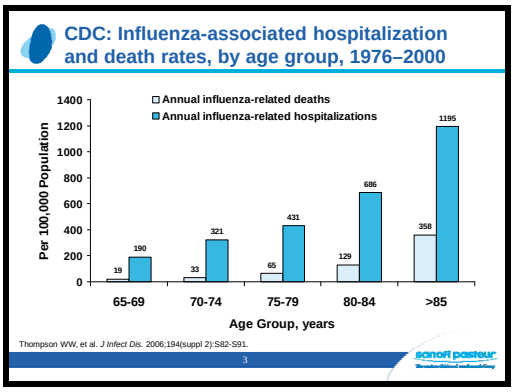
Dr. Fiore replied that there are some studies, but he was not prepared to quote them at this point. He indicated that he would review these and provide them to the members.

Fluzone® High-Dose Vaccine: High-dose Influenza Virus Vaccine for Persons 65 Years of Age and Older

David Greenberg, MD
sanofi pasteur

Dr. Greenberg thanked Dr. Fiore, Dr. Neuzil, and the Influenza Work Group for giving him the opportunity to present data from sanofi pasteur's Fluzone® High-Dose clinical trial during this session. Before discussing the clinical trial data, he briefly reviewed the burden of disease in the older adult population and the rationale for developing this vaccine.

Based on a retrospective analysis of some 25 years of influenza seasons (1976–2000) demonstrating the influenza-related hospitalizations and death rates among the older population, hospitalization and death rates increase quite dramatically in the oldest age groups as reflected in the following graphic [Thompson WW, et al. *J Infect Dis*. 2006;194(suppl 2):S82-S91Thompson WW, et al. *J Infect Dis*. 2006;194(suppl 2):S82-S91]:



To put this into context, the rates for healthy adults under age 65 are a fraction of what is shown here. Adults ≥ 65 years of age comprise 15% of the US population, but account for 65% of hospitalizations and 90% of deaths attributable to influenza and its complications each year. Among older adults, influenza causes an estimated 3.2 million illnesses, 136,000 hospitalizations, and 36,000 deaths per year, with annual direct medical costs of $4.2 billion and total economic burden of $56.1 billion. Influenza vaccines provide substantial protection, but older adults respond less well to standard-dose influenza vaccines compared with younger adults. Lower antibody titers leave older adults more vulnerable to serious infection and severe complications [Thompson WW, et al. *J Infect Dis*. 2006;194(Suppl. 2):S82-S91**.** Zheng B, et al. *J Immunol*. 2007;179(9):6153-6159. Molinari NM, et al. *Vaccine* 2007;25(27):5086-96].

In terms of standard influenza vaccine and geometric mean titers (GMT) high in responses from one of sanofi pasteur's recent annual Fluzone® release studies, there were remarkably lower antibody responses for adults over age 65 compared to the younger adult population [sanofi pasteur annual release study GRC41].

Decreased immunity against influenza is a result of aging and immunosenescence. Declining humoral and cellular immunity, a result of aging, increases susceptibility of older adults to infection. Older adults have decreased immunologic responses to vaccines due to immunosenescence. Age-related changes in T-cell subsets and in cytokine production profiles affect the magnitude, quality, and persistence of antibody responses to vaccines [Zheng B, et al. *J Immunol*. 2007;179(9):6153-6159. Doria G, et al. *Mech Ageing Dev.* 1997;96(1-3):1-13. Siegrist CA. The immunology of vaccination. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 5th ed. Saunders; 2008].

In response to the increase in calls for vaccines to improve immune responses in this older adult population and to help prevent influenza to a greater degree, sanofi pasteur developed the Fluzone® High-Dose vaccine. The genesis of Fluzone® High-Dose began about a decade ago in discussions between and CDC, National Institute of Health (NIH), sanofi pasteur, and investigators at Baylor and elsewhere. This led to the initiation of sanofi pasteur's Phase I and Phase II trials. In the interest of time, these two trials were not discussed.

During this session, Dr. Greenberg reported on the Fluzone® High-Dose Vaccine Study FIM05 Phase III multicenter, randomized double-blind study of 3876 participants 65 years of age and older. Participants were randomized 2:1 to receive either High-Dose (HD; 60µg HA per strain) or Standard-Dose (SD; 15µg HA per strain). Participants in the High-Dose group were further randomized to receive 1 of 3 different lots of the vaccine. Blood specimens were obtained pre-

vaccine and on Day 28 for evaluation of influenza antibodies. Safety data were collected by diary card (1 week), visits (4 weeks), and telephone calls (up to 6 months) post-vaccination.

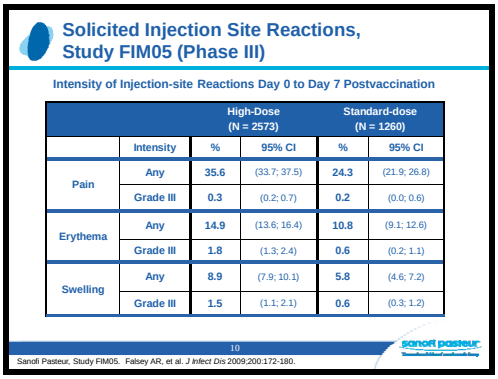
Primary endpoints included the following:

- ❑ Immunogenicity for lot consistency
- ❑ Immunogenicity for superiority
- ❑ GMTs
- ❑ 4-fold rise rates

Secondary endpoints included the following:

- ❑ Immunogenicity for seroprotection rates
- ❑ Solicited safety and reactogenicity
- ❑ Unsolicited adverse events (AEs) and serious adverse events (SAEs)

With regard to safety data from this trial, injection site pain, erythema, and swelling were reported at higher frequencies for High-Dose High-Dose (N = 2573) compared to Standard-Dose recipients (N = 1260). The vast majority of these were Grade I and II, and were mild to moderate. The proportion of Grade III, or severe reactions, was quite low for both groups. Their reactions, for the most part, resolved within three days after vaccination. In terms of the solicited systemic reactions, myalgia, malaise, and headache were reported at about 3 to 4 percentage points higher in the High-Dose compared to Standard-Dose recipients. Fever was just slightly higher. Again, the vast majority of these were mild to moderate and resolved within three days [Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180]. Solicited injection site and systemic reactions are shown in the following tables:



Solicited Injection Site Reactions, Study FIM05 (Phase III)

Intensity of Injection-site Reactions Day 0 to Day 7 Postvaccination

		High-Dose (N = 2573)		Standard-dose (N = 1260)	
	Intensity	%	95% CI	%	95% CI
Pain	Any	35.6	(33.7; 37.5)	24.3	(21.9; 26.8)
	Grade III	0.3	(0.2; 0.7)	0.2	(0.0; 0.6)
Erythema	Any	14.9	(13.6; 16.4)	10.8	(9.1; 12.6)
	Grade III	1.8	(1.3; 2.4)	0.6	(0.2; 1.1)
Swelling	Any	8.9	(7.9; 10.1)	5.8	(4.6; 7.2)
	Grade III	1.5	(1.1; 2.1)	0.6	(0.3; 1.2)

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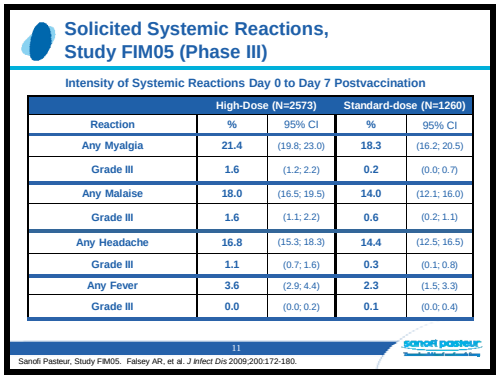
Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.



Solicited Systemic Reactions, Study FIM05 (Phase III)

Intensity of Systemic Reactions Day 0 to Day 7 Postvaccination

	High-Dose (N=2573)		Standard-dose (N=1260)	
Reaction	%	95% CI	%	95% CI
Any Myalgia	21.4	(19.8; 23.0)	18.3	(16.2; 20.5)
Grade III	1.6	(1.2; 2.2)	0.2	(0.0; 0.7)
Any Malaise	18.0	(16.5; 19.5)	14.0	(12.1; 16.0)
Grade III	1.6	(1.1; 2.2)	0.6	(0.2; 1.1)
Any Headache	16.8	(15.3; 18.3)	14.4	(12.5; 16.5)
Grade III	1.1	(0.7; 1.6)	0.3	(0.1; 0.8)
Any Fever	3.6	(2.9; 4.4)	2.3	(1.5; 3.3)
Grade III	0.0	(0.0; 0.2)	0.1	(0.0; 0.4)

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Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

The other safety parameters included immediate reactions within 30 minutes, which occurred at a low rate and were equal between the two groups. Unsolicited adverse events within the first 28 days were the same in both groups at 22%. Rates of SAEs were 6.1% in the High-Dose group and 7.4% in the Standard-Dose group. Only two SAEs were reported by investigators as being vaccine-related. One case of an exacerbation of Crohn's disease occurring two days after vaccination with high-dose and one case of a new diagnosis of myasthenia gravis occurring a month after standard-dose vaccine. There were no deaths within the first 28 days after vaccination in either group and the 23 deaths that were reported through 6 months of follow up, the rates of deaths were the same in the two groups, 0.6%, and they were all considered unrelated to vaccination.

Adverse events occurring in the 30 minutes following vaccination were comparable at 0.3% in both groups. Rates of unsolicited adverse events within 28 days post-vaccination were comparable at 22% in both group. Rates of SAEs were comparable at 6.1% with High-Dose vaccine and 7.4% Standard-Dose vaccine. Only two SAEs were reported by investigators as being vaccine-related: an exacerbation of Crohn's Disease 2 days after vaccination with High-Dose vaccine, and a new diagnosis of myasthenia gravis 1 month after vaccination with Standard-Dose vaccine. No deaths occurred between Day 0 and Day 28, and 23 deaths were reported after Day 28 (0.6% in both groups). All deaths were deemed unrelated to vaccination.

A rigorous approach was applied for superiority assessments. For Fluzone® High-Dose to be considered superior to Fluzone® Standard-Dose, demonstration of superiority for at least two of the three vaccine strains without inferiority of the third strain was required. In most studies, superiority criteria would be met when the lower bound of the 95% confidence interval is greater than 1.0 for GMT ratio or greater than 0% for the difference in 4-fold rise rates. In discussions with the FDA, it was agreed that for this trial, the superiority criteria would require that the lower bound of the 95% CI be greater than 1.5 for the GMT ratio and greater than 10% for the difference in 4-fold rise rates. These substantial margins would not only guarantee statistical superiority, but also would ensure clinical superiority. The GMTs were significantly higher in the High-Dose recipients compared to the Standard-Dose recipients for all three strains. Superiority was achieved for the H1N1 and the H3N2 strains, with non-inferiority for the B strain.

Perhaps the most vulnerable of the elderly populations to influenza and its complications would be those entering the season with negative baseline titers. In a subset of the population in this study who had negative baseline titers (e.g., titers less and 1:10), the GMTs generated by the High-Dose vaccine were statistically significantly higher with the High-Dose compared to the Standard-Dose group for all three strains. In terms of GMT by age, higher GMTs were found for all three age groups in the High-Dose versus Standard-Dose recipients. When the subjects were enrolled, they were asked about history of cardiovascular or respiratory disease. The increased antibody responses with High-Dose vaccine were maintained even in those with a history of cardiovascular or respiratory disease. Based on the FDA criteria, the immunogenicity of Fluzone® High-Dose vaccine was superior to Fluzone® Standard-Dose. The GMT ratios of 1.7, 1.8, and 1.3 demonstrate that High-Dose induced 70%, 80%, and 30% higher antibody titers compared to Standard-Dose for H1N1, H3N2, and B strains. In addition, the High-Dose vaccine induced 4-fold rise rates more often than Standard-Dose vaccine by differences of 25%, 18%, and 12%. The pre-defined endpoints for superiority were met for the two A strains and non-inferiority for the B strain. For that B strain, the GMT ratio of 1.3 and the difference in 4-fold rise rates of 12% were statistically significant [Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180].

In summary, rates of solicited injection-site and systemic reactions were more frequent with High-Dose vaccine, but were transient and well-tolerated. Fluzone® High-Dose vaccine was significantly more immunogenic than Standard-Dose vaccine against all 3 strains as measured by GMTs, 4-fold rise rates, and seroprotection rates. Benefit were maintained across age, underlying condition, and gender. Fluzone® High-Dose vaccine met the pre-specified FDA-defined superiority criteria. Fluzone® High-Dose vaccine induced superior antibody responses compared with Standard-Dose vaccine against H1N1 and H3N2 strains (70% and 80% higher), and was non-inferior against B strain (30% higher).

Regarding licensure and next steps, the Center for Biologics Evaluation and Research (CBER) licensed Fluzone® High-Dose vaccine on December 23, 2009. This vaccine will available for the upcoming 2010-2011 season. A post-licensure efficacy trial was begun in September 2009. This is a study of approximately 30,000 subjects, all 65 years of age and older. It is a three-year study. Subjects are randomized 2:1 to High-Dose or Standard-Dose vaccines, double blind. Post-vaccination blood draws are being obtained from about one-third of the subjects. There is active surveillance for influenza-like illness (ILI) and respiratory specimens collected for culture and PCR. Safety will be monitored for 6 months after vaccination at a minimum, through the following influenza season. The superiority criterion for this study is the lower bound of the 95% confidence interval for the relative vaccine efficacy of Fluzone® High-Dose compared with Standard-Dose greater than 9.1%. The first subject was enrolled September 22, 2009 and the enrollment for the first year completed in early November 2009 with over 9000 subjects enrolled across the US. Surveillance for ILI and collection of respiratory specimens for culture and PCR are on-going. An independent data monitoring committee will review the safety and efficacy trial as it progresses. As noted, Fluzone® High-Dose vaccine will be available for the upcoming season in preservative-free, non-adjuvanted, 0.5mL pre-filled syringes. sanofi pasteur began accepting reservations for this vaccine on February 15, 2010. Medicare Part B coverage is expected.

Discussion

Dr. Baker inquired as to whether there were plans to use High-Dose vaccine exclusively for the 65 and older age group with the licensure. In other words, will the supply of 60µg for the older persons affect the supply for those persons under 65 years of age?

Dr. Greenberg responded that because this is the launch year for the vaccine, he did not think that supply would be an issue.

Dr. Hosbach (sanofi pasteur) added that in terms of the overall influenza supply, sanofi pasteur anticipates providing more vaccine than provided last year. That will be dependent upon the reservations accepted as well as the performance and yield of the strains. They fully anticipate being able to supply more of the regular vaccine as well as, including this additional vaccine.

Dr. Baker noted that the motivation behind her questions was that it was hypothesized that running out of preservative-free pediatric vaccine was due to the redirection of sanofi pasteur's efforts toward H1N1.

Dr. Hosbach responded that he did not believe this was the case, and that sanofi pasteur achieved all of its numbers in terms of commitments for influenza vaccine supply in the US last year. He did not think they ran out. There was probably greater demand for some of the 0.5mL product than anticipated. He thought they still had 0.25mL pediatric left over.

Dr. Baker replied that this was very bad.

Dr. Sawyer pointed out that they now had the wonderful problem of yet another influenza preparation. Given that there are now at least 15 products, there will inevitable confusion in the refrigerator. As they learned this season, some people received 2 doses of H1N1 and no doses of seasonal and vice versa. With that in mind, he wondered whether sanofi pasteur had any experience with the High-Dose product in younger individuals, including children, in terms of what might happen to someone with a more robust immune system if they receive this vaccine.

Dr. Greenberg responded that High-Dose vaccine has not been administered to individuals under 65 years of age, but he reflected on what happened with other seasonal and pandemic H1N1 vaccines in younger individuals. For all manufacturers, there was a very robust antibody response to the California 7 H1N1 vaccine antigen. In fact, in the clinical trials that were conducted, higher doses (30 µg) were administered to children and young adults. To his knowledge, there has never been any evidence increased adverse reactions with a robust antibody response.

Dr. Keitel noted that while this specific High-Dose vaccine has not been studied in younger people, there certainly are a number of clinical trials assessing high dose influenza vaccines. Doses up to 425 µg of HA have a higher injection site reaction, but have been well-tolerated. She asked whether there were any data regarding how many of the people in the study were vaccinated previously and if so whether they were they stratified according to prior receipt of vaccine before randomization, and whether the endpoints were analyzed according to prior receipt of vaccine.

Dr. Greenberg replied that analyses were not the analyses were not stratified by vaccination background information. This was done in-season, so prior vaccinations would have been received a full year or longer before the study. Some studies have shown decreased response when an individual had been vaccinated within a few months prior to their vaccination.

Dr. Meissner inquired as to how much more the High-Dose Fluzone® would cost than regular Fluzone ®.

Dr. Hosbach replied that the list price for High-Dose Fluzone® will be $25 for the single dose, non-preserved syringe. This is about twice the amount of the syringe-based product, with 4 times the amount of antigen. Percentagewise, the cost is about double.

Dr. Meissner found this to be significant, but Dr. Baker pointed out that part of this is due to the use of prefilled syringes.

In the absence of any efficacy data, Dr. Meissner wondered whether sanofi pasteur had any assays of functional antibody. He also wondered whether there were any data on decay of antibody, given that adults tend to lose their antibodies more rapidly.

Dr. Greenberg responded that for the Phase III clinical trial, they used the hemagglutinin inhibition (HI) antibody assay. Neutralization tests were done in the early Phase I study, which neutralization assay results showed significantly higher responses with High-Dose compared to Standard-Dose. They did not collect long-term antibody data. Blood was not collected beyond one month post-vaccination. Based on what is known with Standard-Dose vaccines, protection is provided throughout the season. Certainly, he would expect no less from this vaccine. If antibodies decay at a similar rate, there would likely be a season of higher titers with High-Dose than with Standard-Dose, but that is speculation since there are no specific antibody data.

Thinking about the rapid increase in mortality in those over 80 years of age, Dr. Judson inquired as to the overall goals in terms of quality of life and worthwhile life expectancy in simply preventing influenza.

Dr. Plotkin protested the question.

Regarding efficacy or functional antibody, Dr. Dubin (GSK) reported that GSK is developing an adjuvanted vaccine, which is a different approach to try to improve efficacy in individuals over 65 years of age. Because there is no accepted correlate of protection in the 2008 / 2009 season, GSK initiated an efficacy study that has enrolled over 43,000 subjects who are now being followed through two influenza seasons. GSK looks forward to being able to share the results of that trial, once they are analyzed, hopefully in the near future.

Dr. Foster (APhA) wondered whether, if ACIP made a full recommendation, there would be ample supply to cover all elderly people.

Dr. Hosbach (sanofi pasteur) Replied that in terms of their supply, he did not believe they were anticipating some sort of preference for this vaccine. However, if that were to occur, they would have to adjust their thinking and report back to ACIP whatever they believe they can accomplish.

Dr. Schmader (AGS) noted that most elders, even when demented, would not like to have influenza. Routine immunization programs are used in nursing homes throughout the country. Along that line, it is known that the health of older adults is quite heterogeneous. He assumed that in the immunogenicity studies, most of the individuals were community-dwelling elders who are independent and are not frail or functionally impaired.

Dr. Greenberg responded that this was correct. These studies were all conducted in physicians' offices. While the participants could have had a host of underlying medical conditions, they were ambulatory.

With that in mind, Dr. Schmader (AGS) suggested that it would be important to know the performance of the High-Dose vaccine in a large segment of older adults who are frail and complex.

Dr. Greenberg replied that the studies were not targeted in long-term care facilities or nursing homes, but this is an area that sanofi pasteur is interested in and would like to explore.

Having spent a great deal of her career working on a vaccine that will never come to fruition, and understanding GMCs, GMTs, and the data this hides, Dr. Baker asked what percent of these individuals had titers less than 1:40 post-immunization with the 60 µg dose. She was thinking that this would be a heterogeneous group and that age would not necessarily tell them who has true senescence.

Dr. Greenberg responded that 10% had titers less than 1:40 against H1N1, 1% for H3N2 , and 21% for the B strain one month after immunization.

Following up on Dr. Sawyer's earlier remarks about potential medical errors, Dr. Lett inquired as to how different the labeling and packaging would be for the High-Dose. She wondered if FDA was more mindful about this after H1N1, given the difficultly in differentiating between the seasonal and the H1N1 formulations of a manufacturer.

Dr. Greenberg replied that the packaging is distinct and that the plunger is a different color for the High-Dose. Dr. Hosbach added that 65+ is shown in very large font on the front.

Dr. Temte inquired as to whether CMS would consider High-Dose to be a routine influenza vaccine that would be covered under Medicare in the same way that seasonal vaccine is covered.

Ms. Murphy (CMS) responded that she works in Medicaid and could not speak for Medicare. She indicated that if someone would email the question to her, she would be happy to find an answer.

Dr. Hosbach (sanofi pasteur) added that they have been engaged in conversations with CMS and have provided them with all of the information they need. It is fully anticipated that the High-Dose vaccine will be covered under Medicare.

Dr. Schaffner (NFID) asked what the age distribution was of the people in this trial.

Dr. Greenberg responded that the GMTs are stratified by age. Of 65 through 74 year olds there were 1648 in the High-Dose group; in the 75 through 84 years of age group there were 779 in the High-Dose group; and in the 85 years of age group there were 117 in the High-Dose group.

Dr. Schaffner (NFID) inquired as to whether there were any plans to investigate this vaccine in those younger than age 65 who might also have immunocomprising conditions.

Dr. Greenberg indicated that the licensure request just came a couple of months ago, so sanofi pasteur is currently highly invested in and spending a lot of time on the efficacy trial. However, they are open to and would be interested in studying populations under 65 who are immunocompromised. They welcome investigator proposals, and will review them to determine whether they could support them.

Influenza Vaccine Workgroup Discussions and Recommendations November 2009-February 2010

Anthony Fiore, MD, MPH
Influenza Division, NCIRD, CDC

Dr. Fiore began by thanking the members of the work group, particularly given that this past season has been an enormous challenge. Everybody stepped up and attended the much more frequent calls, engaged in numerous telephone discussions, and addressed many emails. He especially expressed gratitude to his Chairperson, Dr. Neuzil.

The Influenza Work Group engaged discussions during scheduled teleconferences twice per month, and through on-going e-mails and ad hoc discussions in between the teleconferences. The major topics this group addressed over the past several months pertained to updates on and the response to the pandemic, with a focus on the implications of the pandemic for the upcoming seasonal influenza vaccine recommendations. The group discussed vaccine coverage, the immunization program, and the safety and immunogenicity of the 2009 H1N1 vaccines. Their second major topic regarded vaccine recommendations for the upcoming influenza season. In the proposed 2010–2011 season recommendations, there are new vaccine strains in the vaccine as determined by WHO and FDA over the past few days. There are new age indications and formulations for some of the currently licensed vaccines, which is good news. There is also the newly licensed vaccine, Fluzone® High-Dose trivalent inactivated

vaccine. The work group has particularly focused on which children should receive two doses, and whether there should be a universal recommendation for adults.

The overall objectives for 2009 H1N1 vaccine safety monitoring that were developed before the vaccine was rolled out were as follows:

- Identify clinically significant adverse events following receipt of 2009 HINI vaccine in a timely manner
- Rapidly evaluate serious adverse events following receipt of 2009 H1N1 vaccine and determine public health importance
- Evaluate if there is a risk of Guillain-Barré syndrome (GBS) associated with the 2009 H1N1 vaccine
- Communicate vaccine safety information in a clear and transparent manner to healthcare providers, public health officials, and the public

As part of this, the H1N1 VSRAWG was formed and reported to NVAC. Its purpose was to conduct independent, rapid reviews of available federal immunization safety monitoring data for the 2009 H1N1 influenza vaccines. It was comprised of 8 members from various federal advisory committees, the IOM, and the public. VSRAWG met every two weeks and reported to NVAC. Other federal agencies (e.g., BARDA, CDC, DoD, FDA, HIS,VA and NVPO) contribute scientific expertise and data, and NVPO coordinates these activities [Acknowledgment: Claudia Vellozzi and colleagues Immunization Safety Office].

Reports have been submitted to NVAC approximately every month. The last report available is from January 20, 2010 from which Dr. Fiore shared the following quote:

> "Working Group concluded that the data are adequate to assess the presence or absence of a signal. Additionally, the Working Group concluded that the data do not favor a signal between the outcomes examined and the H1N1 vaccines. A signal is defined as an event that could be temporally occurring more often after vaccine receipt than anticipated by chance alone."

This is good news, and additional good news is anticipated in the next report to the NVAC due to be submitted within the week or two following this ACIP meeting [January 20, 2010 (next update available Feb 26, 2010); available at http://www.hhs.gov/nvpo/nvac/reports/2010vaccinesafetyreport.html. Acknowledgment: Claudia Vellozzi and colleagues Immunization Safety Office].

In terms of the immunogenicity of influenza A(H1N1) 2009 monovalent vaccines, after 1 dose, hemagglutinin inhibition (HI) titers considered to be protective (≥40) develop in 93% to 98% of older children and adults; 72% to 93% of children 3 years through 9 years of age; and 45% to 92% of children ages 6 months through 35 months. After 2 doses, >90% of infants and young children develop antibody response considered to be protective [Data sources: Greenberg N Engl J Med 2009; Nolan JAMA 2009; Plennevaux Lancet 2009; Arguedas NEJM 2010]. The work group concluded that the safety profile appears to be similar to seasonal vaccine based on the data thus far, and that the immunogenicity is similar to or better than the seasonal vaccine in all age groups.

The second the work group addressed was the recommendations for the upcoming influenza season. As reported earlier, the vaccine strain recommendations for 2010-2011 seasonal influenza vaccines is as follows [FDA. Vaccines and Related Biological Products Advisory Committee meeting, February 24, 2010]:

- An A/California/7 2009 (H1N1)-like virus
  - → Same strain as in the 2009 H1N1 monovalent vaccine

- An A/Perth/16/2009 (H3N2)-like virus
  - → New strain for N Hemisphere vaccine
  - → Same strain as 2010 S hemisphere seasonal vaccine

- A B/Brisbane/60/2008-like virus
  - → No change from last season

New seasonal influenza vaccines and age indications include the following:

- Newly licensed standard dose vaccine
  - → Novartis: Agriflu (18 years and older)

- New age indications
  - → CSL: Afluria (6 months and older)
  - → GSK: Fluarix (36 months and older)

- New higher dose inactivated vaccine
  - → Sanofi: Fluzone High Dose (65 years and older)

With regard to the new Fluzone® High-Dose by sanofi pasteur, the Influenza Vaccine Work Group agrees that compared to standard dose inactivated vaccine, Fluzone® High-Dose has equal or superior immunogenicity. While there was a slight increase in local reactogenicity among seniors, these reactions were mild and self-limited. Licensure expands options for adults 65 or older. Persons 65 years or older and their providers can choose any of the currently licensed inactivated vaccines, including Fluzone® High-Dose. A pivotal vaccine effectiveness trial of High-Dose versus Standard-Dose is underway.

So for the 2010 – 2011 vaccine recommendations for young children, Dr. Fiore described some of the discussions held by the influenza vaccine workgroup regarding vaccination of children ages 6 months through 8 years.

No changes are proposed for the 2010-2011 influenza vaccine recommendations for children ages 6 months through 8 years. These currently are as follows:

- All children aged 6 months through 18 years should be vaccinated annually

- Children and adolescents at higher risk for influenza complications should continue to be a focus of vaccination efforts, including those:
  - → aged 6 months through 4 years;
  - → who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, cognitive, neurological, neuromuscular, hematological or metabolic disorders (including diabetes mellitus);
  - → who are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus);
  - → who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
  - → who are receiving long-term aspirin therapy who therefore might be at risk for experiencing Reye syndrome after influenza virus infection;
  - → who are residents of chronic-care facilities; and
  - → who will be pregnant during the influenza season.

  Note: Children aged <6 months cannot receive influenza vaccination. Household and other close contacts (e.g., daycare providers) of children aged <6 months, including older children and adolescents, should be vaccinated.

With respect to the number of vaccine doses for children ages 6 months through 8 years old, previous studies indicate that children <9 years old should receive 2 doses in the current season if they have never received trivalent vaccine before; or if they only received 1 dose last season and it was the first time they had ever been vaccinated. Children <9 years old who have been vaccinated in a year before last season (e.g., 2008-09 or before) receive 1 dose annually. The need for two doses is believed to be due to the need for a priming dose followed by a booster. Many children <9 years old lack previous experience with influenza or influenza vaccine. Seasonal vaccine coverage among young children is low (<25%). Many, perhaps most, young children enter each season recommended for 2 doses because they have never been vaccinated.

For the upcoming influenza season, the 2009 H1N1-like virus is expected to continue to circulate. Thus, the question remains with respect to how many doses of the 2010-2011 seasonal vaccine a child should receive who did not receive any of the monovalent vaccine doses. Following considerable discussion over the past few weeks, the work group concluded that at this point, they do not recommend a changed in the current recommendations. The reason for this decision is that it is not urgent to make a decision at this time. Most children are not affected because they are either due for two doses anyway or received monovalent vaccine(s). More data to inform the decision likely to be available within 3 months include additional analyses from the immunogenicity studies, updated monovalent and seasonal vaccine coverage data, the potential for additional seroprevalence and epidemiologic data, and the potential for a decision analysis approach. This allows more time for additional work group discussion and, if needed, a vote during the June 2010 ACIP meeting and to harmonize these issues with CDC's partners.

Regarding the 2010-2011 influenza vaccine recommendations for healthy adults 19 through 49 years old, an estimated 50% already have an indication for annual vaccination, including the following:

- Women who will be pregnant during influenza season and their contacts

- Persons who are contacts of
  - → Children younger than 5 years old
  - → Adults 50 and older
  - → Children and adults with chronic medical conditions that confer higher risk of influenza complications

- Healthcare workers

There has been a longstanding permissive recommendation for "Anyone who wants to be vaccinated." Nevertheless, there has been low coverage among 19 through 49 year olds regardless of their indication for vaccination. Healthcare worker coverage has also been low. There is some evidence that coverage is low among persons who are contacts of high risk persons, and coverage of pregnant women has been notoriously low in the 15% to 20% range for many years. At this point, only about 15% of the population does not have an annual indication for vaccination. Conversely, 85% of the population has an annual indication.

Over the past several months, the work group has considered a number of critical factors regarding expanding the annual vaccination recommendations to include all adults ages 19 through 49 that were raised during the October 2009 ACIP meeting, including: vaccine supply (excess vaccines in recent seasons), vaccine safety (severe adverse events are rare in young healthy adults), vaccine effectiveness (50% to 90%, depending on match / season), disease burden (lower burden of hospitalizations and deaths compared with older adults / young children; similar to adolescents; estimated 0.5 to 2.5 days work lost per illness), cost-effectiveness (unlikely to be cost-saving; $/QALY and $/illness averted are influenced by vaccination cost / administration venue—most expensive in physician offices, work loss estimate; similar to costs for older adolescents), feasibility (no VFC equivalent; potential for workplace interest), acceptability, and implementation [Source: Workgroup Discussions May through September 2008].

Acceptability continues to be a poorly understood factor of why people in this age group do not get vaccinated. Studies indicate that lack of concern about influenza risk and excessive concern about vaccine safety are primary reasons for adults not getting vaccinated among those currently recommended for vaccination, including health care workers. More information is needed on what could better inform adults who are reluctant to be vaccinated. Many adults with a vaccine indication do not know they should be vaccinated. With respect to timing, there were some rapid recommendations changes (including the childhood universal indication voted in that year) and persistent low coverage in all recommended groups except the elderly. There was some concern that focus might be lost on those at higher risk for complications.

The work group was also looking forward to some preliminary evaluation of expansion to school-aged children needed. No change was proposed in the recommendations for healthy adults ages 19 through 49 in October 2008, which were as follows:

- ❑ No change in recommendations for healthy adults ages 19 through 49 year old at that time

- ❑ Continued support for routine vaccination of contacts of persons at risk for influenza complications, including healthy adult contacts of:
  - → Persons 50 years old or older
  - → Persons younger than 5 years old
  - → Pregnant women
  - → Persons with chronic medical conditions

- ❑ Continued support for permissive recommendation: any healthy adult who wants to be vaccinated should be vaccinated

With regard to why the work group was raising the issue of vaccination recommendations for healthy adults ages 19 through 49, the primary impetus was the issues raised by the 2009 H1N1 pandemic. During the 2009 H1N1 pandemic, an estimated 87% of hospitalizations and deaths were among those <65 years old, including many among 19 through 49 year olds. There was an unprecedented demand for seasonal and 2009 H1N1 monovalent vaccines. Many new immunization programs were instituted that vaccinated adults. The 2009 H1N1 vaccination was targeted for 19 through 24 year olds during the time of limited vaccine availability. The 2009 H1N1-like virus is likely to continue circulation in the 2010-2011 season. The proportion of healthy adults now immune to the 2009 H1N1 pandemic virus is unknown. The 2009 H1N1-like virus will now be in 2010-11 seasonal vaccines. There is a possible new or newly recognized medical risk factor for influenza complications of obesity / morbid obesity. There were a disproportionate number of obese, particularly morbidly obese, patients among the severely ill during the 2009 H1N1 pandemic. This was found to be an independent risk factor for severe illness in one unpublished analysis. Most (60-80%) obese or morbidly obese with influenza complications (hospitalization or death) had chronic medical condition(s). In the US adult population, 28% of adults are obese and 5% are morbidly obese.

Another observation was that influenza-related complications differed by race / ethnicity African-Americans and Hispanics experienced higher hospitalization rates. American Indians and Alaska Natives had a four-fold increased mortality compared with other racial and ethnic groups during 2009 pandemic in 1 study [*MMWR* Dec 2009]. The reasons for the differences are uncertain but might include differences in prevalence of underlying medical conditions and obesity, differences in medical care, and / or race / ethnicity based differences in influenza pathogenesis. These differences require further study.

Based on the information available and the work group discussions, the work group considered the following 5 options for the influenza vaccine recommendations for adults 19 through 49 years old:

1. No change

2. Add new possible risk factor indications

3. Provisional new risk factor indication(s) for 2010-11 season; re-evaluate later

4. Provisional universal recommendation for 2010-11 season; re-evaluate later

5. Universal recommendation: Two sub-options
   a) Full implementation immediately in 2010-11, or
   b) Phase-in: 2 stage as was done for universal childhood recommendation
      1) Begin vaccinating all adults in 2010-11 season where feasible, with special efforts to reach adults with newly recognized risk factors
      2) Full implementation 2011-12 season

The work group discussed this on several calls and voted amongst themselves to determine where they stood. No one favored the status quo (e.g., no change), incremental addition of new risk factor indications, or provisional recommendations. All favored advancing to a universal recommendation, with the discussion focused on immediate implementation versus phased in implementation over two influenza seasons. The rationale for a recommendation to vaccinate all people ages 6 months or older included several considerations. Annual influenza vaccination is a safe and effective prevention measure that provides a potential benefit for people in all age groups. Morbidity and mortality occurs in all age groups, including among adults aged 19 through 49. Some persons who have influenza complications have no previously identified risk factors, or have risk factors but are unaware that they should be vaccinated. A recommendation that all people ages 6 months or older receive an annual influenza vaccination eliminates the need to determine whether each person has an indication for vaccination; emphasizes the importance of preventing influenza across the population spectrum; and reduces potential barriers to increasing the number of persons protected from influenza, including lack of awareness about vaccine indications among persons at higher risk for influenza complications and their close contacts.

While a universal vaccination recommendation for adults would be proposed, in order to maintain emphasis on those at higher risk for influenza complications, the work group also proposed to include last season's recommendation for those at higher risk of complications from influenza, which reads as follows:

- Certain people should continue to be a focus of vaccination efforts, because they are at higher risk for influenza complications, or are close contacts of persons at higher risk, including:
  - → children aged 6 months through 4 years
  - → adults aged ≥50 years;
  - → women who will be pregnant during the influenza season;
  - → persons who have chronic pulmonary, cardiovascular, renal, hepatic, neurological, neuromuscular, hematological or metabolic disorders;
  - → persons who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus);
  - → residents of nursing homes and other chronic-care facilities;
  - → health-care personnel;
  - → household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months; and,

Emphasis will also be placed on possible new risk factors for influenza complications, with the following language proposed:

- Preliminary data indicates that certain persons had higher rates of influenza-related complications such as hospitalizations or deaths during the 2009 pandemic. The cause(s) of this increased risk for influenza complications is under investigation, but likely includes an increased prevalence of medical risk factors in these persons. Medical risk factors might be present but not known to the patient or provider. Immunization providers and programs should emphasize vaccination for these persons as well as those with known medical risk factors:
  - → Adults who are obese (BMI≥30), particularly those who are morbidly obese (BMI≥40)
  - → Adults who are African American, Hispanic, American Indian, or Alaskan Native

The following options were proposed for a vote for a universal recommendation:

- Option 1: Vaccinate all adults beginning with the 2010-11 season.

- Option 2: Annual vaccination of all adults should begin in September or as soon as vaccine is available for the 2010-11 influenza season, if feasible, but annual vaccination of all adults should begin no later than during the 2011-12 influenza season.

Work group members who favored phased in approach believed the approach was effective for the childhood universal recommendation. They were concerned that immediate implementation would create new additional demands on programs with insufficient notice. They were also concerned that vaccine pre-booking had already occurred and might lead to demand exceeding supply for some providers and programs. Those who favored immediate implementation believed that because 2009 H1N1-like viruses would likely continue to circulate in 2010-11, they would continue to cause increased morbidity among young adults, including those who do not currently have a vaccine indication. They were troubled by the phase-in approach because it does not fully address the problem that persons at risk may not self-identify until 2011-12. They were also concerned that such an approach would add complexity, and that it would not fully take advantage of opportunities created by programs developed during the pandemic, and new interest in vaccination among younger adults.

Discussion

Dr. Baker inquired as to whether Dr. Fiore had information regarding how many people ages 19 through 49, either by occupation or parenting, are around infants less than 6 months of age and how many obtain influenza vaccine. A cocoon has been recommended for years for those babies who cannot be vaccinated. Many of the parents are in this age group, but it is not clear that they even know that they should be immunized for influenza.

Dr. Fiore replied that it would be somewhat hard, particularly before this season, to identify some of the contact indications. As he recalled, Dr. Singleton's data showed coverage of 20% to 25%, which is striking because that was a sub-prioritization group that was recommended for vaccination from the outset.

With regard to communications if a universal recommendation is made, Dr. Baker suggested that this those in this age group who are around infants under 6 months of age should be targeted to motivate them to get vaccinated to help protect these young children.

Dr. Lett reported that the Association of Immunization Program Managers (AIPM) conducted a survey to determine Program Managers' beliefs about these options. Though not unanimous, there was fairly overwhelming support for Option 2 (75%). A number of Program Managers submitted comments about their concerns. There has been a lot of success with H1N1, but there was a lot of infrastructure funding available to support that success in terms of payment for vaccine administration and the vaccine itself being free. This type of funding will not be available in the future, and if there is not support in the private sector for this beyond what can be reimbursed, it is going to place burdens on the public sector. Many state and county health departments purchase and provide a lot of influenza vaccine for adults. Pre-booking has occurred, and most Program Mangers are concerned that the supply will not be sufficient to meet the demand. They are skeptical that if supplies are not sufficient to meet the demand or that there is another delay, ACIP should at least have a back-up of prioritization should that occur. A number of groups have plans to use what resources they do have to purchase vaccine for school-based immunization efforts this season. However, a considerable amount of support will still be needed for training and vaccine administration.

Ms. Ehresmann added that in an ideal world in which an adult vaccine infrastructure already existed, implementing a universal vaccine could be done immediately and likely with few challenges. However, because it is not an ideal world, she thought they needed to make the decision to move forward on universal vaccination in the absence of that, but her hope was that with this type of recommendation and in light of all of the other recommendations that ACIP has made for adults, that this will start to drive funding and emphasis for formal adult vaccination programs. One of the questions in their background documents was: We have made these recommendations for adults. Why are they not happening? While she did not think federal and state programs were a panacea, some they are the glue that is needed to coordinate these programs. In the absence of that, it is difficult to be successful. She wanted to acknowledge what Program Managers have said, but also wanted to use this as a platform to promote the idea of moving toward a stronger adult program once the vote is made. Some Program Managers did believe that universal vaccination could move forward immediately. In some ways, with H1N1, they had a painful but good year in which they reached out to providers they had not worked with in the past. They should build on that going forward.

Dr. Judson took the other side for Option 1. He thought they had practiced creeping and staging for the last 10 to 15 years, and if there was any evidence that enhancing or enlarging the group for whom vaccines were recommended detracted from achieving other goals of previously recommended target groups, then it would be a reasonable argument to select Option 2. Or, if there were any evidence that clearly and consistently demand was exceeding supply, they would have to consider Option 2. There are now a large number of suppliers with ample capacity to produce a large number of vaccines; therefore, supply is not likely to be a long-term, consistent problem. There are only 15% of people for whom influenza vaccine is not recommended. From an administrative standpoint, it is often more costly and difficult to try to sort out the 15% for whom the vaccine is not recommended than to simply offer it to everyone. In speaking to people at Kaiser, this is the way they view it. H1N1 was great because they had an excess supply and they offered to everyone who came through their doors.

Dr. Baker clarified that her question about the percent of those 19 to 49 years of age who are around young children was to try to tease out what proportion of those people should be getting vaccinated.

Dr. Meissner reminded everyone that when ACIP made the phase-in recommendation for children, similar wording was utilized. There was very consistent feedback from pediatricians who had no idea how to interpret that sort of recommendation. Thus, they waited until the next year. Therefore, he favored Option 1.

Dr. Neuzil said she also strongly favored Option 1. She did not believe that waiting a year would solve the adult immunization problem. Therefore, they should move ahead. In recognition of the very practical challenge raised about pre-booking, she suggested to the manufacturers that they consider extending the pre-booking period. This has been a very exceptional year from which people are still reeling. The hope is that providers are still administering monovalent pandemic vaccine. That would be a wonderful gesture as they herald universal influenza immunization in this country to extend the pre-booking period.

Dr. Englund reported that their pediatricians welcomed the fact that they had a year to plan. Their hospital worked with community practitioners to set up evening and Saturday clinics. They got buy-in from practitioners to administer vaccination in the hospital away from the primary medical home. That helped them very much to prepare for the H1N1 outbreak. Given the administrative logistical issues, she favored Option 2.

Dr. Neuzil added that in adults this is already done. She got her vaccine at Safeway, and her oldest son got it in O'Hare Airport. Adults are much more comfortable with that already.

Dr. Pickering read Dr. Poland's (ACP) comments into the record, given that he was unable to attend. They were as follows: Our vote today is both historic and personally gratifying! Historic in that a universal recommendation for flu vaccine in all adults brings this into line with all other vaccines for respiratory viruses—that of universal use! Historic too in that we have moved over the many decades we have had this vaccine from very limited use, through the latest period of creeping incrementalism where nearly every year brought another indication, to finally recognizing the need for and simplicity of a universal recommendation. Personally gratifying in that I first began advocating for this 26 years ago! In these nearly 3 decades, I've given hundreds of talks on the topic and published these views in the peer-reviewed literature. An Olympic effort! All this reached a "tipping point" in the late 1990s and early 2000s when I was an ACIP member. At that time I introduced the idea, and called for a vote. There was mostly solid support for the recommendation, but concerns over vaccine supply. Over those intervening years, use of the flu vaccine in younger adults did not increase, and every year tens of millions of doses of vaccine went unused and wasted. Most of these concerns I would characterize as "trying to drive into the future by looking through the rear view mirror." I raised the issue again during Dale Morse's 2006-2009 tenure as Chair of ACIP, this time garnering more support as more recognized the significant morbidity of influenza in younger adults, significant loss of schools and work time and productivity, an adequate vaccine supply, and the desire by clinicians for a simpler and more practical approach. Dale vowed to get this passed before the end of his tenure. No one can easily recall the 20-some odd current indications that ironically cover all but 15% of the population already! So thank you! Thank you on behalf of the physicians and professional societies who take care of and who advocate for the health of adults. Now the word needs to go out—without ambivalence—that influenza is a serious infection, it can be prevented safely and effectively by vaccine, and the vaccine is recommended for ALL! FINALLY!

Dr. Foster (APhA) reported that when pharmacies first began administering vaccines about three years ago, the statistics were that pharmacies administered about 7% of the vaccines. This year they administered 10% even though they did not receive vaccine until late in the season. He thought if pharmacy had access, they already have the infrastructure to increase adult immunization. Most of the adults in this age group do not present to physicians anyway. Most of them are seen in emergency departments (ED), so if they could increase the rates of vaccines administered there, that would be beneficial as well. When pharmacies turned people away this season because they did not have vaccine, they did not return later to acquire the vaccine. They could not give the vaccine away after that point. He knew of one facility that would soon be throwing away 300 doses because it would expire March 1. Therefore, he highly encouraged voting for Option 1.

As Co-Chair for the Vaccine National Influenza Summit, which is an organization that represents about 130 national partners in influenza, Dr. Tan (AMA) reported for the record that in 2005 the Summit voted on this and urged that ACIP move toward a universal recommendation as soon as possible.

Dr. Sawyer commented that he is the ACIP member who sits on the NVAC Safety Committee that is reviewing H1N1 safety. As reported earlier, there has been absolutely no signal to data to raise any concern. They should take this opportunity to assure the public that in the coming season that at least that component of the vaccine is very safe. He also supported Option 1 for this and all of the other reasons stated in favor of this option.

Dr. Fryhofer (ACP) also agreed with Option 1 for the reasons that had been mentioned. She is also a practicing physician, and she thought this would be much simpler. With Option 1, physicians will not have to figure out who can receive vaccine now, who has to come back later, et cetera and there is typically vaccine left over. By voting for Option 1, they can protect everybody.

Dr. Turner (ACHA) also expressed support for Option 1. He thought it tragic that for the last couple of years millions of doses of unused influenza vaccine have been thrown away. He heard earlier that 21 million doses of H1N1 vaccine were sitting in a warehouse currently. He pointed out that the manufacturers had “stepped up to the plate” and delivered supply, and that they needed to create demand. In due respect to the providers worried about not having the infrastructure, the way to build infrastructure is to create demand. If there was unmet demand, they could probably argue with their financial supporters that more infrastructure is needed.

Ms. Ehresmann inquired as to whether there were any data regarding how much of the seasonal influenza vaccine was utilized. With the universal recommendation, she wondered if they would continue in a shortage situation to revert to using priority groups from the past or maintain a universal recommendation.

Dr. Baker replied that all of the seasonal vaccine was utilized.

Dr. Fiore responded that they could describe how much vaccine was distributed, but they lose track of the ability to know whether vaccine was actually all utilized once it was out. Certainly, seasonal vaccine supply was tight at one point in the Fall due to the demand generated by the pandemic. He heard of vaccine availability in the last month or two that he assumed would go unused. He thought less would be thrown away this season than in the past. In terms of what would occur in a shortage, Dr. Fiore thought they would probably revert to the priority groups discussed during the 2004-2005 shortage. However, this would depend upon the formulations

for which there were shortages and would have to be addressed at the time they became aware of a shortage.

Dr. Schuchat added that they are basically virtually out of seasonal influenza vaccine.

Dr. Baker reminded everyone that in the shortage year, high demand was created, but millions of doses were ultimately thrown away.

Dr. Morse stated that approximately four years ago as a rookie or novice ACIP member, he had the humbling experience of being on the wrong but arguably the right side of Greg Poland who made an unexpected, unscripted, but passionate motion to by-pass a phase-in approach and go directly to a universal recommendation for influenza recommendation. As he recalled, Dr. Morse was sitting where Dr. Sumaya was sitting today when the vote reached him 6 to 2 or 7 to 1 in favor and he felt obligated to vote "no" and there ended up being a 7 to 8 vote against the motion. Dr. Morse voted "no" not because he did not support the concept, but because he was concerned that there had not been an adequate scientific base vetting of the proposal. Coming on the heels of the vaccine shortage of 2004-2005, he also felt that without careful planning there could be unintended consequences of vaccinating health individuals creating an iatrogenic shortage among high risk populations with accompanying increased morbidity and mortality. That day was the wrong place, the wrong day, the wrong time. However, the goal was the right one. Since then, ACIP has used scientific evidence to systematically inch closer to a universal recommendation. Based on that progress, two years ago in February 2008, as Chair Dr. Morse urged the ACIP Influenza Work Group to speed up the original proposed time table that stretched out until 2013 by continuing discussions and bringing back recommendations with a vote within a year, hoping that the phased-in approach for universal vaccine, which began in early 2000 would be accomplished during his tenure and by the end of the decade similar to the US's previous success to reach the moon. The work group delivered the review as requested and provided sufficient science-based evidence to support such a recommendation as Dr. Fiore outlined earlier, but stopped short of a universal recommendation because of remaining feasibility and implementation questions. Dr. Morse's personal opinion was that during this session, a strong case for a universal influenza vaccination had been made stronger based on more complete science-based evidence and increased feasibility that came from the implantation experience during the 2009 H1N1 pandemic. While they still have not reached the levels of immunization that they would like, ACIP has the opportunity to build upon the momentum gained over the past year. They must remember that this is a marathon—not a sprint. As with smoking cessation programs, it will take persistent to make progress. If they could not make the case for universal influenza immunization now, when could they? Either Option 1 or 2 would get them to where they needed to be, but he favored Option 1 because it would get them there quicker. He initially leaned toward Option 2, but this would seem to ignore the potential for 2009 H1N1's return. The evidence for increased risk among certain populations (e.g., obese / morbidly obese; racial / ethnic groups) also warrants a stronger recommendation for the upcoming year. It would seem that Option 2 would first need to make a strong recommendation to add these high risk groups and phased-in encouragement for the rest, which would again add complexity to an already confusing picture. This is further complicated by what to do with the 19 to 24 year old age group. H1N1 is still circulating and a number of individuals in this age group are still not covered. When all of these groups are added together, the picture is almost completed anyway. Why not go for the gold instead of settling for the bronze. From his perspective, this was the right place, the right day, and the right time. It's Poland time. While such an accomplishment did not occur within his or Dr. Poland's ACIP tenure, given that the first expansion occurred in 2000 and this was 2010, on a

technicality the recommendation could still be successfully adapted within a decade. Dr. Morse concluded that "The goal and the moon are still within our reach. Let's grab it."

John Redd (IHS) indicated that the IHS supports universal adult recommendation and plans to implement it with great vigor. However, they wanted to point out that with either option, they would like American Indians / Alaska Natives included as a general high risk group which has great impact in settings of vaccine scarcity and for priority. He wanted to get this on the record because they have observed disparate impact for influenza in American Indians / Alaska Natives through the entire spectrum of disease (e.g., outpatient illness to death). In an *MMWR* report in December 2009, 12 states were discussed that are American Indian / Alaska heavy. These states included more than 50% of the American Indian / Alaska Native population in the country, so those data were considered to be very helpful. The disparities observed in the entire range of influenza illness have occurred in this past season despite quite good vaccination coverage through IHS. Their coverage ranged from approximately 23% to 24% for H1N1 for the monovalent vaccine to over 40% in the pediatric population (6 to 59 months). The disparity that impacted Native Americans / Alaska Natives is partially accounted for by the presence of risk factors for morbidity and mortality. However, there are no models in which disparities have been entirely accounted for by risk factors.

Regarding the percentage of people in the 19 to 49 year old age group, Lt. Col. (Dr.) Philip Gould (Office of the Air Force Surgeon General) reported that the Air Force has been tracking high risk groups for the last three years. This past season, seasonal influenza coverage as of the week before the ACIP meeting was approximately 30% for this with children and slightly higher at 40% for pregnant women. H1N1 was slightly higher by about 5% in both of those groups. Regarding whether they are in the 19 to 49 year old age group, these could also be family members in attendance of those small children as well. He can supply that breakdown to ACIP.

Kelly Moore (Tennessee Immunization Program) strongly supported Option 1. They would like to continue to sustain the momentum gained from 2009 H1N1, knowing that many in that age group were not vaccinated against 2009 H1N1 and remain at risk in the coming season from the same virus that has disproportionately affected them. They also understand that other states feel a greater degree responsibility than Tennessee does for covering adults, but many states' immunization programs are focused on the VFC-eligible population and are not in public health primarily responsible for meeting the needs of adults. Until Option 1 is vote on, there is nothing to present to legislators to argue for funding and infrastructure to meet those needs. These adults are unlikely to be vaccinated with an optional recommendation, unlikely to be seen in doctors' offices, and are still at risk from 2009 H1N1. With that in mind, Tennessee supports Option 1.

Steve Allred (GetAFluShot.com) added that another reason to favor Option 1 is that a major obstacle to increasing vaccinations in the US is insurance coverage. Many insurance companies have high deductibles, exclusions, or co-payments that apply vaccinations. GetAFluShot.com administers tens of thousands of influenza vaccinations in worksites every year. When influenza vaccination is covered by the insurance company, 2 to 4 times as many people participate in vaccinations than if people have to reach into their own pockets to pay for vaccine. A universal vaccination may not be a panacea, but it will put pressure on insurance companies, hopefully supported by other means as well, to eliminate this very important barrier to vaccination.

Dr. Baker said she thought that CDC and its many partners had done a wonderful job of communication this season with H1N1. The public is much better informed, and can continue to be much more informed about how serious influenza is, especially in young, seemingly healthy people. The previous week, she cared for a 140 kilo 12-year old who needed an MRI and could not fit in their machine. She was told by the child's mother that she was "just a big girl." Calculating BMI and helping people to understand this is another communication issue that could be very useful in a positive way. Dr. Baker congratulated CDC for the improved communication efforts, and emphasized the importance of building upon that.

Dr. Keitel inquired as to whether there could be any emphasis placed on encouraging monovalent vaccine, given that there is still in the warehouses.

Dr. Baker replied that this would probably not be a component of the vote, but they could discuss it further subsequent to the vote.

Motion: Universal Adult Influenza Vaccination

Dr. Sumaya made a motion to approve Option 1: Vaccinate all adults beginning with the 2010-11 season. Ms. Ehresmann seconded the motion. The motion carried with 12 affirmative votes, 1 abstention, 0 negative votes, and thunderous applause.

Discussion

Given the vote for universal influenza vaccination, Dr. Fiore indicated that Dr. Santoli's presentation and a VFC vote would not be necessary.

Regarding Dr. Keitel's suggestion pertaining to the vaccine remaining in the warehouses, Dr. Baker did not believe a vote was needed. The messaging from all partners and CDC has been to encourage / recommend continued H1N1 immunization. During the 1968 pandemic, Dr. Baker was infected and was quite ill during the third wave. Therefore, she thought it was too soon to know whether there would be more disease. That has been a very clear communization message from partner organizations, liaison organizations, and CDC.

Dr. Schuchat responded that CDC has been working with state health departments the CDC communications team to sort through the best way to message how vaccine should continue to be used. Key points are that the virus continues to circulate and illness, hospitalizations, and deaths continue although the rates of disease are lower than observed in the Fall of 2009. A lot is now known about the vaccine in terms of safety, which CDC believes will be reassuring to many. Continuing to make vaccine available and accessible to people makes a lot of sense. These are the components of CDC's key package of messaging they are trying to communicate.

Dr. Baker reminded everyone that work group meetings would begin at 6 PM. With no further business posed, she officially adjourned the first day of the meeting.

Day 1 : Public Comments

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

February 25, 2010

Welcome / Unfinished Business

Dr. Carol Baker
Chair, ACIP

Dr. Baker called the meeting to order and welcomed those present. She indicated that there was no unfinished business carried over from the previous day, and that while no public comment session was held during the first day because no one signed up, there would be a public comment session at the end of the presentations for the second day.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Anne Schuchat indicated that the next National Immunization Conference will be convened in Atlanta on April 19-22, 2010. She welcomed everyone to register for and attend that meeting. With regard to the stimulus program, the American Recovery and Reinvestment Act (ARRA), $300 million was designated for immunization strengthening. An innovative component of that funding is focused on strengthening the laboratory detection of vaccine preventable diseases. A series of training courses for public health laboratories have been on-going, with recent training for mumps and pertussis diagnostics. These courses have been extremely popular, well-received, and a great use of the one-time ARRA resources to help improve capacity. In addition, she noted that the members were provided with a small card at their tables. For years there have been discussions regarding challenges with provider / parent interactions pertaining to vaccines in terms of trying to better address parents' concerns and improve the office visit experience. CDC has been working with the American Academy of Family Physicians (AAFP), the American Academy of Pediatrics (AAP), and communication experts to develop a suite of materials that have been posted on the web and continue to be rolled out. She expressed her hope that everyone would offer feedback, and that they would make these tools known so that providers can address this important gap.

Centers for Medicare and Medicaid Services (CMS)

Linda Murphy reported on the status of the administration rates. The rates are under review, and had made it to the highest level at the time of this ACIP meeting. She expressed her hope that they would soon be published in the *Federal Register*.

Discussion

Dr. Chilton requested information regarding progress with respect to reimbursement for multiple component vaccines. The American Academy of Pediatrics (AAP) news included an article a few months ago stating that as of January 1, 2010 reimbursement will be based on the number of individual components in vaccines rather than on the number of vaccines per se.

Ms. Murphy responded that CMS did not make this determination; however, some individual states have determined that they are going to have a sliding scale of administration fees based on the number of antigens in the immunization. CMS has permitted this. The new schedule will still allow for this, but there is going to be more flexibility for states. CMS only states that if it is medically feasible to administer all antigens in one shot, they must do so. If providers are charging for three separate shots (MMR for example), they cannot do this. They can only charge for the one shot. Some of the states have said that single antigen is one amount, two antigens are $2 more, and three antigens are $3. CMS has also allowed this.

In response to Miss Murphy's comments, Dr. Katz indicated that he checked with Dr. Feinberg to be certain and learned that Merck no longer manufactures monovalent MMR.

Dr. Murphy thanked Dr. Katz for the update, clarifying that MMR was just an example that they had used for years.

LJ Tan, AMA announced that effective in 2011, there will be new Current Procedural Terminology (CPT) codes that will be based on the antigen content of the vaccine.

Department of Defense (DoD)

Dr. Wayne Hachey reported on the policy of mandatory immunization for all active duty members for both seasonal and pandemic flu vaccines. As of the previous week, the seasonal influenza coverage was 92% of DoD's population. For novel H1N1, their coverage rate was 82% and climbing. The DoD's Vaccine Safety Surveillance Network (VSSN) now has well over a million people enrolled. Like CDC, they have identified no increased signals. The Naval Health Research Center in San Diego, which was the first to identify the novel H1N1 virus, also has provided seed strain for next year's seasonal H1N1 vaccine component. Like their university colleagues, they had also noted, at least in the previous week or so, an increase in Influenza-Like Illness (ILI), although it was still well below the seasonal influenza threshold. It could be adenovirus or the predicted third wave of novel H1N1.

Department of Veterans Affairs (DVA)

Terri Murphy reported that the DVA's primary biosurveillance for tracking ILI is known as the Electronic Surveillance System for Early Notification of Community-Based Epidemics (ESSENCE). ESSENCE calculates the percent of all visits seen for ILI and compares the VA numbers to the CDC ILI-Net. In general, the VA trends have been comparable to those reported by CDC, except that they did not observe the large bump this past fall that was seen by the ILI-Net providers. For the 2009 H1N1 vaccine, the VA expanded its availability beyond the initial target groups to all patients and employees on December 23, 2009. As of February 15, 2010, they received approximately 1.6 million doses and vaccinated over 600,000 patients and about 132,000 employees. For seasonal influenza vaccine, their goals for 2010 are to vaccinate 75% of their patients over 50 years of age and 70% of their employees. Last year they succeeded in vaccinating about 69% of the patients age 50 to 64, 83% of those 65 and older, and about 64% of their employees without mandatory declination or mandatory vaccination.

Food and Drug Administration (FDA)

Dr. Wellington Sun offered brief highlights of the FDA's major approvals for 2009. There were 18 approvals, 10 of which were related to influenza. There were four original BLAs approved: one for Japanese Encephalitis (JE) vaccine, one for a booster dose of Hib (HIBERIX®), the new influenza vaccine from Novartis, and the second licensed HPV vaccine in the US with a new adjuvant (Cervarix®). There were also 4 concomitant Administration Efficacy Supplements, three of which were infant vaccinations and one of which was for the elderly. The FDA approved the pneumococcal conjugate vaccine, Prevnar 13™, for two indications: 1) invasive pneumococcal disease for all 13 serotypes; and 2) otitis media for the 7 common serotypes with Prevnar® for vaccination of infants 6 weeks to 5 years of age.

Heath Resources and Services Administration (HRSA)

Dr. Geoffrey Evans from HRSA was unable to attend due to inclement weather. However, he submitted a written report for the record, which was provided to ACIP members and read as follows:

National Vaccine Injury Compensation Program (VICP)
Summary of Current Issues

February 2010

V**ICP Thimerosal/MMRvaccine/Autism Litigation**

- In 2002, the Chief Special Master of the U. S. Court of Federal Claims ordered a process for adjudicating petitions filed with the National Vaccine Injury Compensation Program (VICP) alleging autism or autism spectrum disorder (ASD) from either the MMR vaccine, thimerosal-containing vaccines, or a combination of both. Most of these cases have been consolidated into the Omnibus Autism Proceeding (OAP).
- As of February 1, over 5,600 autism claims have been filed with the VICP, although the trend in filed claims has significantly decreased over the past year. Only 8 autism claims have been filed in FY 2010 versus 108 autism claims filed in FY 2009.

- Nearly 5,000 pending cases have been divided among the three presiding special masters. The remaining cases were either dismissed at the request of petitioners or dismissed by the Court because of jurisdictional issues.
- In 2007, Petitioners' Steering Committee (PSC) and the respondent presented testimony concerning the "general causation issue" for the first theory (a combined theory that both MMR vaccines and thimerosal-containing vaccines cause autism or ASD). The parties also presented evidence on the specific causation issue in three test cases for the combined theory.
- On February 12, 2009, three special masters issued decisions in the three test cases under the first combined theory. In each test case, the special master ruled in favor of respondent, concluding that petitioners failed to demonstrate that the combination of thimerosal-containing vaccines and MMR vaccines cause autism. Petitioners appealed all three test cases to a judge of the US Court of Federal Claims. On 7/24, Judge Wiese ruled in favor of HHS in *Hazelhurst*, Judge Wheeler ruled similarly in *Cedillo* on 8/6, as did Judge Sweeney, in *Snyder*, on 8/12. Notices of appeal to the US Court of Appeals for the Federal Circuit have been filed in *Hazelhurst* and *Cedillo*. The time period for filing a similar notice in *Snyder* expired. Federal Circuit decisions in the two test cases are not expected until late 2010 or 2011.
- In 2008, the Court heard testimony on the general causation issues for the second theory, that thimerosal-containing vaccines cause autism or ASD. Evidence in three test cases for the second theory was also presented. Decisions on theory two are expected in 2010.
- Petitioners are no longer pursuing the third theory (i.e., MMR vaccine alone causes autism or ASD).

Institute of Medicine Meeting

- The Institute of Medicine Committee to Review Adverse Effects of Vaccines continues work on assessing adverse events for varicella, influenza, hepatitis A, hepatitis B, meningococcal, human papilliomavirus vaccines and DTaP and MMR vaccines (in various combination). The latter four vaccines were added to the contract in the fall of 2009, and the working list of adverse events for the second four vaccines was posted on the IOM website and an announcement on the project listserv on December 2, 2009. The last public workshop was in August 2009, and additional open workshops will be scheduled later this year. The Committee's final report is expected in 2011.

Advisory Commission on Childhood Vaccines

- On December 3-4, the Advisory Commission on Childhood Vaccines held its 74th quarterly meeting in Rockville. Agenda items included reports from HRSA's Division of Vaccine Injury Compensation and the Department of Justice; reports from the Causation, Petitioners Payment and Outreach Workgroups; reports on the VICP outreach contract; reports from ACCV ex-officio members; and consideration of a Departmental proposal to add hepatitis A, trivalent influenza, meningococcal and human papillomavirus vaccines as separate categories in the Vaccine Injury Table. The ACCV voted unanimously in favor of the proposal.
- The ACCV will hold its next quarterly meeting on March 4-5.

Indian Health Services (IHS)

Dr. John Redd presented the report for IHS. He reported that most of their activity has pertained to novel H1N1. Early in the outbreak, they developed a system known as the IHS Influenza Awareness System, which is a new real-time data collection methodology. IHS is quite a widely distributed system. They are now receiving data, most of which are uploaded and updated on a daily basis, from over 500 sites around the county covering more than 60% of the visits to IHS. The first component assessed with this system is ILI. From that, they developed an ICD-9 (International Classification of Diseases, Ninth Revision) and temperature-based system for detecting ILI, which worked quite well. The data are generally completed for the previous influenza week ending Saturday at midnight by the close of business on the following Tuesday, so it is a rapid system. IHS observed a peak in the second wave around Halloween. Their general trends were very similar to the rest of the country in terms of the temporal associations. Also as part of that system, continuously updated data are collected on vaccine delivery for both seasonal and novel H1N1. They are approaching 250,000 doses of nH1N1. Approximately 70% of those doses have been documented to be delivered to people who are in one of the traditional high risk groups for novel H1N1. A very exciting effort in which IHS is involved is an active collaboration with the FDA. IHS is part of the Vaccine Safety Risk Assessment Working Group (VSRAWG) and have been collecting adverse events data following H1N1 and seasonal influenza vaccine administration. They have detected no signals to date. They are also receiving coverage data, including risk factor group data on novel H1N1 coverage.

National Institutes of Health (NIH)

No update provided.

National Vaccine Program Office (NVPO)

Dr. Mark Grabowski discussed two relevant new initiatives from the Secretary of Health, Howard Koh, who is also the Director of the National Vaccine Program Office (NVPO). Dr. Koh has created a new Office of Adolescent Health (OAH) with Evelyn Kappeler serving as the Acting Director. NVPO will be working with that office to assure that adolescent vaccination is on their agenda. Dr. Koh has also convened a new Viral Hepatitis Inter-Agency Working Group. John Ward of CDC is going to Washington to help with the start-up of that group. At this point, NVPO is completing an inventory of agency assets and activities involving hepatitis and, over the coming months, will develop a new HHS strategic plan on viral hepatitis prevention and care.

With regard to vaccine finance, a supplement on financing on childhood and adolescent and vaccines was published in the *Journal of Pediatrics* in December 2009, which arose out of an NVAC working group, with financial and technical support from CDC. This supplement contains original research, NVAC recommendations, and stakeholder comments. Dr. Grabowski shared a few copies of this publication.

NVAC also put forth a recommendation for all health insurance plans to voluntarily eliminate cost sharing with the administration of vaccines and requested the recommendation to be costed. NVPO has contracted with the National Opinion Research Center (NORC) to provide a comprehensive policy brief that will include a literature review, expert interviews, and a cost estimate. The cost estimate will be derived from combining National Immunization Survey (NIS) coverage data with the market scan database containing employer sponsored claims data. Also, providers have long voiced concerns over low reimbursement rates for purchasing

administration of vaccines. NVPO has contracted with Surveillance Data Incorporated to examine payment and reimbursement practices of providers who purchase and administer vaccines. Essentially, they will assess third party electronic claims data and identify billing trends such as time frame to be reimbursed; percent of claims that were paid, denied, or modified; and reasons for modified claims. This contract will produce a report and list by different variables such as geography and specialty type.

With regard to vaccine safety, the H1N1 Vaccine Safety Risk Assessment Working Group, the VSRAWG, has completed three reports to the NVAC. They have concluded that there are enough data to assess that no signals have been detected for H1N1. The NVAC Safety Working Group is writing a White Paper pertaining to what the optimal safety system ought to include to detect adverse events in a timely manner when they occur, and to improve public confidence. The first informational gathering meeting was convened in July 2009. Additional stakeholder meetings are being planned and a report is anticipated in September 2010.

In terms of communications, throughout the H1N1 pandemic, NVPO has convened weekly calls with agency communicators to discuss vaccine safety communications. Building on these lessons learned from flu.gov, this Interagency Communications Working Group will become the steering committee for a new cross-departmental website called vaccines.gov. In its first phase, vaccines.gov will be a consumer portal for HHS-related vaccines and immunization content. The site is scheduled to launch in the summer of 2010.

National Vaccine Advisory Committee (NVAC)

Dr. Gus Birkhead was unable to attend due to inclement weather. However, he submitted a written summary report of his slides for the record, which was provided to ACIP members and read as follows:

The National Vaccine Advisory Committee (NVAC) approved its 2009 State of the National Vaccine Program Report on February 4, 2010. This report reviewed recent activities of the National Vaccine Program Office and NVAC, as well as provided a framework of priorities for the NVAC in 2010. Following review of the most recent draft of the National Vaccine Plan currently under revision, as well as Institute of Medicine recommendations on the draft Plan, the NVAC provided a series of recommendations for the draft Plan. Regarding H1N1 influenza, NVAC continues to hold monthly meetings by teleconference to receive updates as necessary and to consider and vote on recommendations of the NVAC H1N1 Vaccine Safety Risk Assessment Working Group related to the ongoing Federal H1N1 vaccine safety monitoring programs.

Liaison Member Updates

National Medical Association (NMA)

Dr. Whitley-Williams reported that prior to the ACIP meeting, she was informed by her Executive Director that the NMA will be convening a consensus panel to assess management of infants with RSV in terms of RSV prophylaxis.

American College of Physicians (ACP)

Dr. Fryhofer reported that ACP is in the process of developing an adult immunization manual, about which they are very excited.

Dr. Poland was unable to attend. However, he submitted a written report for the record, which was provided to ACIP members and read as follows:

Our vote today is both historic and personally gratifying! Historic in that a universal recommendation for flu vaccine in all adults brings this into line with all other vaccines for respiratory viruses—that of universal use! Historic too in that we have moved over the 7 decades we have had this vaccine from very limited use, through the latest period of creeping incrementalism where nearly every year brought another indication, to finally recognizing the need for and simplicity of a universal recommendation. Personally gratifying in that I first began advocating for this 26 years ago! In these nearly 3 decades, I've given hundreds of talks on the topic and published these views in the peer-reviewed literature. An Olympic effort!

All this reached a "tipping point" in the late 1990s and early 2000s when I was an ACIP member. At that time I introduced the idea, and called for a vote. There was mostly solid support for the recommendation, but concerns over vaccine supply. Over those intervening years, use of the flu vaccine in younger adults did not increase, and every year tens of millions of doses of vaccine went unused and wasted. Most of these concerns I would characterize as "trying to drive into the future by looking through the rear view mirror."

I raised the issue again during Dale Morse's 2006-2009 tenure as Chair of ACIP, this time garnering more support as more recognized the significant morbidity of influenza in younger adults, significant loss of schools and work time and productivity, an adequate vaccine supply, and the desire by clinicians for a simpler and more practical approach. Dale vowed to get this passed before the end of his tenure. No one can easily recall the 20-some odd current indications that ironically cover all but 15% of the population already!

So thank you! Thank you on behalf of the physicians and professional societies who take care of and who advocate for the health of adults. Now the word needs to go out—without ambivalence—that influenza is a serious infection, it can be prevented safely and effectively by vaccine, and the vaccine is recommended for ALL! FINALLY!

American Medical Association (AMA)

Dr. Tan reported that the AMA has been working with state medical societies to conduct a vaccine safety state level program to educate physicians regarding vaccine safety issues along the lines of the card that Dr. Schuchat distributed. The next program will be in Portland, Oregon on March 8-9, 2010. They are already engaged with the regional chapter of AAP there as well. AMA conducts about four to five of these programs per year. The last program was in Tennessee. Kelly Moore was very involved in that. Dr. Tan also reminded everyone that CDC and AMA co-host the National Influenza Vaccine Summit, which will be held May 17-19, 2010 in Scottsdale, Arizona. The registration website is now live for those who are invited to attend.

Department of Health, United Kingdom (UK)

Dr. Salisbury mentioned that as a follow-up to a discussion the previous day, the UK will be switching from 7- to 13-valent pneumococcal conjugate vaccine as of the beginning of April 2010. They will do this as a seamless change from one product to the other. As the stocks of one expire, they will supply 13-valent. They are not changing the schedule or recommending any sort of catch-up program. These children will be switched during the course of immunization, apart from those who are in risk groups for pneumococcal disease, for those for whom they have recommended one additional dose at the first opportunity of a medical visit . They will also continue with a 2 + 1 schedule, given that the vaccine is licensed in Europe in that manner.

Healthcare Infection Control Practices Advisory Committee (HICPAC)

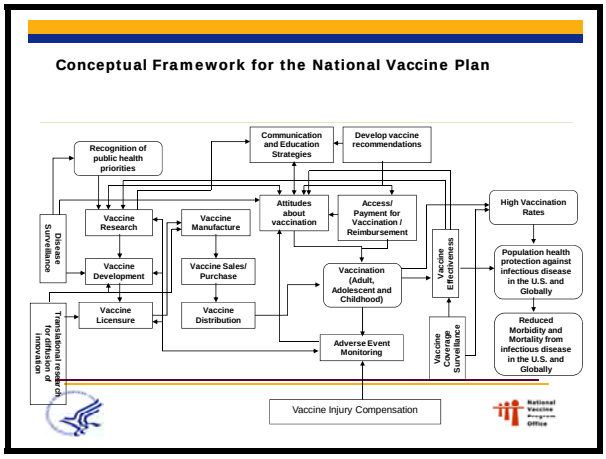
Dr. Elward reported that HICPAC is updating the *Occupational Health Guidelines* and will be harmonizing with the Health Care Personnel Immunization Work Group to coordinate that with ACIP.

National Vaccine Plan Update

Raymond A. Strikas, MD
Immunization Services Division
National Immunization Program
Coordinating Center for Infectious Diseases
Centers for Disease Control and Prevention

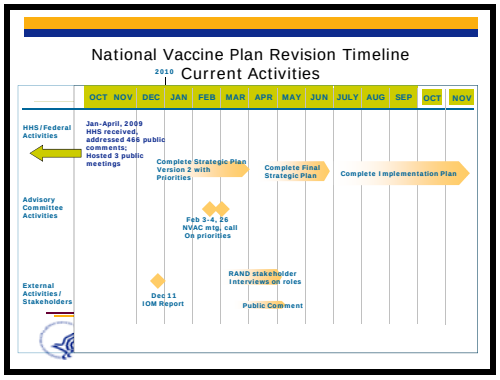
Dr. Strikas said he was pleased on behalf of NVPO and many other colleagues in the federal government to discuss the National Vaccine Plan (NVP). NVPO commissioned an Institute of Medicine (IOM) report titled *Priorities for the National Vaccine* Plan that was published December 11, 2009. His office was authorized to develop an NVP in the original legislation in 1986. That plan was issued in 1994. The original legislation called for annual updates to the plan; however, because this did not occur, the legislation was revised such that annual updates are not required. They began working on a revised plan in 2007. The first draft of that plan was issued for public comment in November 2008. They soon hope to have a second draft out. They envision a 10-year plan that extends through 2020 to be in concert with Healthy People 2020 objectives for the nation, which will include a number of immunization infectious disease objectives.

The following reflects the conceptual framework that has been developed for the National Vaccine Plan:



The 2008 Draft Strategic National Vaccine Plan includes the following goals: 1) develop new and improved vaccines; 2) enhance the safety of vaccines and vaccination practices; 3) support informed vaccine decision-making by the public, providers, and policy-makers; 4) ensure a stable supply of recommended vaccines and achieve better use of existing vaccines to prevent disease, disability, and death in the US; and 5) Increase global prevention of death and disease through safe and effective vaccination. The fifth goal was not included in the 1994 plan.

The following is a truncated timeline:



Not shown in the timeline is that the draft was issued in November 2008. Also not shown is NVAC's stakeholder meeting convened in February 2008, which led to work on the vision for the plan. NVAC is reviewing the IOM Expert Committee report. There are 5 goals, 36 objectives, and about 130 strategies. Consideration must be given to the most important achievements that must be made by 2020. Once NVAC is finished considering those achievements, or priorities, NVPO hopes to issue the plan publicly in early April 2010 for public comment, and then to subsequently complete the final strategic plan. The implementation plan must still be developed to include action steps, time tables, roles and responsibilities, et cetera. Work on the implementation plan is expected to begin in the summer of 2010 and to end by the end of the year. That will be done in concert with all of the stakeholders.

IOM worked on the plan beginning in 2008 through the end of 2009. They convened a series of public meetings beginning in 2008 to address each of the goals, which were as follows: Goal 4 (July 24, 2008), Goal 1 (December 1, 2008), Goal 3 (February 2, 2009), Goal 2 (April 14, 2009), and Goal 5 (June 4, 2009). As noted, the final report was issued on December 11, 2009 and can be found at the following site: http://www.iom.edu/Activities/PublicHealth/NatVaxPlan.aspx The IOM reported 20 priorities, of which 19 related to the existing Goals and Objectives in the draft strategic plan. Goal 6, regarding coordination in general, is an overarching recommendation. Selected recommendations from 12/11/09 IOM Report on Priorities for the National Vaccine Plan include the following:

- Goal 1 – Vaccine Development
  - Vaccine prioritization
  - Address non-infectious diseases' vaccines (not a priority for this office, but important to do)

- Goal 2 – Vaccine Safety
  - Develop prioritized research agenda for all federal agencies and stakeholders

- Goal 3 – Communications / Informed Decision-Making
  - Develop national communications strategy

- Goal 4 – Vaccine Supply and Use
  - Assure a stable vaccines' supply
  - Eliminate financial barriers to vaccination
  - Assume active role in national health information initiative
  - Assess national health reform outcomes' role in the Plan

- Goal 5 – Global Vaccine Issues
  - Support low-middle income countries' capacity building to implement new vaccines
  - Provide expertise and resources to incorporate new vaccines, strengthen infrastructure, and achieve higher vaccination levels

- Recommendation 6-1: The Secretary of HHS should actively demonstrate the Department's support for the National Vaccine Plan by:
  - (1) clarifying its primacy as the strategic planning tool applicable to all federal agencies with roles in the National Vaccine Program, and
  - (2) allocating the resources necessary to assure robust planning and implementation, with coordination by the National Vaccine Program office.

NVAC's criteria to recommend priorities for the draft strategic National Vaccine Plan include the following:

- Feasibility (financial and technical)
- Potential impact on morbidity and mortality
- Strategic opportunity (likely to require, motivate multi-stakeholder involvement)
- Public salience (derived from public engagement meetings' priority areas)

Discussion

Dr. Duchin (NACCHO) noted that the desire to have an adult immunization program analogous to the VFC program has been stated on numerous occasions. He wondered how that fit into the NVP.

Dr. Strikas replied that while he did not know how this would play out in terms of the top priorities, objective 4.2 addresses eliminating financial and non-financial barriers to immunization for all age groups. Several strategies deal with the public health infrastructure for adult immunization and improving vaccination rates for all groups. So this issue is generally addressed. Action steps will be addressed in the implementation plan: Are we going to recommend a vaccine program for uninsured adults? Can we do that with some confidence that there are resources to support such an effort? NVPO hopes to host a meeting in the summer with all of the partners they can think of to determine who is willing to put forth resources to move this plan forward.

Meningococcal Vaccine

Introduction

H. Cody Meissner, MD
Meningococcal Work Group Chair
Advisory Committee on Immunization Practices

Dr. Meissner began by acknowledging the work group members and expressing his appreciation for all of their efforts in the many discussions they had regarding meningococcal issues.

Currently, meningococcal vaccination is recommended for all children 11 through 18 years of age. Routine vaccination of persons 2 through 55 years of age who are at increased risk of meningococcal disease is also recommended. Following FDA licensure the previous Friday of the Novartis vaccine, either of the following two conjugate meningococcal vaccines may be used for immunization of persons 11 through 55 years of age:

- MCV4-D (Sanofi) licensed for persons 2 through55 years of age
- MenACWY-CRM_{197} (Novartis) licensed 2/19/2010 for persons aged 11 through55 years of age

For use in infants and toddlers, three investigational conjugate meningococcal vaccines are under consideration. These three vaccines are likely to be licensed by the FDA for use in children less than 2 years of age in either 2010 or 2011:

- HibMenCY is manufactured by GlaxoSmithKline (GSK). This vaccine contains polysaccharides from groups C and Y and haemophilus influenza Type B conjugated to tetanus toxoid. GSK has submitted a BLA for this meningococcal vaccine. The vaccine would be administered as a 4-dose series at 2, 4, 6 months of age, with a booster dose at 12 to 15 months.

- MenACWY-CRM_{197} is manufactured by Novartis. This is a tetravalent meningococcal ACY W135 vaccine. This vaccine contains polysaccharide from four groups that are conjugated to CRM_{197}, a naturally occurring mutant diphtheria toxin. This vaccine would also be administered as a 4-dose series at 2, 4, and 6 months of age, with a booster dose at 12 to 15 months.

- MCV4-D is a tetravalent meningococcal vaccine containing capsulate polysaccharide from serogroups A, C, Y, and W135 conjugated to a chemically altered diphtheria toxoid. This vaccine is manufactured by sanofi Pasteur, and was licensed in January 2005 for use among persons 11 through 55 years. Presently, it is licensed for children as young as 2 years of age. The new indication for this vaccine would extend the use of this vaccine to toddlers as a 2-dose series starting at 9 months, with a booster dose at 12 to 15 months.

During the October 2009 ACIP, three presentations were delivered regarding meningococcal vaccine. GSK presented data for a phase III non-inferiority immunogenicity and safety trial with the combination Hib and *Neisseria meningitidis* serogroup C and Y conjugate vaccine. Immunogenicity and antibody persistence data from two other trials were also presented. The second presentation reviewed the epidemiology of meningococcal disease in infants and young children less than 5 years of age. Surveillance data from the Active Bacterial Core Surveillance system (ABCs) and the National Notifiable Diseases Surveillance System (NNDSS) were presented. Two conclusions were established. First, rates of meningococcal disease are presently at historically low levels—levels that are approximately half the lowest rates ever recorded. Second, the epidemiology of meningococcal disease is dynamic and will need careful monitoring for change in disease patterns among infants and children, as well as among adolescents and adults. The third presentation was an overview of considerations by the work group in regard to a possible recommendation for the use of meningococcal conjugate vaccine in infants and toddlers. The work group conclusion was that the amount of meningococcal disease that can be prevented with infant and toddler vaccination is low based on the present epidemiology of meningococcal disease as well as the investigational vaccines under consideration, which do not offer protection against serogroup B.

During the ACIP discussions that followed, there was general agreement that a recommendation for routine vaccination of infants and toddlers is not appropriate at the present time, and not vote was taken. This conclusion was based on a number of considerations. The current incidence of meningococcal is 0.3 cases per 100,000 population. While several theories have been proposed, it is not clear why the rates have fallen to historically low levels; therefore, it is not possible to predict whether this is a permanent decline perhaps due to societal changes and that rates will continue to fall. Perhaps rates will rise in the years ahead. It is also not clear if changes in serogroup predominance may occur.

In addition, serogroup b is not included in any of the three investigational vaccinations under consideration. Overall, serogroup B accounts for about 35% to 40% of meningococcal disease in the US, but among children less than 5 years of age, serogroup B is the most important cause of disease, accounting for 231 of the 381 average number of meningococcal cases occurring during the first 5 years of life. Thus, more than 60% of all meningococcal cases in this age group would not be prevented even with 100% update and 100% efficacy of these vaccines. Moreover, case fatality rates and complications are lower in the first year of life than later in life. Nonetheless, it is important to remember that an estimated 8 deaths occur in the first 5 years of life due to serogroup C and Y, which might be prevented by these vaccines. While the duration of immunity following infant immunization is not known, it is unlikely that protection will last until the time of the first 11-year meningococcal dose. This means that an

unknown number of booster doses will be required to maintain protection through the first decade of life. Finally, vaccination of infants will likely have little impact on overall meningococcal carriage rates. However, with maturation of the adolescent immunization program, as increasing numbers of teenagers and young adults in their early twenties become vaccinated, a benefit among infants and young children from herd immunity may be observed.

Since the last ACIP meeting, work group discussions have focused on three areas. First, a cost effectiveness analysis was presented. Second, data were reviewed on provider attitudes toward infant immunization. Data were presented from a University of Colorado survey and from a GSK market survey regarding HibMenCY vaccine. Third, the work group has spent a considerable amount of time considering the possibility of a recommendation for permissive use of any of the three infant meningococcal vaccines. Specifically, the following question was addressed: In the absence of a recommendation for routine use, would a permissive recommendation be appropriate? The answer will come with the understanding that a vaccine which does not receive a recommendation for routine use and which is not recommended for permissive use will not be covered by the VFC program. The work group discussions also included the option that the HibMenCY vaccine might be considered as a Hib vaccine.

The challenges presented by the three infant meningococcal conjugate vaccines are extremely complex, and work group members have struggled with these issues. The consequences of meningococcal disease are often tragic. They are well known by physicians on the work group through personal experience with their patients. However, the amount of disease prevented must be balanced as objectively as possible against ACIP's role for responsible stewardship of limited resources. A recommendation for either routine use or permissive use of a meningococcal vaccine must be weighed thoughtfully against the benefits derived.

The work group had a number of concerns about either a routine recommendation or a permissive recommendation for any of the three investigational meningococcal conjugate vaccines. At this time, these concerns appear to override the benefit of either recommendation. As noted, 60% of the meningococcal disease in the first year of life is due to serogroup B and therefore will not be prevented. Disease due to serogroup C and Y peaks at 4 to 5 months of age, which is too soon to be protected by three doses of vaccine administered at 2, 4, and 6 months of age. An infant vaccine program will prevent an estimated 80 to 120 cases, only about one-third of the approximately 381 cases of meningococcal disease in the first 5 years of life. The duration of immunity is likely to be short-term, meaning a gap in protection will occur before the 11-year dose. This means at least one additional booster dose after the 12- to 15-month dose and before the 11-year dose will be necessary to maintain protection. The need for the 11-year dose is unlikely to be eliminated. Finally, the impact of adolescent immunization on herd immunity is presently unknown, but it is possible that as more adolescents are vaccinated, less transmission from adolescents and young adults to infants and young children will occur. In addition, concerns were raised about considering the HibMenCY vaccine as a Hib vaccine. This combination vaccine would be more expensive than a monovalent vaccine. Even if the cost of the HibMenCY vaccine were the same as monovalent Hib, the benefit from the meningococcal serogroup CY component would be low for reasons just articulated.

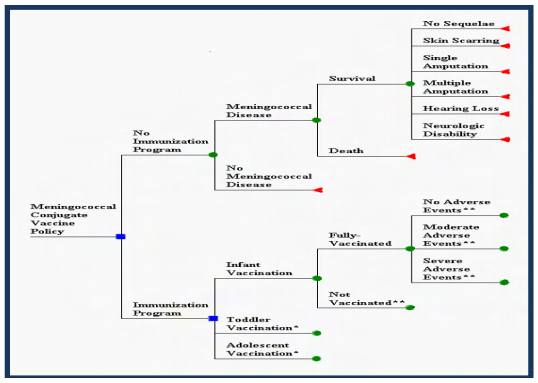
The goals of this session were to present a cost-effectiveness analysis of infant meningococcal vaccines; review the rationale for not recommending routine use of infant vaccines; and discuss language options for permissive use of these vaccines and then discuss issues surrounding the HibMenCY vaccine. No vote was taken during this session.

Changes in the Cost-Effectiveness of Meningococcal Vaccination Strategies in the United States

Ismael Ortega-Sanchez, PhD
National Center for Immunization and Respiratory Diseases (NCIRD)

Dr. Ortega-Sanchez discussed the changes in the cost-effectiveness of the meningococcal vaccination in the US. He thanked his collaborators from NCIRD, and noted that this presentation followed the *ACIP Guidance for Health Economics Studies*.

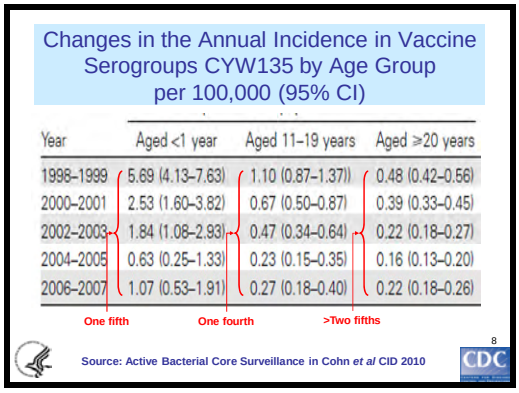
The objective of this study was to analyze the effectiveness and cost-effectiveness of meningococcal vaccination program in infants and toddlers in the US under the changing epidemiology, using the societal perspective. For this purpose, the following model was utilized:



This model was utilized to compare four strategies: three with vaccination for each age group and one without vaccination. To calculate the number of cases as well as the number of dates or number of survivors with sequelae, the model includes notes that describe meningococcal disease infection rates and probabilities of specific outcomes.

With respect to the design, Monte Carlo simulation analysis was utilized. This simulation allows for the calculation of the most likely or base case estimates for health benefits and costs. Two hypothetical populations of equal size were used: 4 million birth cohort and 4 million adolescent cohort (11-years old). A 22-year timeframe was used, but the benefits of vaccination are estimated using age-specific life expectancy (e.g., analytic horizon). The typical discount rate was used for both cost and benefits: 3% (0%-5%). Once the core of the model was set, it was filled with the base data and physical assumptions. The investigators also consulted with the work group and many other experts. At first, they needed to include the base available data and to have an unbiased model. Inputs included epidemiologic data, resource utilization, indirect costs, vaccine characteristics, quality of life after meningococcal disease, and other parameters. Three important components of the epidemiology data include age-, year-, and C+Y+W135 serogroup-specific incidence rates (1991-2007); age- and serogroup-specific case fatality ratios; and the proportion of survivors with sequelae by condition.

The following table illustrates shows market changes in the annual incidence in vaccine serogroups CYW135 by age group per 100,000 (95% CI) [Active Bacterial Core Surveillance in Cohn et al CID 2010]:



In particular, children aged less than one year showed the largest reduction. The 2006-2007 rates were one-fifth what they were in 1998-1999. The other groups also experienced reductions; however, to keep the variability of the data in the model, a wider range of years data were used from the ABCs for each age group. Nevertheless, more weight was given to the most recent data.

In terms of fitting probabilities in case fatality ratios for Serogroups C-Y-W135, as in previous analyses, proportions of survivor cases with specific sequelae reported in the literature were used. The most common, long-term sequelae for most survivors with meningococcal disease for which reliable data exists are skin scarring, single amputation, multiple amputations, and hearing loss [Edwards *et al*. Complications and sequelae of meningococcal infections in children. J Pediatrics 1981; 99:540-5], and significant long-term neurological disability [Baraff *et al*. Outcomes of Bacterial meningitis in children: a meta-analysis PIDJ 1993;12:389-94].

With respect to vaccine characteristics, in relation to the already established one dose of adolescent vaccination strategy, two additional studies were modeled on the birth cohort: 1) A toddler strategy with two doses given and 9 and 12 months of age; and 2) An infant strategy with four doses given at 2, 4, 6, and 12 to 15 months of age. For the birth cohort, year one begins at birth. Since vaccination occurs part way to year one, age-specific incidence data were used. For effectiveness, it was assumed that the first dose of the toddler and infant schedules had a vaccine efficacy equal to zero. Two scenarios were modeled for efficacy duration, one with 10 years of duration and one with 5 years. For the base case analysis, a 10-year duration was used [Pichichero et al., *Pediatr Infect Dis J* 2005; Shepard et al., *Pediatrics* 2005; Snape et al., *JAMA*. 2008; Sanofi Pasteur 2-10y-MCV4 Insert 2007].

Vaccine coverage rates were used in the model from the national coverage data acquired for vaccines currently and routinely administered to infant, toddlers, and adolescents. The rates of coverage are specific to the doses for infants and toddlers. Coverage rates for adolescents are based on 2008 Tdap vaccine for 11 year olds, given that the uptake of the meningococcal vaccine seems to be lower than that.

To adjust the incidence rates and vaccination, a formula was applied that weighted vaccine coverage and vaccine effectiveness. This adjusted rate was then multiplied by the population denominator to generate the number of expected cases of meningococcal disease with vaccination. To cost incidence burden, one-time costs related to the acute phase of meningococcal disease and lifetime costs based on the recurring charges for caring for sequelae were used.

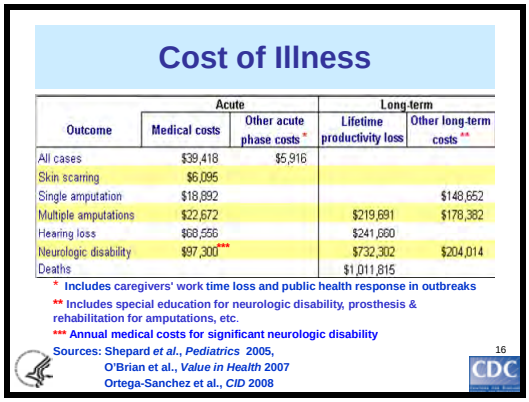
For each age group and for each strategy the following formula was utilized:

$$MDI_{vacc} = MDI_{no\ vacc} * [1-(Vcov * Veff)]$$

Where:

- MDI_{vacc} = *Meningococcal disease incidence under vaccination*
- $MDI_{no\ vacc}$ = *Meningococcal disease incidence without vaccination*
- *Vcov* = *Vaccination coverage*
- *Veff* = *Vaccine efficacy*

In the model, all meningococcal cases were hospitalized and included medical and indirect costs during the acute phase of the disease. Those included in the model who suffered sequelae incurred specific medical costs in addition to costs related to acute meningococcal disease, as illustrated in the following:



Cost of Illness

Outcome	Acute: Medical costs	Acute: Other acute phase costs *	Long-term: Lifetime productivity loss	Long-term: Other long-term costs **
All cases	$39,418	$5,916		
Skin scarring	$6,095			
Single amputation	$18,892			$148,652
Multiple amputations	$22,672		$219,691	$178,382
Hearing loss	$68,556		$241,660	
Neurologic disability	$97,300***		$732,302	$204,014
Deaths			$1,011,815	

* Includes caregivers' work time loss and public health response in outbreaks

** Includes special education for neurologic disability, prosthesis & rehabilitation for amputations, etc.

*** Annual medical costs for significant neurologic disability

Sources: Shepard *et al.*, *Pediatrics* 2005,
O'Brian et al., *Value in Health* 2007
Ortega-Sanchez et al., *CID* 2008

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Given that the analysis is from a societal perspective, costs associated with productivity losses were included for death (labor market earnings + household production), neurologic sequelae (labor market earnings), multiple amputations (30% of labor market earnings), and hearing loss (33% of labor market earnings) [Haddix AC et al., Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation. 2nd ed. 2003 Oxford University Press, New York. Age-specific values, US population, 3% discount rate].

Differences in quality of life among survivors of meningococcal disease with long-term sequelae were accounted for. Because there are no published measurements of loss of quality of life specific to meningococcal disease, published health-related QALY scores were used for conditions closely resembling each of the meningococcal-related long-term sequelae. Note that because meningococcal disease follows a very rapid clinical course, decreases in quality of life associated with this acute phase were not estimated [Several sources cited in: Shepard *et al.*, *Pediatrics* 2005; Ortega-Sanchez et al., *CID* 2008].

Since each strategy uses a different vaccine, vaccine costs are differentiated. For infants, the only cost is the meningococcal component of the combo vaccine, in this case, the HibMenCY. This was assumed to be $2 per dose (range $15-$60) + $AEs. For toddlers, $20 per dose (range $15-$60) +$AEs* +$Adm was assumed for the meningococcal conjugate MCV4 that is recommended for toddlers at 9 to 15 months of age. For adolescents, the 2009 public and private sector prices were used for MCV4 of $90 per dose (range $80-$103) +$AEs* +$Adm. In each one of these cases, the cost of adverse events was included, which were taken from the adverse event rates from the UK experience with MCC [Trotter et al., *BMJ* 2002; Ortega-Sanchez et al., *CID* 2008]. Importantly, the infant vaccination strategy does not include any vaccine administration costs; whereas, the toddler and adolescent vaccination strategies include administration costs.

Using the recommendations by the United States Panel on Cost-Effectiveness in Health and Medicine, incremental cost-effectiveness ratios can be calculated as difference in the net costs divided by the difference in the health benefits:

Incremental cost-effectiveness ratio, ICE

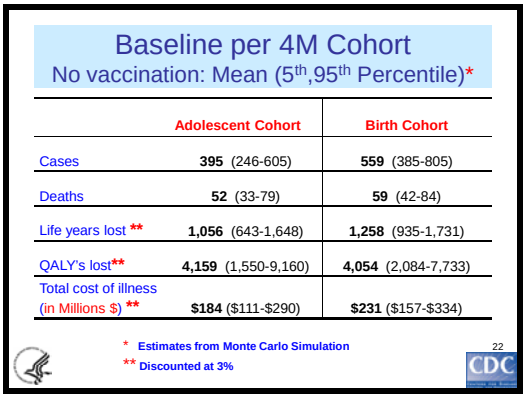
$$ICE = \frac{NC_{vacc} - NC_{unvacc}}{HO_{vacc} - HO_{unvacc}}$$

Where:

- *NCvacc* = Net cost of vaccination strategy *
- *NCunvacc* = Net cost of no vaccination *
- *HOvacc* = Health outcome of vaccination strategy *
- *HOunvacc* = Health outcome of no vaccination strategy*

*Net costs and health outcomes were discounted

With regard to the preliminary results, the mean baseline estimates for the 4 million cohort and no vaccination with the 5th and 95th percentiles are presented in the following table:



Baseline per 4M Cohort

No vaccination: Mean (5th,95th Percentile)*

	Adolescent Cohort	Birth Cohort
Cases	**395** (246-605)	**559** (385-805)
Deaths	**52** (33-79)	**59** (42-84)
Life years lost **	**1,056** (643-1,648)	**1,258** (935-1,731)
QALY's lost**	**4,159** (1,550-9,160)	**4,054** (2,084-7,733)
Total cost of illness (in Millions $) **	**$184** ($111-$290)	**$231** ($157-$334)

* Estimates from Monte Carlo Simulation

** Discounted at 3%

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These baseline estimates are the consequences of the epidemiology data, bearing in mind that the investigators used a very wide span of incidence data with significant weight on the recent data. To these estimates, the three vaccination programs were applied.

In terms of the new number of cases prevented for the three strategies (e.g., adolescents, toddlers, and infants), in the base case scenario, meningococcal vaccination would prevent approximately 195 cases if the infant strategy was adopted for the 4 million cohort, 160 cases in the toddler strategy, and 176 cases in the adolescent-based strategy. Vaccination in adolescents prevents approximately 176 cases. Two additional scenarios were compared with the base case scenario: 1) changes in vaccine efficacy duration from 10 years (the base case) to 5 years; and 2) changes in vaccine efficacy on the first dose from 0% (base case) to 50% in the infant and toddler strategies. Compared to the base case estimates, with only 5 years duration, an adolescent strategy would prevent only 106 cases as opposed to 176 cases of the base case scenario. The infant strategy would prevent 67 fewer cases; whereas, the toddler strategy would prevent 65 fewer cases. Conversely, always making a comparison to the base case scenario with a 50% vaccine efficacy in the first dose, the toddler strategy would prevent 22 more cases and the infant strategy would prevent 10 more cases. All results are for the 4 million cohort. The first dose vaccine efficacy for the adolescents was not changed because only one dose is scheduled for that strategy.

For deaths, the analyses are similar. In the base case scenario, meningococcal vaccination would prevent approximately 13 deaths in the infant strategy, 12 deaths in the toddler strategy, and 21 deaths in the adolescent strategy. For the two alternative scenarios compared to the base case scenario, with only 5 years duration, an adolescent strategy would prevent 8 fewer deaths, and the toddler and infant strategies would prevent 5 fewer deaths each. In contrast, with a 50% vaccine efficacy on the first dose, the toddler strategy would prevent one more death and the infant strategy would prevent 2 more deaths. Along with the base case scenario, estimates for life years saved were calculated for the two alternative scenarios in comparison with the base case. Estimates for QALYs saved are for the two alternate scenarios in comparison with the base case increase when vaccine efficacy for the first dose is assumed to be 50% as opposed to 0%, and decreases when the duration of vaccine efficacy is only 5 years as opposed to 10 years.

In terms of the cost-effectiveness estimate for cost per life year saved and cost per QALY saved, the average costs per life year saved were $707,000 for the infant strategy; $786,000 for the toddler strategy; and $390,000 for the adolescent strategy. This relationship changed somewhat when another measure, the cost per QALY, was used. The average costs per QALY saved were $139,000 for the infant strategy; $229,000 for the toddler strategy; and $145,000 for the adolescent strategy.

The medical costs of acute meningococcal disease and the lifetime costs of long-term sequelae did not result in large changes on the societal cost per QALY saved in either direction. That was not the case for when the cost per dose of vaccination was changed. Overall, the strategies show higher sensitivity to variations in vaccine price. In particular, when the vaccine price per dose was $15 in toddlers and infants, the cost per QALY was approximately $65,000 for toddlers and $85,000 for infants. When the vaccine price was $60, which is four times what was assumed in the previous scenario, the cost per QALY ratios increased to $387,000 for toddlers and $425,000 for infants.

A number of sensitivity analyses were performed, most of which were probabilistic. With regard to the sensitivity analyses for the toddler and the infant strategies using a specific methodology, the sensitivity of cost per QALY ratio to variable analysis is measured to the standardized coefficient b. Vaccine cost per dose is regulated first, which means that positive changes in the vaccine cost, with increments in the vaccine cost per dose, will increase the cost per QALY. This makes the strategy for toddlers less cost-effective; whereas, increases in the incidence of the disease will decrease the cost per QALY. The infant and toddler vaccination strategies show higher sensitivity to variations in vaccine costs.

The strengths of the model are that complex modeling is utilized to uncover the uncertainties and to objectively and explicitly show them; and incidence and CFR surveillance data for MCV4 vaccine-containing serogroups are explicitly used. Limitations are that data on vaccine effectiveness are from clinical trials, and quality of life during the acute phase of the disease is not assessed.

In conclusion, disease incidence and cost of vaccine drive the analyses (more doses => more expensive => less cost-effective). Although additional cases could be prevented by either an infant or toddler vaccination strategy, they do so at higher cost. Using the last 10 years of epidemiology data increases the cost of all strategies compared to previous analyses.

Considerations for Use of Meningococcal Conjugate Vaccines in Infants

Amanda Cohn, MD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Cohn expanded upon some of the issues Dr. Meissner raised, and discussed the working group's current thinking and struggles regarding the use of infant meningococcal vaccines. This vaccine is not yet licensed; therefore, the work group did not propose specific recommendations or call for a vote during this ACIP meeting.

During the October 2009 ACIP meeting, GSK presented on the safety and immunogenicity of HibMenCY vaccine. The four dose series is highly immunogenic, with 82% (y) and 94% (c) of subjects having a seroresponse after two doses to serogroup Y and C respectively, and 96 % (y) and 99% (c) of subjects having a seroresponse after dose 3. The Hib response was non-inferior to monovalent Hib vaccine. Mild and local systemic reactions were similar to monovalent Hib vaccine, and there were no serious adverse events. Duration of protection of the serogroup Y and C components is unknown, but 84% and 97% of subjects had persistence of bactericidal response for serogroups Y and C respectively, one year after the fourth dose.

The work group interpretation of the immunogenicity and safety data is that HibMenCY is a safe and effective vaccine for Hib and serogroups C and Y meningococcal disease after either the second or third dose, and for one year after the fourth dose. Evidence of waning immunity, especially for serogroup Y, indicates that the vaccine is unlikely to provide protection against meningococcal disease until 11 to 12 years of age, and boosting may be required to maintain immunity throughout childhood.

Meningococcal disease has always been a rare, but serious infectious disease. With regard to the incidence of meningococcal disease in the US from 1970 to 2008, rates of disease have been declining for the last 10 years. The US is currently at a historic nadir of disease incidence. It is not known why disease incidence has continued to remain so low, but it is unlikely to be due

to the introduction of MCV4. This decrease is observed in all age groups—not just in adolescents, occurs for serogroup B as well as for serogroups C and Y, and the most significant declines occurred prior to introduction of MCV4 [1921-1996 NNDSS data, 1997-2008 ABCs data projected to U.S. population].

Even with very low incidence, there are cases of meningococcal disease in young children every year. Regarding the average number of cases of meningococcal disease annually in children less than 5 years based on data from 1999 to 2008, there are approximately 221 cases of serogroup B and 139 cases of serogroups C and Y combined annually. However, a large proportion of cases are in children less than 6 months of age, most of whom will be too young to be protected by this vaccine. In children 6 months to 4 years of age, there are approximately 89 cases of serogroup C and Y disease annually. With respect to the nadir in incidence, in 2008, the number of cases of serogroup C and Y disease decreases to approximately 50 or 60 cases [ABCs cases from 1999-2008 and projected to the U.S. population].

The working group has reviewed the epidemiology of meningococcal disease in infants, and has come to the conclusion that the low burden of potential vaccine-preventable disease does not justify addition of HibMenCY to the routine infant vaccination program. The working group recognizes that the epidemiology of meningococcal disease is dynamic and rates of disease may increase, but rates may also continue to decline, especially if there is an indirect impact of adolescent immunization on infant disease. The working group cannot say what magic number or rate of increase would be the trigger point for vaccination, but is committed to regularly reevaluate this issue.

Programmatic considerations were also addressed during the October 2009 ACIP meeting. Over the last several months, the working group has reviewed programmatic considerations for HibMenCY specifically. Beginning with the MenCY component of this vaccine, depending on the other products used, HibMenCY may add no additional shots. However, two standalone vaccines are likely to be licensed in the next 12 to 18 months, which will require additional shots. Regardless, there will have to be adjustments to the infant schedule. Additionally, given that the burden of disease in infants occurs primarily in infants less than 6 months of age, the need to attain high coverage early in an infant's life to prevent a majority of the disease would be a programmatic challenge.

There are also programmatic considerations for the Hib component of HibMenCY vaccine. Supply of Hib vaccine was discussed in the working group. These discussions occurred during and shortly after a major Hib vaccine shortage. There are currently 3 monovalent Hib vaccine products available, and Hib supply is stable. The working group does not think concerns about Hib vaccine supply should influence a recommendation for meningococcal vaccines, but having an additional Hib vaccine is a benefit of HibMenCY. On the other hand, a routine recommendation for HibMenCY would have the opposite effect and would limit the use of other available combination vaccines containing the Hib component, especially during the period of time with no standalone infant meningococcal vaccines.

The working group concluded that if the burden of disease justified use of this vaccine, programmatic complexities would not prevent a recommendation. But in this setting of very low disease incidence, the working group felt strongly there should be a judicious approach to adding vaccines to the infant schedule. Achieving programmatic balance and high coverage with an increasing number of vaccines in the infant schedule is challenging. Adding HibMenCY or any meningococcal vaccine to the infant schedule would have an impact on society, health departments, providers, and parents.

The working group has known that an infant meningococcal vaccine would not be cost-effective, as presented earlier by Dr. Ortega-Sanchez. The incremental cost of HibMenCY over monovalent Hib vaccine would have to be under $20 to be comparable with the adolescent meningococcal vaccine effectiveness. This analysis also used the best case scenario assumptions, including a 10-year duration of protection with no waning, and a long time-span of epidemiological data to include both sides of the peak of disease observed in the late 1990s. Finally, the working group understands that this price of $20 does not include any administration fees because it was assumed that HibMenCY would not add any additional injections. With the stand-alone vaccines, a price of $20 is impossible because of the added $15 to $20 administration costs.

Once again, if the burden of disease justified use of this vaccine, the cost-effectiveness analysis would not impact the working group decision to make a routine recommendation. However, in the setting of low disease burden, there was a strong consensus to not recommend vaccine regardless of price. Even if HibMenCY vaccine is the same price as the monovalent Hib vaccine, the opportunity costs of adding this vaccine to the infant schedule are immeasurable, but important. Additionally, the price of vaccine is not fixed over time.

Dr. Cohn then offered a summary of some of the data presented on a working group call from a provider survey conducted by Allison Kempe at the University of Colorado. Beginning in December 2009, physicians were surveyed who are in an existing sentinel network recruited from random samples of American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP). Questions were asked about MCV4 practices among adolescents and knowledge and attitudes about infant meningococcal vaccination. The response rate was 72%, with 59% response for family practitioners and 85% response from pediatricians.

Regarding the strength of providers' recommendation for infant meningococcal vaccination under different scenarios if an infant meningococcal vaccine is recommended by ACIP, AAP, and AAFP, approximately 90% of providers would recommend infant meningococcal vaccine in the setting of a recommendation if there are no additional injections. Among pediatricians, only 52% would strongly recommend if there were 4 additional injections, and only 39% would strongly recommend if it required a change to different vaccine products than what the provider is currently using. The same pattern holds true for family medicine physicians. If ACIP, AAP, and AAFP do not recommend infant vaccination for routine use, the proportion of providers who would recommend this vaccine decreases to about 40% and 32% among pediatricians and family medicine providers, respectively. If there were no additional injections, 19% of pediatricians and 17% of family practitioners would strongly recommend this vaccine. The working group took from this presentation that most providers will use meningococcal vaccines in infants only if recommended by ACIP, AAP, and AAFP. Additional injections and the need to change their current use of products would impact acceptability. The working group is acutely aware of the impact their proposed recommendations would have on the use and uptake of infant meningococcal vaccines.

Many working group calls have started with the question: How can we not recommend a vaccine we know will prevent 4 to 8 deaths in 10 to 15 children from having long-term disability a year? But when the working group works through their rationale using a societal, not an individual perspective, the discussion returns to a strong consensus that the best public health decision is to not recommend routine infant vaccination at this time. The primary rationale is the current low burden of meningococcal disease combined with the high proportion of serogroup B cases in infants that are not prevented by this vaccine. But an additional important reason is

that if infants are vaccinated, booster doses will likely be required to maintain immunity. The working group is uncomfortable with the potential for a child to be protected through 5 years old, but then to lose protection, given that this course would likely commit them to a booster dose at 4 to 6 years old. High-risk infants would be recommended for vaccination.

In terms of some of the complicated discussions pertaining to the language for the use of HibMenCY, the working group is thinking through permissive language about the use of HibMenCY to prevent Hib disease, and the implications this language has in relation to the inclusion of HibMenCY in the VFC program. The working group discussed language about the use of HibMenCY as a Hib vaccine. This vaccine can definitely be used as a Hib vaccine. The work group does do not think there is an increase in risk from the additional antigens, but there is a benefit from the meningococcal components, which is limited. The working group discussed indicating a preference for HibMenCY as a Hib product, especially if the vaccine were priced competitively with other Hib vaccine products, but determined that even if the price of this vaccine is equivalent, stating a preference is not very different from making a routine recommendation. Providers can have preferences, but from a societal perspective, there is not sufficient public health benefit to have ACIP state a preference. There was consensus to acknowledge the added benefit of MenCY component of HibMenCY without stating a preference. An example of the kind of language being considered is as follows:

> *HibMenCY may be used in infants for routine vaccination against Hib. At the current time, the additional benefit of the serogroup C and Y meningococcal component of this vaccine is limited; serogroup B meningococcal disease not prevented by this vaccine. Protection from the MenCY component may be of short duration (4-5 years) and booster doses are likely needed to maintain protection until the 11-12 year-old dose*.

The working group recognizes that permissive use recommendations are confusing to providers and the question of what exactly a permissive recommendation is has been debated. An FDA approved vaccine means it is safe and effective, and several working group members believe licensure indicates permission to use. The working group grappled quite a bit with how permissive language translates into a VFC resolution, and is taking the approach that decisions about permissive language should be independent of considerations for VFC inclusion.

The working group has discussed three options from no language to broader language. First, there could be no language about permissive use of vaccine, and there would only be language around recommendations for high-risk infants, including use during community outbreaks. In the middle is language to communicate that this is a safe and effective licensed vaccine, and can be used. The more broad language option is to add after *HibMenCY is a safe and immunogenic vaccine* that *Parents and providers may vaccinate infants with HibMenCY for protection against meningococcal disease*…

The working group discussed these language options extensively. There is a preference from some working group members to limit permissive language, with the understanding that licensure allows for use of the vaccine and that permissive language may be more broadly interpreted than intended. It is not the intention of the working group to discourage use of this vaccine, and understanding the nuances of how permissive language impacts health departments, providers, and parents is still being worked through. If the working group does propose permissive language, it should reflect the conviction of the working group that the risk of disease is low and vaccination is not recommended. In other words, it should be clear that the working group is not waffling.

There are various scenarios for inclusion of HibMenCY in VFC if ACIP does not recommend routine vaccination. The first would be to have permissive use of infant meningococcal vaccines added to the meningococcal VFC resolution. Another scenario would be to add HibMenCY to the Hib vaccine resolution as an additional Hib vaccine choice. The final scenario is to include only high-risk infants in the meningococcal VFC resolution, and infants who are not high-risk would not be eligible for HibMenCY or any meningococcal vaccine.

The working group has had complex discussions around inclusion of this vaccine in the VFC program. These discussions have raised issues of public health stewardship, desire for this vaccine to be available, use of limited resources, and consistency with ACIP recommendations. The working group is continuing to be educated about the VFC program and understands that the direct and indirect implications of this decision are important.

In conclusion, the epidemiology of meningococcal disease is dynamic, and there is currently a historic nadir. The current low burden of disease is the primary rationale for no routine vaccination for infants at this time. The working group is committed to frequently evaluating changes in the burden of disease and to recognizing increases rapidly. What the working group also understands if that if they do not recommend this vaccine now, there may be a delay in getting the vaccine back quickly if it is needed. The working group is in agreement with this conclusion, but has been through tough conversations. The members are committed to disease prevention and have struggled with the implications of this decision. The working group recognizes the incredible impact this disease has on children and families, and anticipates that one day vaccinating infants against meningococcal disease will be the right public health decision. For all of the reasons outlined, they feel that even more so than usual, communicating the rationale for these recommendations needs to be clear and consistent.

Discussion

Dr. Baker reiterated that the new vaccine, Menveo®, that was licensed recently for ages 11 through 55 will automatically go into the adolescent program as a second vaccine. That was not up for discussion during this session. She also reminded everyone that this information would not lead to a vote during this session.

Dr. Keitel requested comments on the epidemiology of the disease in other countries, particularly those which do not have an adolescent immunization strategy.

Dr. Cohn replied that meningococcal disease is very different throughout the world. In Europe specifically, many countries had very high rates, higher rates than the US, of MenC disease. However, they do not have any MenY disease. Many countries in Europe have introduced meningococcal C conjugate vaccines. Currently, those countries still have a burden of meningococcal B disease, which is still higher than in the US. There are other countries in which it is believed that the burden of meningococcal disease has been reduced similarly to the US. In Sub-Saharan Africa, MenA disease occurs at much higher rates than in the US.

Dr. Judson pointed out that, in terms of tracking the long-term secular incidence trends in meningococcal disease, it seems that things develop very slowly over multiple years. Thus, there does not seem to be any evidence to suggest that there will be a radical increase in the next year or two. Regarding the concerns raised about forcing a huge increase in costs on the VFC, if this is a permissive recommendation, it seems that the use of the HibMenCY as a Hib vaccine could create a situation in which anybody could request that preferentially with the

rationale that, “It’s all free. Why not just get a little extra protection no matter how small it may be for meningococcal disease?”

Dr. Santoli emphasized that being able to use this vaccine would depend upon the decision that ACIP ultimately makes about including it in the VFC program. When there is a licensed product, that will come up as a vote. It might be a vote about including it as a Hib vaccine or it might be a vote about including it as a meningococcal, but if there is not a recommendation, ACIP members would have to decide if they want to put this forward as a VFC resolution. There is an opportunity to do things different in the VFC program, but it is really the thinking of this group that would decide if this vaccine should be included in the VFC program.

Dr. Meissner said that in terms of the declining incidence, he thought they were very close to observing some impact from the adolescent immunization program, because meningococcal disease is acquired primarily from individuals in their late teens and early twenties. As that program matures and there are more individuals who are immunized, hopefully there will be fewer carriers and there will be less disease in younger children as has been observed with Hib and pneumococcal disease. One of the reservations about a permissive use, which would include coverage of this vaccine by VFC, is that if they believe meningococcal disease should be prevented and that it is a serious / extensive enough problem in the US, they should move forward with that recommendation. He was uncomfortable with the concept of telling people they could prevent meningococcal disease if they wanted to, but that it would be only a few cases.

With regard to the modeling, Dr. Temte asked Dr. Ortega to clarify whether inherent in the toddler and infant programs they were you still looking at maintaining an adolescent program or would replace an adolescent program. He wondered whether the costs of an adolescent program were reflected in the infant and the toddler data or the analyses.

Dr. Ortega-Sanchez replied that the comparisons made for a vaccination program were that it gains no vaccination so it is not a replacement. The reason for this is that they assumed only 10 years duration of vaccine efficacy. Because of the timeframe during which infants and toddlers are vaccinated, they will need to be vaccinated at 11 years old. The comparisons are made against no vaccination. They followed the cohort 22 years to determine the impact of the intervention. The birth cohort was followed from Day 1 to 22 years of age, and a number of cases were calculated that would come out of this vaccination program with and without the vaccination program.

Dr. Temte asked if the infant program would involve just the vaccination costs associated with the infant program, but not presumably as that infant ages to 11 or 12 years old and would received an additional meningococcal vaccine. If the adolescent program was included, the cost per QALY would balloon.

Dr. Ortega-Sanchez replied that the vaccination of the infants has been included in the strategy for the infants. Including adolescents would be a different strategy, with a booster dose at 11 years old. It is not an infant study with only the four doses at one-year old.

Dr. Cohn pointed out that because the adolescent program already exists, it was not included the cost of the adolescent program. Because they would then be preventing a similar number of cases if they used the QALYs of the adolescent program, it would work out to be pretty similar because costs would be added, but more disease would also be prevented. It would probably not balloon the cost per QALY.

Dr. Cieslak inquired as to whether any analyses were conducted in the model for serogroup B vaccine.

Dr. Ortega-Sanchez replied that he is trying to do this.

Dr. Chilton inquired about the other three serotypes that are not in the MenCY vaccine, and said he assumed that the A and W135 are not current contributors. He also wondered how close they were to a serogroup B vaccine.

Dr. Cohn responded that serogroup A disease in the US is extremely rare, and in the past 10 to 15 years, there have been no identified cases of serogroup A disease among infants based on 10% of the US population that has been under active surveillance. There has been one serogroup W135 case, so the burden of W135 disease definitely exists in infants. There are probably a few cases per year, but it is not to the same extent as serogroup C and Y. In terms of when there will be a serogroup B vaccine, there have been extensive discussions with some of the pharmaceutical companies. She requested that the companies comment on this.

Dr. Howe (GSK) responded that this was discussed during the October 2009 ACIP meeting. GSK has a serogroup B vaccine under development, but it is in the very early phases of development, so it is a number of years away.

Dr. Dull (Novartis) replied that Novartis has phase III studies on-going in Europe with its multi-component MenB vaccine. They are striving to bring that to the US for phase III studies, but have not yet begun phase III studies in the US. He could not put a timeframe on this.

Dr. Paradiso (Pfizer) indicated that Pfizer is currently testing a meningococcal B vaccine formulation in adolescents, which will be followed up in infants as well.

Dr. Dekker (sanofi pasteur) indicated that sanofi pasteur is also working on the development of a meningococcal B vaccine.

Dr. Katz reported that he was recently attending a meeting in Buenos Aires and was very impressed that group B meningococcal disease is highly prevalent in many Latin American countries. He thought that cast another aspect to the epidemiology in terms of what should be considered as they think optimistically about the inclusion of group B. Group B is prevalent in infants, older children, and adults.

Regarding the continual comments that it is not understood why the incidence of meningococcal disease has been decreasing since 2000, Dr. Turner (ACHA) pointed out that one way to protect infants is to vaccinate adolescents and young adults. ACHA has been conducting surveys of its students about vaccines for a number of years. In the year 2000, shortly after the first recommendation was made for meningococcal vaccines in college students, ACHA had achieved 24% uptake of polysaccharide. By the spring of 2005, before conjugate was available, they had already achieved 55% uptake. Since conjugate has become available, they have been at about 60% uptake. While he realized that serotype B had fallen during the same period, Dr. Turner submitted that vaccinating over half of the college students in America since the year 2000 had perhaps had an impact on the decline of incidence. He thought they should emphasize adolescent and young adult vaccine to prevent the disease among infants.

Ms. Murphy (CMS) mention that as the CMS representative for the VFC program, she does not care for permissive used in the votes for the VFC, although she did understand the need for doing so. When the word "permissive" is going to be used, she suggested that they be very careful to spell out that they mean "permissive for parents and providers" so that no one else can interpret this as their ability to determine whether they are going to cover the vaccine within the state or region.

Dr. Baker pointed out that upon FDA licensure, providers may purchase vaccine and parents may request it. The permissive language for VFC is a different "kettle of fish."

Dr. Salisbury (DOH, UK) said he thought the UK experience was worth mentioning because there are some similarities and some considerable differences. Regarding the epidemiology in the UK, in the mid to late 1990s, they observed about 3 cases per 100,000 total population of meningococcal C disease, which would relate to something on the order of 7,500 US cases, and 750 deaths. The scale of what the UK is now facing differs from the current US scale. The UK introduced meningococcal C conjugate vaccine for infants at 2, 3, and 4 months. A catch-up campaign was conducted for the remainder of the population up to 18 years of age for one dose. In the catch up campaign, there was about 85% coverage and approximately 90% to 93% coverage with three doses in the infant program. Meningococcal C disease has virtually disappeared. However, vaccine efficacy is short-lived in the infants, and it was clear that vaccinating at 2, 3, and 4 months did not offer long-lasting protection. Thus, they changed the schedule, dropping one infant dose. They now vaccinate with meningococcal C conjugate at 3 months and 4 months and give a HibMenC combined conjugate boost at 12 months. The consequence of that is that there are nearly 0 levels of MenC extending through the ages. The result of the catch-up program administered at a very high coverage rate has been enormous, and has lasted at least a decade. Clearly, they are assessing carefully to ensure that there is no adolescent resurgence of disease, but thus far there has been absolutely none. In 2008 and 2009, there was not a single death from meningococcal C in the under 18 age group in the UK. However, all of that is predicated on very different epidemiology in which the burden of the disease was of the order of log differences compared with American disease.

Dr. Baker inquired as to what happened to group B disease in the UK during this interval.

Dr. Salisbury responded that group B disease has fallen somewhat, but to the low levels observed in the US. The UK still experiences about 1,000 cases, which would be on the order of 5,000 US cases of group B disease per year.

Dr. Langley (NACI) reported that Canada's experience was a variation of the UK experience. Canada had large outbreaks in 2001. Immunization campaigns were conducted using a bivalent product and a MenC product. Infant programs were introduced as well. Initially, they were introduced according to the schedule that Dr. Salisbury mentioned. As they learned that not having a dose after one year of age led to waning immunity, they had fewer infant doses. Most provinces use a single dose at 1-year, which is given at the same time as the MMR visit. Now the adolescent dose is a booster dose. The result of that is that C disease is now about .25 per 100,000 and the most common serotype is B at .3 per 100,000.

Dr. Judson inquired as to whether, from a general perspective, they should revisit the use of the "permissive" category and whether it was leading to unhelpful confusion, increased costs, and unintended VFC entitlements.

Dr. Baker replied that there has been some concern, but that they would unlikely be able to solve that particular question during this session.

Dr. Sawyer said he thought that a permissive recommendation would lead to a great deal of confusion. Most physicians are not aware of the change in epidemiology and would likely have the general reaction that the workgroup had: How can we not immunize? It is likely that they will not understand a permissive recommendation from ACIP. He supported the work group's effort to be very clear, but would not favor a permissive recommendation.

Dr. Englund said she thought their group needed to support the work group in defining who is at high risk. There are certainly high risk children, and that needs to be covered by the VFC program. The work group has already made some inroads in that, which she would totally support.

Dr. Pickering inquired as to whether the number of high risk infants who have disease impact the total disease rate and if so, how that impacts the economic analysis.

Dr. Cohn responded that they cannot answer that question. It is known that the number of high risk children in the US is very low. Most infants will not have complement deficiencies recognized. Very few children have functional asplenia. Even children with sickle cell disease sometimes as infants still have their spleens. There are probably not many infants traveling to endemic countries where meningococcal disease is hyper endemic, such as the Sub-Saharan meningitis belt. Fewer children are believed to be in the high risk age group compared to the 2- to 10-year olds. Because there are so few high risk children, most cases of meningococcal disease in infants are not occurring in high risk infants. There would certainly be some, but there is no way of knowing that. The definition of "high risk" that they would want to include, which a couple of work group members have strongly encouraged, is used during local community outbreaks of C and Y disease for which vaccination is recommended. This would be a really great option, and previously there has not been a good option for vaccination of less than 2-year olds in community outbreaks. This language would be included in the VFC resolution.

Dr. Baker noted that most states have a sickle cell disease screening program even though they are not functionally asplenic as young as two months. She assumed that all of these individuals would be considered high risk.

Dr. Cohn replied that the language could be made clear about this point as well, perhaps even suggesting that giving these children a full 4-dose series would be better than giving them a single dose at 2 years.

Dr. Baker thought this should be considered before they came to a vote, because the newborn screening programs will identify those infants early. Some of them will acquire disease before they are two years of age with CY-containing serogroups.

Dr. Judson inquired as to how common screening is for C3, C4 complement deficiency in infants.

Dr. Baker responded that most of those children show up in the 2- to 10-year old and adolescent age groups.

Dr. Howe (GSK) stated that GSK is committed to bringing products of value to the market. They believe their candidate HibMenCY vaccine is an excellent Hib vaccine, which was also developed to address an important non-medical need for vaccination in infants and toddlers. Despite the observed recent historic low rate, meningococcal disease remains a serious illness and the impact of the disease can be devastating. Meningococcal disease is known to have a cyclical nature, which means that the low rates may not be sustained long-term. As reported earlier in this session, vaccines to prevent serogroup B disease are in earlier stages of development, so they will not be available in the short-term. Therefore, GSK believes in the value of HibCY vaccine, as approximately 40% of infant disease is caused by serogroups C and Y. Now ACIP has implemented recommendations that address the risk of disease in adolescents. HibCY vaccine was developed to address vaccine preventable meningococcal disease in infants and toddlers, for whom the risk is even higher. Based on the health outcomes data presented during this session, infants and adolescents can be immunized at a similar level of cost-effectiveness, and that does not consider the additional value of the Hib component, which is highly cost-effective if not cost saving. In October 2009, ACIP heard about the clinical trials involving more than 9,000 infants and toddlers conducted over 7 years with HibMenCY in which the HibCY vaccine was shown to be safe and immunogenic, with a large majority of children maintaining protection through the highest period of risk. This product was developed specifically for the US to fit within the existing pediatric schedule without additional shots, office visits, or administrative fees, and it will be priced at an appropriate value to enable equitable patient access. We believe our product would be a valuable addition to infant immunization. If licensed and with a recommendation with VFC resolution, which one would expect to be justified based on the Hib component, GSK's HibCY vaccine would broaden provider choices and give parents access to a vaccine to prevent these serious diseases.

Dr. Katz noted that aside from Dr. Plotkin, he may be the only one old enough to remember the history of meningococcal vaccines in the ACIP. Meningococcal vaccines were originally used by the Armed Forces for their recruits. ACIP has repeatedly discussed meningococcal vaccines and made no recommendation until one day during the public comment session, parents brought in their children in with the amputations, scarring, et cetera. That changed the attitude of ACIP members. He wondered what might happen with the parents of children who have been damaged by C and Y, even thought the numbers are small.

Dr. Ehresmann stressed that this has been a really challenging discussion for all members of the work group, and that they have all wrestled with the issues. She thought the presenters did an excellent job of conveying the challenges faced by the work group members and the method by which they came to their decisions.

Dr. Keitel asked whether the countries that have had experience implementing immunization against MenC intend for that vaccine to remain in the schedule though they now have on-going low levels of disease.

Dr. Salisbury (DOH, UK) replied that the UK dropped one of its infant doses. They include a HibMenC at one year of age. Their disease rates remain exceptionally low. He thought it would be a very brave step to assume that that success is just due to natural variation and the prevalence of meningococci.

Dr. Langley (NACI) responded that their committee has increasingly seen control of meningococcal disease on the population level rather than the individual protection level. In terms of indirect effects from immunizing adolescents and how that affects children, Canada believes that control is only as good as the re-immunization program and that on-going

immunization is needed to control disease. She could not imagine that they would stop a toddler or infant program. Given that they address this on a population level, they also take into consideration the effects on public health. When there is a case of meningococcal, public health resources are totally diverted to the communication of difficulties, fear in the community, and the effect of that fear on confidence in vaccine programs in general. Those are also issues of concern for infant vaccine programs.

Dr. Meissner acknowledged the very thoughtful comments by Dr. Katz, and noted that most of the members of the work group committee are pediatricians who have dealt with the devastating consequences of meningococcal disease. Making public health policy decisions necessitates an inherent tension between what is best for society and the individual perspective they all feel as advocates for patients as physicians. It is not by any means an easy issue to resolve, but he thought they must maintain a balanced perspective. In this era of increasingly limited resources, a societal rather than individual perspective must be taken as difficult and painful as that is.

Dr. Paradiso (Pfizer) pointed out that obviously, Pfizer is watching with great interest the thinking and recommendations of ACIP related to meningococcal disease as Pfizer makes decisions about making fairly substantial investments in the phase III programs for meningococcal B vaccine. The implications of these discussions are beyond the HibCY vaccine, and they all must make decisions about how to proceed.

Dr. Lewin (Novartis) reiterated Dr. Paradiso's comments from Novartis's perspective. While it is premature to speculate, Novartis also develops vaccines to meet unmet public health needs in the US. They, too, carefully and closely watch ACIP decisions and continually re-evaluate their programs in light of these decisions.

Dr. Plotkin thought it would be useful for the industry to hear from the work group what kind of incidence would lead to general recommendations.

Dr. Meissner responded that it is extremely difficult to answer that question. It is a critical question, and everyone on the work group and ACIP is also concerned about the ramifications that this sort of decision has on the pharmaceutical industry. However, he did not believe it would be possible to cite specific incidence figures that would determine what decisions might be made in the future, given that this is simply too complex an issue.

Dr. Cohn added that the work group would consider not only the level of incidence, but also the rate of rise of incidence. These discussions have taken place among the work group members, and they do not believe this can be done currently.

Frankie Milley (Meningitis Angels) indicated that Meningitis Angels represents over 600 families across the US, and is the mother of an only child who died with meningococcal meningitis at the age of 18. Given that Meningitis Angels is seeing more and more meningococcal disease among children under 5 years of age, it concerned her the data presented were three years old.

Dr. Cohn responded that the reason they present data that are a couple of years old is because that is the best data they have that can separate which serogroups are causing disease. C and Y versus B data come from a different surveillance system than the national surveillance system. Reports from state health departments to CDC in 2008 and 2009 both showed decreases each year compared to 2007. In 2008, in total for B, C, and Y combined, there were 137 cases of meningococcal disease in 6 month olds to 5 year olds. Although the reporting is

not completely closed, there may be a couple more in 2009, there were 104 cases. That includes both serogroups, and CDC thinks that about 45% of those are likely to be serogroup C or Y. A decrease is still being observed in the nationally reported data.

Dr. Baker clarified that the data pertaining to the epidemiology were through December 2008, so the data are only about a year old.

Public Comment: Meningococcal Vaccine

Frankie Milley
Meningitis Angels

This is my son. I would like to remind everybody—I think the thing that really burns me the most is that we all need to realize that meningococcal does not stop at the dorm room door. It doesn't stop. It doesn't just affect kids living in dorms. It affects kids living outside the dorm, and it affects teenagers and tweens. We recently did a survey among some of our people. We took 17 of those interviews, and out of the 17 people that were interviewed, 9 of those children died and they were under the age of 5. The ones who died, if you want to look at economic impact, out of the 9 who died, 5 were under three years old. Just the medical bills for them, from the time they went to the hospital to the time of death, were over half a million dollars. To bury those children cost those families almost $200,000. The 8 that survived have lost limbs, have severe seizure disorders, kidney transplants, blindness, deafness, and their medical bills are into the millions of dollars and continue. I can't tell you how hard this is. We had 8 parents lined up to come here today, but we only have 5. One of them, 8 years later after their son had meningitis, he's been in the hospital three times this year already for severe seizure disorders, and his mom told me the other day is her greatest fear is she will go in to wake her baby up and he will be gone.

The economic and social impact is horrendous. You guys have done an amazing job by recommending it for college freshmen. You've done an amazing job doing it for adolescents. I know because I've been there every step of the way. You know, it's like if you have a cruise ship and you only have 40 life rafts. Are you going not let as many people on the life raft as you can or are you going to let everybody sink with the ship? We've got to save as many kids as we have. If you look at us, you can't tell a parent who's lost a child or who lives with a child so severely debilitated that is draining them financially, draining them emotionally, you can't tell them their one child is not worth a recommendation. I thank you and commend you for the job you do, but I am begging you with all of my heart, please consider this carefully. Please take into account the lives that are affected. Please take into account some of the lives you are going to hear about today. Please understand that with meningitis, once children come out of the hospital is not over. It goes on for a lifetime. Thank you.

Chris Boone
Meningitis Angels

I'm Chris Boone. This is my wife, Heather, and my son, Ethan. Ethan contracted meningitis or meningococcal at seven months old. He lost both legs, both arms, and has major facial scarring. He has many more surgeries to go to help his face. His nose practically fell off of his face. Please recommend this vaccine. Thank you.

Aida D'Antona
Meningitis Angels

Hi, my name is Aida D'Antona and I'm from New York. At the age of 3, my son John contracted meningococcal meningitis. As a result, he lost the top of an ear and three fingertips. They had to amputate both of his legs above the knee, and it affected his brain in 5 places. He has short-term memory loss and he is learning disabled now. He was in the hospital for 5 ½ months. It's 12 years later. He had 20 surgeries by the time he was 7 years old and he's still not done. He suffers every day of his life. I beg you to please recommend this vaccine so that no child has to endure what my child does every day. Thank you.

Jennifer Bax
Meningitis Angels

My name is Jennifer Bax and this Riley, my little boy. He contracted meningococcal when he was 3. He has severe hearing loss and is learning disabled now as well. We beg you to please recommend this vaccine so that no other parent or child ever has to see this. Thank you.

Wendy Meigs
Meningitis Angels

My name is Wendy Meigs and this is my daughter Leslie. She contracted meningococcal meningitis in 1998. She was 8 years old. This is a picture of her before she got sick. She spent two months in the hospital—a month in ICU, and three weeks on a ventilator. She has extensive nerve damage, scarring, and poor circulation. We go in periodically because she has to have part of her bone removed as it dies off. Although she was 8, the situation is the same. I believe the vaccine was not available. The other thing that she left with was dialysis. She was in kidney failure, which I didn't see mentioned. Three months after we left the hospital, Medicare called me to tell me that she was now Medicare Primary. But it was an unusual week. It turned out that her kidneys had begun working again and she was able to get her catheter removed. We dealt with kidney failure for 12 years. At 11 years old last April, she received a kidney transplant. She's doing better, but she still has all of the issues that are associated with renal failure. So what I'm asking you is to please, please approve this vaccine and allow this vaccination to take place so that children do not have to suffer illnesses that are life-long and will continue. You have the opportunity to save these infants and protect them, so I ask you to please save the babies. Thank you.

Lisa Nauman
National Meningitis Association

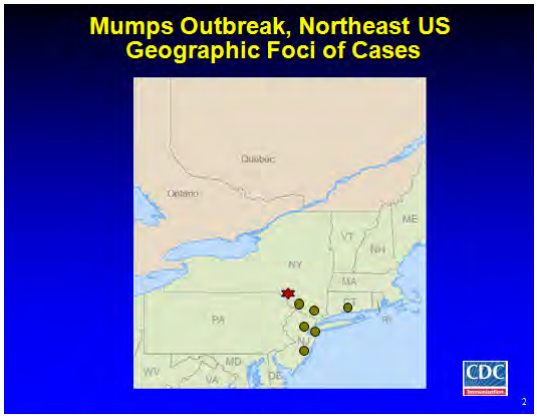
Hi, my name is Lisa and you're going to see a video of my daughter Sarah [Video was played and then Ms. Neuman offered her comments]. My daughter suffered more than the physical devastation you just watched. She also had neurological complications from the meningococcal disease. Her condition has left her dependent on others, and her cognitive level will never be that of an adult. Sarah just turned 15 this month, and she has received physical therapy weekly for the past 14 years. She's endured multiple facial and surgical procedures to reconstruct her nose and lip. Being confined to the wheelchair, she has developed severe scoliosis, which will require surgery in the near future. As a parent, I urge you to make the vaccine available to infants. Parents need to have information to make decisions about the disease, and no child should be lost or suffer from a vaccine preventable disease. Here's Sarah today [photograph shown].

Dr.Baker thanked everyone for their public comments about meningococcal disease. Speaking on behalf of the committee and CDC staff, she emphasized that they care about parents and their children and are sorry for these consequences.

On-Going Mumps Outbreaks Northeast United States June 2009 to Present

Kathleen Gallagher, DSc, MPH
Division of Viral Diseases, NCIRD, CDC

Dr. Gallagher provided an update on the status on the on-going mumps outbreak in the Northeastern US that began in June 2009. This outbreak began when an 11 year old boy returned to a Jewish summer camp in upstate New York (NY) in June 2009 after a visit to the United Kingdom (UK). This location is depicted on the following map by the red star:



The child subsequently developed parotitis and infected additional campers, who subsequently developed disease. When the camp ended in August, the children, some of whom were incubating mumps, returned to their homes in Brooklyn and Rockland County where additional cases occurred. Further spread to Ocean County, New Jersey (NJ) and Orange County, NY occurred in the fall. In the past few weeks, additional cases have been reported from Connecticut (CT) and Northern NJ. The green dots on the above map represent the locations where outbreaks of mumps are currently occurring in the US. This outbreak was also exported to Quebec and Israel.

This is the largest outbreak of mumps in the US since 2006. A total of 2,336 cases were reported to CDC through February 19, 2010. The median age of cases is 15, with a range in age from 3 months to 90 years. Of the cases, 74% are in males. The majority of cases are reporting typical clinical presentations, with most patients reporting either unilateral or bilateral parotitis. 84 persons (about 4%) have reported complications, the majority of which have been Orchitis (70). Other complications have included pancreatitis(6), meningitis(5), oophorotis (1), mastitis (1), deafness (1), Bell's Palsy (1), and meningoencephalitis (1). Cases continue to be reported. Of the case patients, more than 98% thus far belong to the Hasidic Jewish community. Of the 45 cases that have been reported outside of these, almost all of them have had some sort of contact with the community through either employment in their community or in a surrounding community. For the most part, this Jewish community has limited interaction with other surrounding communities. The children, for the most part, attend private Jewish

religious schools. The average household size is relatively large. It is not unusual for a family to have 10 or more children.

For the 1,565 (67%) cases for whom measles, mumps, rubella (MMR) vaccination status is known, 76% had 2 doses, 13% had one dose, and 8% had zero doses. Unknown vaccination status is most commonly noted in adults who frequently were not in possession of their immunization records.

There have been several factors in common that contributed both to this outbreak and the mumps outbreak in 2006. Both outbreaks were initiated by importation of the type G genotype from endemic areas outside of the US. For this outbreak, it is known that the importation is from the UK, and it is suspected that this is also true for 2006. Previous studies have estimated that vaccine effectiveness is approximately 73% to 91% after a single dose of mumps vaccine and 79% to 95% after 2 doses. Thus, if mumps is introduced into a highly dense living or educational environment, as is the case currently and was the case in 2006, transmission of mumps might be expected to occur.

In the Jewish community, particularly for boys, long hours are spent at school 5 days per week. Unlike girls, who study in more traditional settings, boys will spend many hours of their day focusing on their religious studies in crowded study halls.

A third dose of MMR vaccine is not currently recommended for mumps outbreak control or post-exposure prophylaxis. However, in Orange County, New York, schools had high 2-dose MMR coverage and still reported on-going mumps transmission in their schools, presumably facilitated by these crowded conditions. Because social distancing measures were not thought to be feasible and because virtually all children in this one community attend one of three religious schools, in collaboration with the county and state health departments and support of the community, CDC chose to offer a third dose of MMR to all fully vaccinated 6 to 12 graders, which was the most affected age group in this community. In addition, a protocol which allows for the receipt of a third dose of MMR vaccine within 5 days of mumps exposure in a household has also just been initiated. These two protocols were submitted to and approved by institutional review boards (IRBs) at CDC and the New York State Department of Health (NYSDH).

Over the next several months, CDC will continue to conduct on-going surveillance for mumps throughout the US, particularly to monitor for changing epidemiology or spread to other geographic locations or communities. As always, CDC continues to promote early recognition, diagnosis, and public health intervention, as well as timely vaccination with 2 doses of MMR vaccine. There are also plans to evaluate the impact of the administration of a third dose of MMR in Orange County to determine if this might be a possible intervention in future outbreaks of mumps.

Discussion

Dr. Baker inquired as to whether the genotype in this outbreak is the same as that in the 2006 outbreak, and whether there was anything special about that strain in terms of transmissibility or virulence compared to other strains.

Dr. Gallagher confirmed that it is the same genotype. CDC has addressed the question of transmissibility and virulence numerous times over the last several months. Thus far, there is no evidence to suggest there is any particular difference.

In terms of duration of immunity, Dr. Cieslak inquired as to whether CDC had assessed case status versus time since vaccination, and whether there was increased incidence with time since vaccination.

Dr. Gallagher responded that they had examined this. The median duration of protection is about 10 years. Some cases have received vaccine more recently. She examined whether there was increased incidence with time since vaccination. It peaks at 10 years and beyond that drops off again. It is a bell-shaped curve. She thought this was in part because the nature of this outbreak is very much focused in religious schools that only certain age groups attend.

Dr. Katz (IDSA) asked whether any serologic or virologic studies had been conducted.

Dr. Gallagher responded that while such studies have not yet been conducted, they are under discussion. A meeting was planned that afternoon to discuss further research. Given that these cases continue, there are opportunities for additional studies.

Dr. Middleman (SAM) inquired as to whether CDC observed a difference in complication rates among those who had 2 doses versus 1 dose versus 0 doses.

Dr. Gallagher replied that they did. The most common complication was Orchitis by far. There is a statistically significant difference between the Orchitis rate in people who have had 1 dose versus 2 doses. It is lower in people who have had 2 doses.

Dr. Lett noted that they would very much be looking forward to the data from the third dose studies. State and local health departments are trying to cope with what to do when they have cases. She wondered whether there were any national plans to communicate to religious groups to encourage people to be vaccinated before the upcoming religious holidays. While most children are vaccinated, a number of people are not or have unknown vaccination status.

Dr. Gallagher indicated that CDC has begun to have these discussions, starting with some of the communities that are affected, given that the Passover holidays were approaching. Jewish boys attend schools called Yeshivas where frequently there is a mix of day students and boys who board there who may be from other parts of the country. During the Jewish holidays, the boys who are boarding will likely return home where they may introduce mumps into a new Orthodox Jewish Community, resulting in further spread. CDC has considered ways to send information home with Yeshiva students, and to disseminate messages to other Orthodox communities within the US that have not been affected so that they will be on heightened alert. Consideration is also being given to potentially sending out a message about being up to date on two doses so that these communities are prepared for potential imports.

Dr. Salisbury (DOH, UK) reported that the UK has experienced measles problems in North London with this same community, particularly in 2007 and 2008. This was not because of any resistance to vaccination amongst this group. It was entirely to do with access. These are families with many children who simply were not availing themselves of the services offered. Working with the local communities certainly helped. Once these families knew the facilities were there for them to be immunized, they made more effort to get their children vaccinated. It was not a resistance to vaccines. It was simply being overwhelmed by the number of children. He alerted everyone that not only was mumps an issue in this community, but also measles can be spread very easily by this group due to their numerous international connections.

Dr. Meissner commented that the mumps component of the MMR does not work as well as the measles and the rubella components. With that in mind, he wondered whether Dr. Katz or Dr. Plotkin would comment on the need for improvement of the mumps strain in the vaccine.

Dr. Katz said that in the absence of poor Dr. Hilleman who died several years ago, he was loathe to make any comments. He suggested that Dr. Offit may be able to comment more knowledgably on the Hilleman family. He also thought it would be interesting to hear from their Japanese visitors. Japan used the Urabe strain for a number of years, which was more reactogenic and produced aseptic meningitis among some of the recipients, so they abandoned it. One wonders if there is that much of a difference in the antigenicity or the immunogenicity of the strains that have been studied. As far as Dr. Katz was aware, the US outbreaks in 2006 and currently suggest that there is not long-lasting immunity for some individuals. For mumps, it is T-cell mediated immunity more than it is B-cell.

Dr. Plotkin agreed that based on the range of efficacy presented, it was clear that the efficacy of a single dose certainly is less than one would wish, and less than the other two components. Japan no longer uses mumps vaccines, and they do have a mumps problem that has been well-written about. For whatever reason, they do not import measles, mumps, and rubella vaccine. As far as the relative safety and efficacy, the Jeryl Lynn strain and the GSK derivative of the Jeryl Lynn strain are the only two strains that are not associated with aseptic meningitis. However, there are comparative data that suggest that the Urabe strain in particular is somewhat more effective than the Jeryl Lynn strain. It also depends upon the duration of immunity—the time since vaccination. It is a complex situation, but he does believe that a better mumps vaccine strain is needed. There are several strains, but none of them is perfect.

Dr. Temte noted that presumably, all of these individuals are being immunized within a limited set of clinics. With that in mind, he wondered whether anything was known about the storage and handling of vaccine at those sites.

Dr. Gallagher responded that they are all being immunized within a limited set of clinics. Within one community that has received the third dose, there are basically four pediatric providers currently and probably over the last 20 or 30 years. Those who have lived in the community during that timeframe would have received vaccine from one of these providers. CDC has not conducted an assessment of the vaccine storage issues in these particular clinics. Many people have moved into this community who probably lived in New York City and may have received their vaccine there. There are many providers in various counties in New York and New Jersey who would have been providing vaccine to this group.

Dr. Jane Zucker (NYCDHMH) reported that NYCDHMH examined the risk of Orchitis with vaccination, finding that there is a 4-fold higher risk of Orchitis in post-pubertal males who did not have any vaccine compared to those who had 2 doses (8% versus 2%, respectively). They conducted assessments and made VFC storage and handling visits to limited providers in the Brooklyn community. There appeared to be no problems with vaccine storage and handling. Among their initial cases, they collected rubella serology as a comparison to determine whether children really had been vaccinated or if records were being falsified for school for some reason (e.g., religious or philosophic exemptions; concerns about vaccination). This was not found to be an issue. In addition to the Passover holidays, there is Purim during which there are many parties and numerous children are gathering together. Last year, New York had a measles outbreak right after Purim, so they conducted numerous vaccination activities in the past few

weeks. They anticipated the holidays and began preparing in advance for uptake in mumps and / or measles cases. They also had an outbreak after the Jewish holidays in September.

Rotavirus Vaccines in Infants with Severe Combined Immunodeficiency

Catherine Yen, MD MPH
Epidemic Intelligence Service Officer
National Center for Immunization and Respiratory Diseases (NCIRD)
Division of Viral Diseases (DVD)

Dr. Yen provided background information regarding severe combined immunodeficiency (SCID) and discussed rotavirus vaccination in infants with SCID.

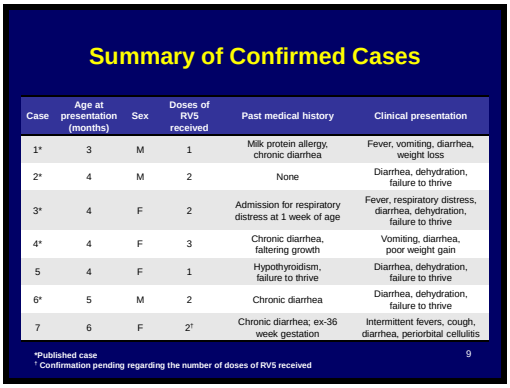
SCID is a rare, heritable primary immunodeficiency characterized by impaired humoral and cell-mediated immunity which is secondary to a lack of T-lymphocytes and low immunoglobulin levels, resulting in an inability to fight off infections of all types. At least 15 single gene disorders associated with SCID have been identified to date. The estimated incidence of SCID is about 1 per 60,000 to 100,000 live births per year, for a total of about 100 infants in the US per year. The median age at diagnosis ranges from 4 to 7 months.

Infants with SCID commonly present with chronic diarrhea, failure to thrive, early onset respiratory infections, and / or other infections that may include rotavirus. Diagnosis is usually made at the time of hospitalization with presentation of more severe disease or infection. However, prenatal diagnosis is available for those with a family history of SCID, though it is important to note that the majority of infants do not have a family history of SCID. Newborn screening techniques are also available, although they are not widely implemented. Currently, pilot newborn screening programs have been implemented in two states. A few other locations are planning to implement such pilot programs as well.

The prevention and treatment of infectious diseases and hematopoietic stem cell transplantation offer the best chance of survival for infants with SCID. More specifically, early diagnosis and transplant before the occurrence of any severe infection offer the greatest chance of cure. Without transplant, death in early childhood due to infection will occur, with the majority of deaths occurring by 1 year of age. One possible exception is for those infants with adenosine deaminase deficiency. These children may survive longer with enzyme replacement therapy while awaiting transplant. Infants with SCID who acquire wild type rotavirus infection may develop chronic infection, which may manifest as prolonged diarrhea and prolonged fecal shedding of rotavirus.

With regard to rotavirus vaccine infection in infants with SCID, in March 2009, a report of 2 infants with diagnoses of SCID and infection with pentavalent vaccine-type rotavirus (RV5) was presented at the American Academy of Allergy, Asthma, and Immunology (AAAAI) Annual Meeting. Since then, 4 additional cases have been identified in the US, two of which have been published and reported to the Vaccine Adverse Event Reporting System (VAERS) and two of which we were notified through personal communication and were subsequently reported to VAERS. Another case from Australia was published in the *Journal of Allergy and Clinical Immunology* in September 2009.

The following tables provide a summary of what is known about these 7 infants with SCID and rotavirus vaccine infection:



Summary of Confirmed Cases

Case	Age at presentation (months)	Sex	Doses of RV5 received	Past medical history	Clinical presentation
1*	3	M	1	Milk protein allergy, chronic diarrhea	Fever, vomiting, diarrhea, weight loss
2*	4	M	2	None	Diarrhea, dehydration, failure to thrive
3*	4	F	2	Admission for respiratory distress at 1 week of age	Fever, respiratory distress, diarrhea, dehydration, failure to thrive
4*	4	F	3	Chronic diarrhea, faltering growth	Vomiting, diarrhea, poor weight gain
5	4	F	1	Hypothyroidism, failure to thrive	Diarrhea, dehydration, failure to thrive
6*	5	M	2	Chronic diarrhea	Diarrhea, dehydration, failure to thrive
7	6	F	2†	Chronic diarrhea; ex-36 week gestation	Intermittent fevers, cough, diarrhea, periorbital cellulitis

*Published case
† Confirmation pending regarding the number of doses of RV5 received

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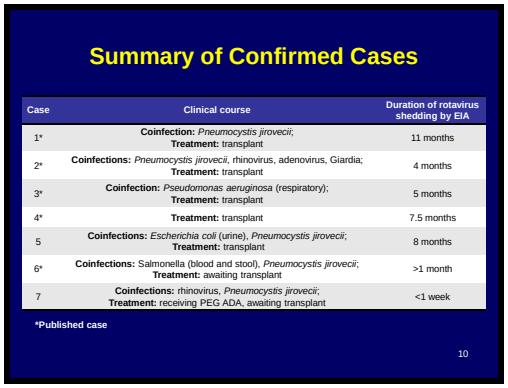

Summary of Confirmed Cases

Case	Clinical course	Duration of rotavirus shedding by EIA
1*	**Coinfection:** *Pneumocystis jirovecii*; **Treatment:** transplant	11 months
2*	**Coinfections:** *Pneumocystis jirovecii*, rhinovirus, adenovirus, Giardia; **Treatment:** transplant	4 months
3*	**Coinfection:** *Pseudomonas aeruginosa* (respiratory); **Treatment:** transplant	5 months
4*	**Treatment:** transplant	7.5 months
5	**Coinfections:** *Escherichia coli* (urine), *Pneumocystis jirovecii*; **Treatment:** transplant	8 months
6*	**Coinfections:** Salmonella (blood and stool), *Pneumocystis jirovecii*; **Treatment:** awaiting transplant	>1 month
7	**Coinfections:** rhinovirus, *Pneumocystis jirovecii*; **Treatment:** receiving PEG ADA, awaiting transplant	<1 week

*Published case

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Information was obtained through publications, VAERS reports, and in some cases, medical records that were sent to the VAERS team. The age at time of presentation of symptoms ranged from 3 to 6 months, and most infants had received either 1 or 2 doses of RV5 prior to presentation. For case number 4, the Australian case, this infant began to experience chronic diarrhea and poor growth at age 4 months, but was not actually diagnosed with SCID until the age of 9 months and had received 3 doses of rotavirus vaccine. Many of the infants had past medical histories significant for chronic diarrhea. All of the infants presented with diarrhea around the time of diagnosis of SCID. For case number 7, where it says confirmation pending regarding the number of doses of RV5 received, it has been confirmed that this infant received 2 doses of vaccine.

The majority of infants who were eventually diagnosed with SCID presented with co-infections, including fungal infection with Pneumocystis jirovecii (otherwise known as PCP), viral infections such as rhinovirus and adenovirus, parasitic infection with Giardia, and bacterial infections with Pseudomonas aeruginosa, E. coli, and Salmonella. At the time of CDC's follow-up of these cases, 5 infants had undergone hematopoietic stem cell transplantation and 2 were awaiting transplant. The duration of rotavirus shedding by enzyme immunoassay (EIA) for these infants, defined as the period between the initial positive rotavirus EIA test and the first negative EIA test, was from less than 1 week to 11 months. This could be a minimum duration of shedding depending on when that first positive test was performed. Additionally, 5 of the infants had multiple stool samples positive for vaccine-type rotavirus.

Given these reports of rotavirus vaccine infection in infants with SCID, Merck and Company requested to add SCID as a contraindication to the RotaTeq™ product label. This request was approved by the FDA on December 23, 2009. Given the change in the RotaTeq™ product label, CDC initiated a discussion regarding this topic with members of the former ACIP Rotavirus Working Group. After discussion and at this time, CDC recommends the addition of SCID as a contraindication for both licensed vaccines, RV5 and the RV1 monovalent vaccine. Though at this time CDC is not aware of an RV1 infection in a US infant with SCID, RV1 will be included in the contraindication given the biological plausibility for RV1 infection in infants with SCID. CDC also recommends the publication of an *MMWR* Policy Note regarding the addition of this contraindication to the current recommendations for rotavirus vaccination. Additionally, CDC will continue to monitor reports of rotavirus vaccine infection in infants with SCID.

Given the importance of early diagnosis of SCID in terms of survival, on January 21, 2010, the Advisory Committee for Heritable Disorders in Newborns and Children (ACHDNC) unanimously voted to recommend the addition of SCID to the core panel of the recommended uniform screening panel for newborns. This recommendation is awaiting approval by the Department of Health and Human Services (DHHS). If approved, this likely will lead to more widespread implementation of newborn screening and earlier diagnosis of SCID for affected infants.

Discussion

Dr. Cieslak said he understood the manufacturer's choice, but rotavirus is essentially universal in unvaccinated children. He inquired as to what occurs when SCID children contract a wild virus as opposed to an attenuated virus.

Dr. Yen replied that the same symptoms could occur.

Dr. Baker pointed out that rotavirus has been seen in these children for a number of years. They are not particularly ill, but they shed for a very long time with intermittent, fairly easy to control diarrhea. They may need hydration, for example.

Vaccine Supply Update

Jeanne M. Santoli, MD, MPH
Vaccine Supply and Assurance Branch

Dr. Santoli presented an update for Hib, Hepatitis B, Hepatitis A, Rotavirus, MMRV, and Zoster vaccines, and reported on supply constraints.

Merck received FDA approval for distribution of monovalent Hib vaccine, PedvaxHIB®, on January 14, 2010. The product became available for order the following week. PedvaxHIB® is one of a number of products currently available for Hib vaccination. Other products available for Hib include monovalent Hib vaccine from sanofi; monovalent Hib from GSK, which is currently licensed for the booster dose only; and the combination Pentacel vaccine from sanofi pasteur. There are two combination Hib vaccines, one from Merck (Comvax) and one from sanofi (TriHIBit) that are not currently available.

CDC is updating website Hib postings to emphasize the recommendation for active recall of children in need of a booster dose based on current supply. The initial discussions about recall were limited to the next medical visit. Next, they were limited to when feasible and when supply permits, but at this point, active recall of these children is recommended to get them caught up.

Both manufacturers are back to full supply of their monovalent pediatric hepatitis B vaccines. There were some doses borrowed from the stockpile last year, which are in the process of being repaid. CDC had been managing orders through allocation to states, which was discontinued on January 1, 2010.

In terms of Hepatitis B vaccines for adults, Merck is not currently distributing its adult or dialysis hepatitis B vaccines. The dialysis formulation is anticipated to return sometime in the third quarter of 2010. The adult formulation will not be available from Merck for the first half of 2010, but there will be an update during the first half to provide information regarding when that vaccine will be available again. Following backorders (> 1 month) in the late fall for both formulations, GSK now has product available and has cleared backorders. GSK expects to have at least one presentation of adult monovalent product continuously available (vials). The combination product, Hep A-Hep B vaccine, is available as an alternative.

There were some product outages of GSK's pediatric hepatitis A vaccines in the second half of 2009. Both manufacturers are currently making vaccine available to the market and utilizing doses from the pediatric stockpiles to fill in gaps as needed.

For adult Hepatitis A vaccine, Merck announced it would not be distributing adult Hepatitis A vaccine for the rest of 2010; however, GSK's production and supply of their monovalent and combination adult vaccines are in adequate supply to meet demand for 2010.

With regard to rotavirus vaccines, GSK experienced some intermittent product outages in November and December 2009, but supply became available in late December and GSK has been able to clear back orders for that product. GSK anticipates that there may be some intermittent backorders until mid-March 2010, but both manufacturers anticipate being able to meet demand for their customers for the two rotavirus products.

Merck had recently delayed the re-launch of MMR-V that was originally set for mid-February. That delay reflects varicella manufacturing prioritizations for 2010 due to a less than expected yield of bulk product. Varicella vaccine remains the first priority for varicella bulk, followed by zoster vaccine, and then MMR-V. Limited doses of the MMRV will be available later this year and Merck will provide more information as it becomes available. Importantly, the supply of varicella and MMR vaccines is sufficient to support current recommendations.

Zoster vaccine is currently available to order, but Merck anticipates that customers will likely experience backorders throughout the year, given that bulk varicella product is prioritized for use in manufacturing the varicella vaccine.

Regarding supply constraints of specific presentations, GSK anticipates intermittent supply constraints during the first half of 2010, including Havrix® pediatric syringes and Kinrix™ syringes; however, alternative presentations (vials) and other brands are available to address these constraints.

CDC's Vaccine Supply / Shortage Webpage can be found at the following url:
http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm

Evidence Based Recommendations Work Group

Introduction

Jonathon Temte, MD, PhD, Chair
Evidence Based Recommendations Work Group

Dr. Temte noted that ACIP is constantly being asked to translate complex information into meaningful and implementable recommendations. The comments from Dr. Frieden the previous day and from the last time he spoke during an ACIP meeting got to the heart of using very good evidence for this process.

The Evidence Based Recommendations Work Group's charge is to develop a uniform approach to making explicit the evidence base for ACIP recommendations. This is fairly straightforward, at least on the surface. This work group was reactivated in November 2007. When Dr. Temte first joined ACIP as an American Academy of Family Physicians (AAFP) liaison in 2004, this group had some activity, but it faded out for a while. He expressed his hope that they would reach a point of bringing some activities to a conclusion. The work group has convened monthly conference calls since January 2008, and has been working on guiding principles and reviewing several evidence-based systems for developing guidelines used by other organizations. For example, the work group has assessed the methods of the following groups and systems:

- US Preventive Services Task Force, www.ahrq.gov/clinic/uspstf08/methods/procmanual5.htm
- Guide to Community Preventive Services, www.thecommunityguide.org/about/methods.html
- GRADE: Grading the quality of evidence and the strength of recommendations, which we will be talking much more through this discussion. www.gradeworkinggroup.org/intro.htm
- National Advisory Committee on Immunization from Canada, www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09pdf/acs-1.pdf
- American Academy of Pediatrics

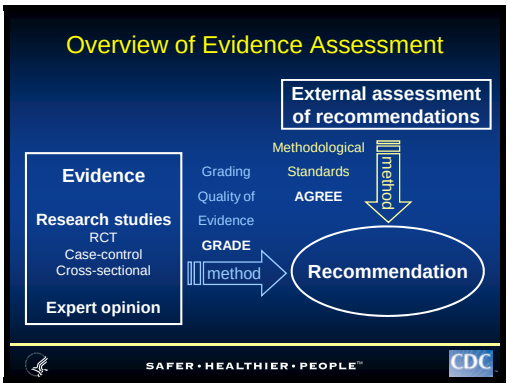
The work group's guiding principles are to focus on transparency; use evidence of varying strengths; consider individual and community health; adopt / adapt an existing system rather than re-creating something that may already exist; continually strive to improve the process; and first apply the proposed process to new vaccines and new indications or restrictions of existing vaccines. The components of evidence-based vaccine recommendations include key elements for consideration (e.g., safety, efficacy, and burden of illness); an assessment method for existing evidence; standardized format for recommendations; and a means for reporting of elements and evidence in a clear and transparent manner.

The work group proposed to adopt the Grades of Recommendation Assessment, Development and Evaluation (GRADE) framework for rating quality of evidence, and to adapt the GRADE system for moving from evidence to recommendations. The GRADE system has had wide uptake from a number of sister groups, such as the following:

- ❑ Agency for Health Care Research and Quality (AHRQ)
- ❑ American College of Chest Physicians
- ❑ American College of Physicians
- ❑ American Thoracic Society
- ❑ Allergic Rhinitis in Asthma Guidelines
- ❑ CDC Healthcare Infection Control Practices Advisory Committee
- ❑ Infectious Diseases Society of America
- ❑ UpToDate
- ❑ British Medical Journal
- ❑ Canadian Cardiovascular Society
- ❑ Clinical Evidence
- ❑ Cochrane Collaboration
- ❑ European Society of Thoracic Surgeons
- ❑ National Institute Clinical Excellence (NICE)
- ❑ Scottish Intercollegiate Guideline Network (SIGN)
- ❑ World Health Organization (WHO)
- ❑ Over 20 other major organizations

Dr. Temte indicated that during this session, presentations would be offered regarding methodological standards for clinical practice guidelines, grading the quality of evidence, and synthesizing and presenting recommendations. He noted that Dr. Craig Umscheid from the University of Pennsylvania, who would present information on the GRADE system, is one of the members of the working group for GRADE.

Dr. Temte clarified how GRADE differs from AGREE:



Appraisal of Guidelines for Research and Evaluation (AGREE) is an external process by which recommendations can be evaluated. There are two different processes: 1) moving from evidence to a recommendation (GRADE); and 2) external assessment of that recommendation of the guidelines (AGREE).

Methodological Standards for Clinical Practice Guidelines

Faruque Ahmed, PhD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Ahmed pointed out that major organizations in the US, Canada, and Europe are increasingly using evidence-based methods to develop clinical practice guidelines. Methodological standards have been developed to direct the development of guidelines. Clinical practice guidelines are systematically developed statements to assist practitioner decisions about appropriate health care for specific clinical circumstances. "Quality of guidelines" means the confidence that the potential biases of guideline development have been addressed adequately.

AGREE is an international collaboration of researchers and policy makers who seek to improve the quality and effectiveness of clinical practice guidelines. The AGREE collaboration developed the AGREE instrument to provide a systematic framework for assessing key components of guideline development. The AGREE instrument includes 23 items grouped into 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence.

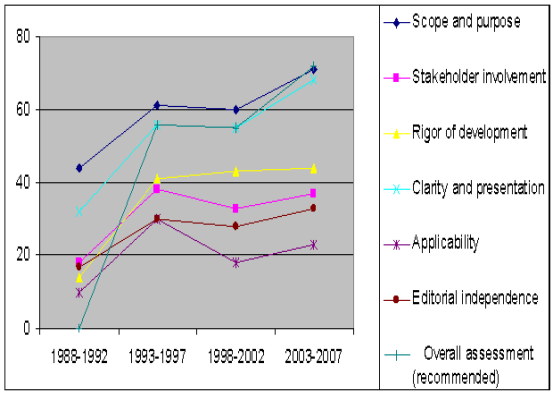
The rigor of development domain, for example, includes the following components:

- ❑ Systematic methods were used to search for evidence
- ❑ The criteria for selecting the evidence are clearly defined
- ❑ The methods used for formulating the recommendations are clearly described
- ❑ The health benefits, side effects and risks have been considered in formulating the recommendations
- ❑ There is an explicit link between the recommendations and the supporting evidence
- ❑ The guideline has been externally reviewed by experts prior to its publication
- ❑ A procedure for updating the guideline is provided

Alonso-Coello et al used the AGREE instrument to assist in the quality of 626 guidelines published from 1988 through 2007. These guidelines are published primarily in North America and Europe by medical societies and governments on a variety of healthcare topics. The number of each is reflected in the following table:

Characteristics	Number
Continent of published guidelines	
North America	264
Europe	264
Other	97
Type of organization responsible for guideline	
Medical society	373
Government	121
Other	110
Healthcare topic	
Internal medicine / critical care / geriatrics	173
Musculoskeletal	136
Oncology	127
Other	184

The mean scores for the 626 guidelines for the AGREE domains were: applicability 22%, editorial independence 30%, stakeholder involvement 35%, rigor of development 43%, clarity and presentation 60%, and scope and purpose 64%. While the mean scores have increased slowly over the last 20 years, there is substantial room for improvement. The mean scores over time for the 6 AGREE domains are depicted in the following graphic:



Use of evidence-based systems such as GRADE can improve the quality of guidelines. As noted, GRADE has two components: assessing the quality of evidence and a process for moving from evidence to recommendations. The quality of evidence is rated as high, moderate, low, or very low. The strength of recommendation is graded as strong or weak. Guideline developers need to incorporate structured and rigorous methodologies to improve the methodological quality of guidelines.

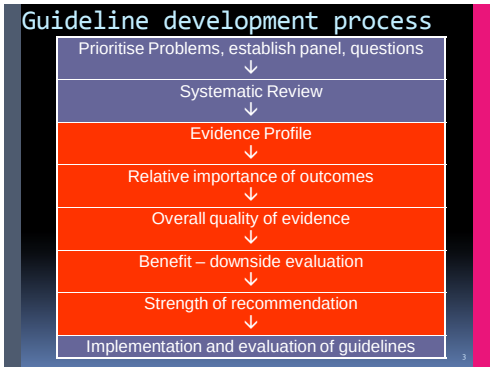
Grading Quality of Evidence; the GRADE approach

Craig A Umscheid, MD, MSCE
Assistant Professor of Medicine
Co-Director, Center for Evidence-based Practice
University of Pennsylvania

Dr. Umscheid indicated that he is a hospitalist clinically and an epidemiologist at the University of Pennsylvania. He explained that one of the reasons he was invited to speak during this ACIP meeting was because he and the center he co-directs at the University of Pennsylvania, the Center for Evidence Based Practice, worked closely with CDC's HICPAC committee to update their guideline methodology. The first guideline using that methodology was recently published in *Infection Control and Hospital Epidemiology*, and is titled *Guideline for Prevention of Catheter-Associated Urinary Tract Infections 2009*.

During this session, Dr. Umscheid focused on how the GRADE system helps to grade the quality of evidence in a guideline, the guideline development processes from higher than a 30,000 foot view, the GRADE approach, and grading of evidence quality.

The following illustrates the general guideline development process:



Dr. Umscheid emphasized that arguably the most important step in the guideline development process is developing the right key question. Guidelines are a way of answering questions about clinical, communication, and organizational or policy interventions in the hope of improving health care or health policy. It is, therefore, helpful to structure a guideline in terms of answerable questions. If the right question is not posed, a guideline will result that does not address the questions that are on the minds of practicing providers. For ACIP, Dr. Umscheid thought that process might be relatively easy in that the questions would be largely circumscribed around the efficacy and safety of particular vaccines. For other groups, question development can be very challenging.

There is information about how Dr. Umscheid's group helped HICPAC update their guideline methodology on the HICPAC website and in a March 2010 in the *American Journal of Infection Control.* He also recommended reading an article by the GRADE Working Group about the GRADE approach published in the *British Medical Journal* in April 2008, which is a very general article about the approach.

To illustrate how to grade the quality of evidence in a guideline, Dr. Umscheid walked through one of many questions that were posed for the HICPAC guideline: Do Texas catheters impact UTI outcomes differently than Foley catheters? A systematic review of the evidence was conducted to determine the answer to this question. The GRADE process was then used to judge the overall quality of the evidence and weigh the risks and benefits in order to make a recommendation. Obviously, GRADE uptake is pretty broad and deep. Probably the most important organizations to emphasize for ACIP that use GRADE are the World Health Organization (WHO), the National Institute Clinical Excellence (NICE), the Infectious Diseases Society of America (IDSA), and most recently HICPAC.

The following table outlines the clinical question asked in the guideline regarding Texas versus Foley catheters in terms of outcomes, quantity and type of evidence, and findings:

Comparison	Outcome	Quantity and Type of Evidence	Findings
Texas vs. Foley catheter	Symptomatic UTI	1 RCT	Decreased risk
	Bacteriuria	1 RCT	No difference
	Bacteremia	1 OBS	No difference
	Patient Satisfaction	1 RCT 1 OBS	Increased satisfaction

Once the systematic review of the literature for the key question done and all of the outcomes available in the literature are determined, consideration must be given to which outcomes are most important in terms of making a decision about how to answer the key question. The importance of the outcome, with the following categories used: critical for decision making, important but not critical for decision making, and of low importance. For this particular question, outcomes that are critical for decision making might be symptomatic UTI - the difference between incidence of symptomatic UTI between the two catheters, and patient satisfaction between the two catheters. An outcome that may be important but not necessarily critical for decision making might be bacteremia. An outcome of low importance might be asymptomatic UTI or bacteriuria. The guideline committee basically agreed with this assessment.

In terms of understanding how the quality of evidence is judged for each of outcome available in the literature, evidence that includes RCTs are considered to be of the highest quality, while OBS [observational studies] are considered to be of low quality evidence. There are 5 factors that can lower the quality of evidence and 3 factors that can increase the quality of evidence. For example, the outcome of symptomatic UTI has an RCT informing it. The initial grade of the evidence is going to be high, but 5 criteria can decrease that grade. One of those criteria is study quality limitations. For each guideline, the specific criteria that will be used to understand whether the quality of the study is limited have to be developed a priori. For example, a study quality might be limited if the randomization in it is incorrect or if there is no blinding. Inconsistency is the next criterion that could decrease the grade of quality for an individual outcome. Basically, inconsistency means that results are not consistent across studies that are informing that outcome. For example, two RCTs assessing symptomatic UTI for Texas versus Foley catheters may differ. One the RCTs might suggest that there is decreased UTI with Texas catheters, while the other might suggest that there is increased UTI with Texas catheters. If these inconsistent results cannot be explained, a point is taken off. Indirectness is another criterion for which a point may be taken off (e.g., no data on male Texas catheters, the study question; but information is available on female Texas catheters versus Foley catheters).

Imprecision simply means that there are very few events in the studies that are informing the outcome. Either there are very few studies, or confidence intervals in the studies are very large. Publication bias simply means that perhaps there are just one or two small studies that show a very large magnitude of effect for condom catheters, but both are published by the manufacturer of Texas catheters. Conversely, beginning with an OBS that is informing one of the outcomes, the grade may start out low, but there are criteria that can be used to increase the quality grade, one of which is strength of association. Dose response is another criterion that could increase the grade. Inclusion of unmeasured confounders would increase the magnitude of effect.

In terms of what these outcomes actually mean, a high overall quality grade means that further research is very unlikely to change confidence in the estimate of effect. Moderate grade means that further research is likely to impact confidence in the estimate of effect, and it may change the estimate. A low quality grade means that further research is very likely to impact confidence in the estimate of effect and is likely to change the estimate. Very low quality means that any estimate of effect is very uncertain.

Specific to symptomatic UTI in the example, because RCTs informed this particular outcome, the quality of the evidence for that outcome started out as high, but one point was taken off for imprecision because there is just one study, so the grade went down to moderate. One RCT informed the outcome of bacteriuria, so the outcome started out as high quality. Again one point was taken off because there was just one RCT. Thus, the grade went down to moderate. Only one OBS informed the bacteremia outcome, so that outcome started out as low quality but one point was taken off for imprecision. Therefore, this outcome dropped to very low. Two studies informed the patient satisfaction outcome (one RCT and one OBS). Because there was an RCT informing this outcome, the quality for the outcome started out as high. No points were taken off for any of the other criteria (e.g., inconsistency, individual study quality, or indirectness) so the quality for that outcome remained high. To obtain a quality for the overall evidence base answering this question, the lowest quality grade for the outcomes deemed critical is used. Symptomatic UTI and patient satisfaction were deemed to be critical, so the lower of these two grades was used for an overall grade of evidence for that outcome was moderate.

In conclusion, GRADE provides a structured approach to assess the quality of evidence across guideline questions and outcomes. Although judgments are involved, as long as those judgments are systematically applied and they are transparent, it is reasonable to make them.

Guidelines for Synthesizing and Presenting Recommendations

Faruque Ahmed, PhD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Ahmed presented the guidelines for formulating and presenting recommendations, discussing the GRADE approach for going from evidence to recommendations; describing how WHO and ACP are using GRADE for the development of recommendations for non-vaccine topics; and discussing how the GRADE approach could be adapted for vaccine recommendations.

GRADE has two components: rating the quality of evidence and grading the strength of the recommendation. GRADE suggests using two grades for the strength of recommendation: strong and weak. Guideline panels may prefer to use the word “conditional” rather than “weak.” Strong or weak recommendations can be either for or against a recommended course of action. That is, a recommendation for a course of action can be strong or weak and a recommendation against a course of action can be strong or weak. Quality of evidence is only one factor in determining the strength of a recommendation.

GRADE deliberately separates judgments regarding the quality of evidence from judgments about the strength of recommendation. Quality of evidence is linked to strength of recommendation, but there is no automatic one-to-one connection. High quality evidence does not necessarily imply strong recommendations, and strong recommendations can arise from low quality evidence. For example, the question may be asked: Should patients with deep vein thrombosis continue to take Warfarin long-term? High quality RCTs show that continuing Warfarin will decrease the risk of recurrent thrombosis, but at a cost of increased risk of bleeding and inconvenience. Because patients with varying values and preferences will make different choices, a weak recommendation becomes appropriate despite the high quality evidence. Guideline panels may offer a weak recommendation in this case [Guyatt et al. BMJ 2008; 336:924-926].

There may be instances where a strong recommendation based on lower quality evidence is appropriate. It will not always be possible or ethical to conduct RCTs. Examples include emergency or emerging situations such as the pharmacological management of avian influenza (H5N1) patients and management of individuals exposed to anthrax. An evidence-based approach entails transparency concerning the evidence that was considered and transparency in how judgments regarding the quality of evidence were made.

As noted, key factors that can weaken the strength of recommendation are lower quality evidence, uncertainty about the balance of benefits versus harms and burdens, uncertainty or differences in values, and uncertainty about whether the net benefits are worth the costs. For example, the ACIP recommendation for use of HPV vaccine in males is a permissive or conditional recommendation because of cost and other factors. Additional factors that can affect recommendations include the burden of disease, equity, and potential for improvement in quality of care. In general, the higher the burden of disease, the higher the magnitude of the benefit of an intervention.

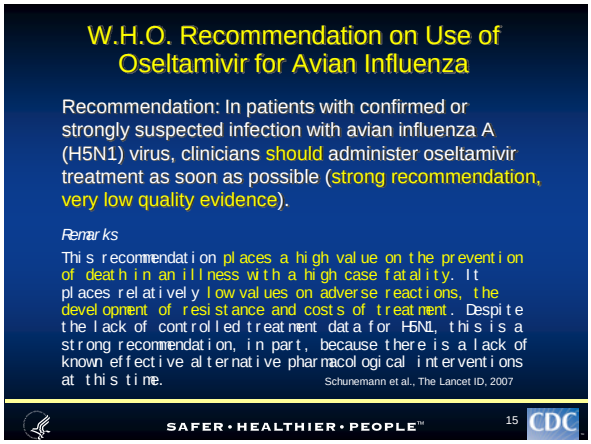
With regard to the implications of strong and weak recommendations for clinicians, a strong recommendation implies that most patients should receive the recommended course of action. A weak recommendation implies that clinicians should be prepared to help each patient arrive at a decision that is consistent with his or her values and preferences. It is important to note that clinicians, patients, insurers, review committees, other stakeholders, and / or the courts should never view recommendations as dictates. Even strong recommendations based on high-quality evidence will not apply to all circumstances and all patients.

Dr. Ahmed presented information about WHO's use of the GRADE method for developing guidelines for the pharmacological management of avian influenza, which was published in *The Lancet* in 2007. Clinical questions were initially identified by clinicians managing patients with avian influenza and refined by the members of the guideline panel. One of the clinical questions was: Should oseltamivir be used for treatment of avian influenza A (H5N1) patients? The outcomes of interest included mortality, hospitalizations, resource use, adverse outcomes, and antimicrobial resistance. In terms of the summary of the evidence, there are no randomized trials of oseltamivir for treatment of avian influenza. There are 4 systematic reviews and health technology assessments that assessed the effectiveness of oseltamivir in seasonal influenza. According to the GRADE framework, these studies provide indirect evidence of the effectiveness of oseltamivir in avian influenza A (H5N1). There are 3 published case series describing H5N1 patients treated with oseltamivir. There are many in vitro and animal studies of the effects of oseltamivir on the H5N1 virus, which provide indirect evidence. There is no alternative that is more promising at present, and the cost of oseltamivir is about $40 per treatment course.

The judgments of the WHO guideline panel on the 4 key factors that determine the strength of the recommendation are reflected in the following comments they made:

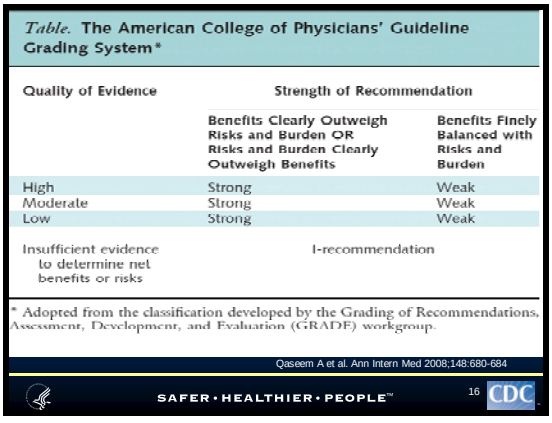
"The benefits are uncertain, but potentially large."
"The quality of the evidence is very low."
"All patients and care providers would accept treatment for H5N1 disease." No alternative.
"The cost is not high for treatment of sporadic cases."

The WHO panel made a strong recommendation for using oseltamivir. Please note the format for presenting the recommendation. The word "should" is used for strong recommendations. The strength of the recommendation and the quality of evidence are shown in parentheses. The remarks section indicates the key considerations underlying the recommendation. This section also explains why this is a strong recommendation, despite the fact that the quality of evidence is low:

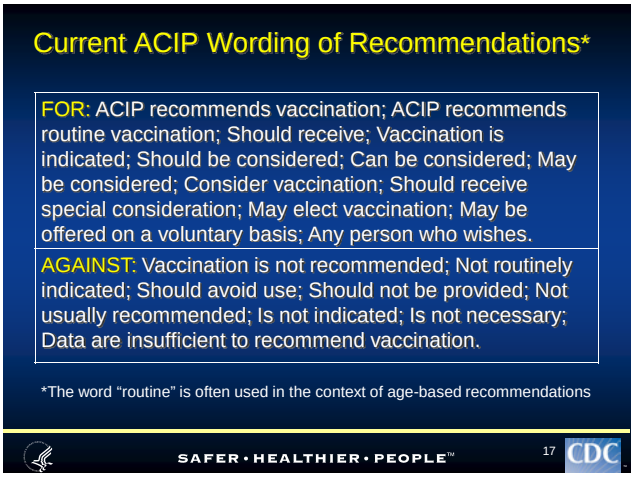


The format makes the strength of recommendation, the quality of evidence, and the thought process underlying the recommendation very transparent.

The following table illustrates the ACP's guideline grading system, which is based on the GRADE approach. The quality of evidence is rated as high, moderate, or low. The strength of recommendation is graded as strong or weak. There is also a category of insufficient evidence to make a recommendation:



The current ACIP wording of recommendations is illustrated in the following recommendations extracted from the ACIP website:



There is a wide range of wording used for recommendations for vaccination and recommendations against vaccination. The word "routine" is often used in the context of age-based recommendations. For example, the ACIP recommends routine HPV vaccination of girls aged 11 or 12 years.

Given that categorizing recommendations as *strong* or *weak* may not be most appropriate for vaccine recommendations, the Evidence Based Recommendations Work Group proposed the following categories for ACIP recommendations:

- ❑ Recommendation for or against (Category I)
- ❑ Optional use (Category II), which is similar to what is currently referred to as a "permissive recommendation;" other suggested terms are "options" and "conditional recommendation"
- ❑ No recommendation/unresolved issue

Key factors for ACIP to make an optional use recommendation include:

- ❑ Uncertainty about the balance between desirable and undesirable effects
- ❑ Lower quality of evidence
- ❑ Uncertainty or variability in values and preferences
- ❑ Uncertainty about whether the net benefits are worth the costs (cost-effectiveness)

These are the same key factors that GRADE suggests for determining the strength of a recommendation.

Examples of desirable effects that are relevant for vaccine recommendations include mortality reduction, reduction in disease, fewer hospitalizations, fewer emergency department visits, and improvement in quality of life. Examples of undesirable effects include deleterious impact on morbidity, mortality, or quality of life. Other factors for formulating vaccine recommendations include burden of disease (the higher the burden of disease, the higher the magnitude of benefit, acceptability of vaccine, vaccine supply, feasibility of implementation, equity, and other ethical considerations.

The work group wrestled with wording for recommendations because this is critical to provide adequate guidance to clinicians. The work group proposed the following wording:

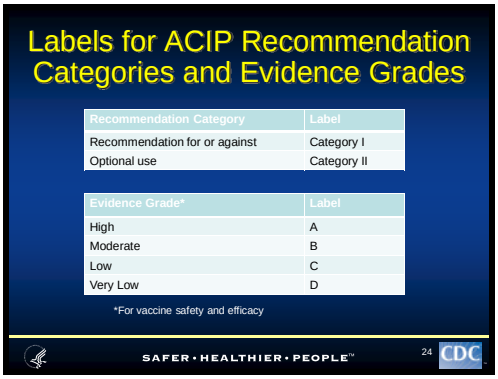
- ❑ For category I, use words like "recommend," "recommend against," "should," and "should not."
- ❑ For category II, use words like "may." For example: *HPV vaccine may be given to males aged 9 through 26 years*.

The proposed format for presenting ACIP recommendations is as follows:

- Recommendation
  - ACIP recommends/does not recommend … (Category, quality of evidence)
- Remarks
  - Explicit consideration of the quality of evidence, benefits, harms, burdens, costs, values and preferences, and other factors for formulating each recommendation should be described here

The ACIP recommendation should be followed in parentheses by the recommendation category and the quality of evidence. The remarks section should describe the key considerations and the thought process underlying the recommendation.

The labels for the recommendation categories and the evidence grades are illustrated as follows:



Recommendation for or recommendation against are to be labeled Category I. Optional use recommendations are to be labeled Category II. The evidence grades are to be labeled A, B, C, or D. Please note that the evidence grades refer to the quality of evidence for vaccine safety and vaccine efficacy. For cost-effectiveness the guidance for health economic studies published by the ACIP Work Group on Economic Analysis should be used. The guidance enhances the transparency and quality of economic materials presented to ACIP. The Evidence Based Recommendations Work Group is not proposing to grade the quality of cost-effectiveness studies.

In summary, the Evidence Based Recommendations Work Group proposed that ACIP adopt the GRADE framework for assessing quality of evidence and for going from evidence to recommendations. The advantages of adopting GRADE include explicit, comprehensive criteria for downgrading and upgrading quality of evidence ratings; a transparent process of going from evidence to recommendations; explicit acknowledgment of values and preferences; balance

between simplicity and methodological rigor; and use by many other organizations, which unifies the meaning of recommendations across organizations.

Discussion

Dr. Pickering pointed out that ACIP now has 14 work groups, some of which will need to learn how to use the GRADE framework if ACIP votes to adopt this system. New work groups will be formed in the future, so there will need to be a continual educational process. He wondered how they would recommend educating people in a simple manner who have various backgrounds with regard to evidence-based medicine so that this system can be applied to future ACIP recommendations.

Dr. Umscheid responded that HICPAC decided to consult with methodologists and provide content experts who worked with his group to produce their guidelines. Another way might be to develop a cadre of methodologists at CDC, perhaps specifically for ACIP, who know how to use this process and who could act as consultants to the content experts for each of the guidelines to be developed. He recommended that the cadre of methodologic experts work with a group that has used this method at least once in the past, in order to prepare to guide others on their own.

Dr. Ahmed reminded everyone that there are two components of GRADE: 1) the quality of evidence, which is more technical and requires expertise; and 2) recommendations, which is not as technical, so ACIP work group members can be trained for this. For the first component, at least one person is needed who is trained in the GRADE method at CDC who would work with the ACIP work group. This could be the CDC lead on that work group. Not all work group members need to know the statistical details of the evidence grading. Perhaps a one- or two-hour presentation would be sufficient to understand the framework.

Dr. Morse congratulated the work group on significant progress in the development of a more uniform evidence-based system to help ACIP make recommendations. This shows great promise as they continue to improve the science-based criteria that ACIP is so dependent upon. However, he reminded everyone that while this is a necessary and important tool to assist ACIP in making complex and difficult decisions, it alone, like cost-benefit analyses, is not sufficient to do so. If it were, there would be computers rather than ACIP members sitting at the inner circle to make decisions. It is critical that the tool does not become the policy. Also, acceptability of the tool is directly related to the ability to understand its use and to explain that to ACIP's customers—the public who is affected by its use. Today's presentation was a great first step, but as ACIP utilizes this tool, it will require continuing education, as Dr. Pickering mentioned, as well as assessment. With that preamble in mind, Dr. Morse inquired as to whether there were plans to pilot test this approach and further improve it before implementation.

Dr. Umscheid responded that this approach and process is really not a "plug and chug process." This is a process which requires a group of methodologists who understand how to conduct systematic reviews and the nuances of that; who understand how to grade the quality of an evidence base and that is going to change depending upon the question being asked; and who understand how to translate that evidence into recommendations and incorporate the values, preferences, risk benefits, and costs. In addition, this process has been used successfully in many different areas across medicine and beyond, not just in infection control (e.g., cardiology, pulmonary critical care, et cetera). In that respect, it has been tested. The strength of the recommendations and the quality of evidence that have come out of these processes have had good validity to support this framework.

Dr. Temte emphasized that what is important is clarity and transparency. What they want to end up with eventually is recommendations that include a remarks section. The values placed on the meningococcal vote from 4 or 5 years ago were very important. A lot of value was placed on the quality of life and individual suffering that went into that decision. He thought of the methodology not as the end, but as the appropriate tool to get from the questions and the evidence to what ACIP is voting on. One thing the work group proposes is run this process on one or two fairly recent previous recommendations as an example.

Dr. Ahmed mentioned that the second component of GRADE, going from evidence to recommendations, is done by ACIP anyway. The concepts are very similar. Using GRADE will simply put a structure around recommendations that is transparent to everyone. The only addition being made with the GRADE framework is assessing the quality of the evidence as high, moderate, low, and very low.

Dr. Baker agreed that they basically use this process anyway. For vaccines, they have the advantage of always having a very robust RCT, which is not always true with other guidelines. The reason they had a Pregnancy Work Group was because the language from vaccine to vaccine differed widely in terms of cautions, recommendations, or no recommendations. She thought that standardization of language from vaccine to vaccine would be a benefit of this framework.

Dr. Langley (NACI) pointed out that there is a culture change that is moving toward this framework. NACI published their method in January 2009. Thought some individual members felt uncomfortable if they did not have a Masters in Clinical Epidemiology, overall using such a framework aids in the decision making process. NACI does not use the GRADE framework, but does use a lot of the same components. They begin with the knowledge synthesis, which is the individual construction of tables of evidence and harm in which each study is listed. The next step is to synthesize that into a recommendation. They considered GRADE when they were developing their construct, but found it difficult how the weighting of plusses and minuses really reflected the domain they were trying to capture. Is a plus really equal to a minus in terms of the weight of how important that factor is? Instead, they assess the evidence itself, but then in summarative text list other factors that were important, like burden of illness and so on. It is a little different, but so far it seems to be working for them. The main effect is that although many people can carry around evidence in their heads, most people are simple folk who really look at it differently when it is objectively listed in a table. NACI posts their tables and literature syntheses on the website, separate from the statement, so anybody can review it. Though they might make a different decision, at least they know how NACI came to their decision.

Dr. Chilton thought this would be very helpful to ACIP as they develop guidelines. He expressed his hope that the RSV immunoprophylaxis workgroup, with which he is associated, will be one of the first adopters of the GRADE framework. When he grades medical students who pass through their rotation, he constantly rails against few choices: outstanding, good, fair, or poor. He keeps wanting a “very good” category. Similarly with GRADE, this is a relatively small number of categories of strength of recommendation, one of which disappeared in the course of Dr. Ahmed’s presentation—the middle grade, which is not sufficient information to offer even a weak recommendation. There will likely be cases when either the evidence is poor or the evidence is balanced plus and minus, so there should be a category for time when a recommendation simply cannot be made.

Dr. Ahmed clarified that this category does exist, but is not assigned a label (Category III).

Dr. Sumaya said that he was very favorable to this process, even knowing that it is something else they are going to have to learn and that will require a change in culture. He thought it would strike at a core number of the issue, particularly in terms of the language in the actual recommendations. He wondered whether the GRADE framework was one size fits all or if some adaptations would have to be made to address ACIP's needs.

Dr. Umscheid replied that one of the strengths of the GRADE process is that even though there are a lot of details to learn, the process itself is relatively flexible. This was why he believed there was uptake by so many different types of organizations. When they worked on the HICPAC guidelines, one of the first things they were asked was to keep the recommendation scheme that HICPAC used in tact and to modify GRADE to fit that scheme. They have 1a, b, and c and 2. The GRADE approach was modified to fit that scheme. There are benefits and harms in doing that. The HICPAC committee thought the benefits outweighed the harms. The benefits were essentially that the users of HICPAC guidelines over years and decades were very familiar with what a category 1a versus 1b versus 1c versus 2 meant, so it was very important to maintain that scheme. That said, he would probably recommend sticking with the very broad GRADE approach as presented. He would also recommend utilizing the criteria presented to increase or decrease the quality of the individual outcomes, although ACIP would have to define what "inconsistent" or "study limitation" means based on each of the guideline reviews conducted. It is key to define criteria and apply standards consistently across all of the studies being evaluated. There is judgment involved in creating some of the schemes, defining criteria to increase or decrease the grade, and in defining values or preferences. However, as long as they are systematic in the application of those judgments, their results will be reasonable.

Peter Briss indicated that he was asked to attend the ACIP meeting because he was an original co-developer of GRADE. He said he anticipated that ACIP would have to develop a cadre of people, internally or externally, who are able to develop and apply these judgments. He expressed skepticism personally about whether this framework could just be pulled off the shelf to meet all of ACIP's needs. Safety and harms are typically difficult to apply. Often, the best conceivable data scores low quality, so ACIP may have to fiddle with the system to figure out how to adapt to that. Although it is argued that people have applied the GRADE system to actual public health interventions, all of the examples to date have been very individual efforts such as anthrax prophylaxis. There are not any population-based examples of which he was aware, and he personally did not believe this system would work very well in population-based interventions where randomized trials are not feasible. To the extent that ACIP has to deal with safety and more population-based questions, they may have adapting to do. While he would be delighted to be wrong about that and it may be that ACIP's first few examples settle such issues, there may be some predictable issues that will be sticky.

Dr. Cieslak said that he also had some skepticism; however, his skepticism regard how much ACIP needed this framework and whether they needed to solve their issues with such an involved process. While he agreed that they need a better standardization of language, he thought they could set some standards without fully adopting this process. He feared that the amount of work it entail to try to fit recommendations into these formats would be considerable. ACIP already does a pretty good job of explaining its rationale in the *MMWR* statements that are published. ACIP recommendations are usually based on randomized clinical trials. When they are not, as with the rabies vaccine or harmonizing the rotavirus vaccine schedules, the rationales for those recommendations were made clear in the statements. He also feared that

the costs in bureaucracy would be significant. They would have to have lengthened time to produce the statements in order to get them into these formats.

Based on recent experiences in the MMRV Safety Work Group, Dr. Temte observed how many of the GRADE components would fit directly. What they strive for in that work group is to be very clear, very transparent, and relate the information. It would have been enhanced if they had a framework to put this into that was recognized by everybody, and that when they presented, it would be in a meaningful way that captures all of those elements (e.g., safety, efficacy, et cetera). Some elements were of critical importance (safety), some were less important, and others were not important. To be able to express this clearly, succinctly, and transparently is of very high importance. He did not perceive that as being a cost or time problem. Instead, he saw it as building efficiency into the process. In terms of language, he said he cringed every time he heard the word "permissive" used, and invited everyone to look the word up in the dictionary. As a parent, he does not like his children to visit the permissive parents' house.

Dr. Umscheid indicated that they were asked to work with HICPAC to update their guideline methodology because they were experiencing a number of challenges, one of which was the inefficiency of their guideline development process. He acknowledged that the area HICPAC address differs from the area that ACIP addresses. By using the GRADE process with HICPAC, they were able to develop guidelines much faster than they had been completed in the past. HICPAC did make an investment in using his group to produce those guidelines, so that is one downside.

Dr. Ahmed clarified that the proposal was for the GRADE framework to be used for new vaccine recommendations or new indications of vaccines. For these situations, the number of studies would be 4 or 5 versus 50 if applied it to existing recommendations.

It was noted that consideration should be given to staffing needs in terms of literature reviews, because they can be daunting.

Dr. Baker noted that at least they were beginning with an internal expert in Peter Briss. While there would be a learning curve, she was personally happy with the framework and hoped that other ACIP members would be as well.

Public Comments Day 2

Kari Hinton Judson
Parent Advocate

While you all are speaking about evidenced-based medicine and recommendations for certain diseases, I would like to advocate for other parents, because the scientific and medical evidence that you publish has our children's lives at stake.

My name is Kari Judson. This is my son, Alexander. Five days before his first birthday, he died. At the same time, his identical twin brother, Dominic, spent 11 days at Children's Healthcare of Atlanta and survived. They did not have a rare disease. They had Respiratory Syncytial Virus (RSV). Because my twins did not go to the neonatal intensive care unit (NICU) when they were born at 36 weeks, I was never told about RSV.

When any illness, including RSV, affects almost every child before their third birthday, parents have a right to know about it. It seems that only the parents of premature or sickly infants are informed of the signs and symptoms of RSV. Because I do have a large network of friends and acquaintances, I believe that knowing Alexander's story has saved several lives. What about the parents who don't know about Alexander or this virus? What about Madison Byrd, the healthy two-year old in Blue Ridge, Georgia, who died two weeks ago due to RSV? Why did her mom know about it? Why didn't this little girl have a chance?

This virus is so common and so contagious, why hasn't every parent in America been told about it? I am doing everything I can to spread the word about RSV, but I'm only one mom who's had a devastating loss. I believe it is up to all of you, the CDC and medical professionals, to do a better job informing parents of the dangers of RSV through education, the development of a vaccine, or more readily and widely available antibodies. Please know that I think every parent needs to know about this potentially fatal virus so more of our children don't die, like my Alexander did.

Dr. Baker thanked Mrs. Judson and expressed everyone's sympathy for her loss.

Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the February 24-25, 2010 ACIP Meeting are accurate and complete.

Date

Dr. Carol Baker, Chair
Advisory Committee on
Immunization Practices (ACIP)

List of Attendees

Last Name	First Name	Citizenship
Abu-Elyazeed	Remon	Egypt
Akhter	Farzana	Bangladesh
Barker	Janine	South Africa
BOGAERTS	Hugues	Belgium
Boseila	Abeer	Egypt
Bryson	Maggie	Canada
Butt	Tausif	United Kingdom
Castaneda Eduardo MD	Suárez	El Salvador
DasGupta	Joy	Canada
Edelman	Laurel	Canada
Ferdinand	Elizabeth	Barbados
Florez	Jorge	Colombia
Franka	Richard	Slovakia
Hassan	Foad	Nicaragua
HENDRICKX	Bernadette	France
HTUN-MYINT	Latt	Burma
Ismail	Shainoor	Canada
Jauregui	Barbara	Argentina
Kamiya	Hajime	Japan
Kim	Yeu-Chun	South Korea
Langley	Joanne	Canada
Lucidi	Bruno	France
MAHAMAN LAWAN	ISSOUFOU	Niger
Matias	Gonçalo	Portugal
Merengwa	Enyinnaya	Saint Kitts and Nevis
Misurski	Derek	Canada
MONTEYNE	Philippe	Belgium
Okabe	Nobuhiko	Japan
Omer	Saad	Pakistan
ORIOL	VALERIE	France
Rappuoli	Rino	Italy
Reynolds	Donna	Canada
ROCHA	CRISANTA	Nicaragua
Saddier	Patricia	France
Saito	Tomoya	Japan
Salisbury	David	United Kingdom
Schodel	Florian	Germany
Seet	Bruce T.	Canada
Tan	Litjen (L.J)	Singapore
Tsuzuki	Daisuke	Japan
Van Brackel	Esthel	Belgium
Verstraeten	Thomas	Belgium
VILLAFANIA	RUBY	Philippines

Vizotti	Carla	Argentina
York	Laura	Canada
Abramson	Allison	United States
Akinsanya-Beysolow	Iyabode	United States
Alexa	Pam	United States
Allen Woodruff	Jennifer	United States
Allen-Sherrod	Deborah	United States
Allred	Stephen	United States
Ambrose	Karita	United States
ARMSTRONG	JENNIFER	United States
Arthur	Phyllis	United States
Ashley	Donald	United States
Atkins	Jennean	United States
Ault	Kevin	United States
Baker	Carol J.	United States
Bandell	Allyn	United States
Bargatze	Robert	United States
Basket	Michelle	United States
Bauer	Christine	United States
Bax	Jennifer	United States
Bax	Riley	United States
Baylor	Norman	United States
Bianchi	Paul	United States
Bibila	Theodora	United States
Billings	Pamela	United States
Birkhead	Guthrie	United States
Blalack	Gary	United States
Bocchini, Jr.	Joseph	United States
Bolanos	Brenda	United States
Boone	Chris	United States
Boone	Heather	United States
Boone	Ethan	United States
Boone	Maggie	United States
Bozio	Catherine	United States
Bozof	Lynn	United States
Bradley	Kimberly	United States
Brady	Michael	United States
Bresnitz	Eddy	United States
Brooks	Dennis	United States
Bugenske	Erin	United States
Bush	Kim	United States
Campos-Outcalt	Doug	United States
Caporizzo	John	United States
Cary	Donna	United States
Center	Kimberly	United States
Chadalawada	Rekha	United States
Chaney	Mike	United States
Chattopadhyay	Sanat	United States
Chavez	Carol	United States

Chilton	Lance	United States
Cieslak	Ted	United States
Cieslak	Paul	United States
Claxton	Isabelle	United States
Clippard	Jessie	United States
Clover	Richard	United States
Coelingh	Kathleen	United States
Coit	Henry	United States
Collins	Heather	United States
Colquitt-hall	Karen	United States
Colwell	Chris	United States
Constantino	Salvatore	United States
Cooley	Brendan	United States
Cooper	Brian	United States
Corsino	Cynthia	United States
Counard	Catherine	United States
Creed	Carlisle	United States
Crumlich	Brittani	United States
Cullison	Mark	United States
Curlin	George	United States
Dalrymple	Donald "Dack"	United States
Dana	Adrian	United States
D''Anthony	Mike	United States
D''Antona	Aida	United States
D''Antona	John	United States
Decker	Michael	United States
DeLong	Lynn	United States
DeNoon	Daniel	United States
Dinovitz	Richard	United States
Donnelly	Jessica	United States
Dormitzer	Philip	United States
Dougherty	Kelley	United States
Dubin	Gary	United States
Duchin	Jeffrey	United States
Duke	Lynn	United States
Dull	Peter	United States
DuPont	Lisa	United States
Ehresmann	Kristen	United States
Eiden	Joseph	United States
Ekhtiar	Rum	United States
Elbasha	Elamin	United States
Elward	Alexis	United States
Englund	Janet	United States
Evans	Jim	United States
Evans	Geoffrey	United States
Faulconer	Brian	United States
Feinberg	Mark	United States
Fisher	Gwen	United States
Foster	Stephan	United States
Friedland	Leonard	United States

Fryhofer	Sandra	United States
Fuller	Yvonne	United States
Fye	Jessica	United States
Gaffoglio	Diane	United States
Gall	Stanley A	United States
Gargano	Lisa	United States
Garrett	Matt	United States
Gaskins	Diana	United States
Geddes	Cathy	United States
Gellin	Bruce	United States
Gensheimer	Kathleen	United States
Gery	Laurie	United States
Gesser	Richard	United States
Giolli	Chris	United States
Glode	Mary	United States
Goldstein	Mitch	United States
Gordon	Lili	United States
Gordon-Evans	Jill	United States
Gorham	Millicent	United States
Goveia	Michelle	United States
Grabenstein	John	United States
Grabowsky	Mark	United States
Greenberg	David	United States
Greenspan	Joel	United States
Grogg	Stanley	United States
Gromyko	Natalya	United States
Groom	Amy	United States
Groothuis	Jessie	United States
Hachey	Wayne	United States
Hahn	Christine	United States
Halsey	Neal	United States
Hammer	Sandra	United States
Hannan	Claire	United States
Harriman	Kathleen	United States
Haupt	Richard	United States
Hazelwood	Kimberley	United States
Henry	Stephanie	United States
Hering	David	United States
Heyward	William	United States
Higgins	Jacqueline	United States
Hightower	Dwan	United States
Hogan	Cathy	United States
Hogrefe	Wayne	United States
Hosbach	Phil	United States
Howe	Barbara	United States
Hughes	Jim	United States
Hull	Harry	United States
Humphrey-Franklin	Donelle	United States
Iconis	Rosemary	United States
Jackson Grant	Melonie	United States

Jain	Varsha	United States
James	Chuntiel	United States
Janssen	Alan P.	United States
Johnson	David	United States
Johnson	Amy	United States
Jones	Eric	United States
Jones	Abbey	United States
Judson	Kari	United States
Judson	Franklyn N	United States
Kagan	Stephen	United States
Kanesa-thasan	Niranjan	United States
Kaslow	David C.	United States
Kates	Jesse	United States
Katz	Samuel	United States
Kauffman	Richard	United States
Kaye	Bronwen	United States
Keane	Margaret	United States
Keitel	Wendy	United States
Keyserling	Harry	United States
Kimberlin	David	United States
Kinsinger	Linda	United States
Kitchen	Chester	United States
Kondos	Leeza	United States
Kudis	Amanda	United States
Kuter	Barbara	United States
Laird	Susan	United States
Lake	Fred	United States
Lammers	Peter	United States
Landry	Sarah	United States
Lawson	Herschel	United States
Lee	Lucia	United States
Leger	Marie-Michele	United States
Leroy	Zanie	United States
Lett	Susan	United States
Lewin	Clement	United States
Lewis	Tamara	United States
Link-Gelles	Ruth	United States
Lorick	Suchita	United States
Mahadevia	Parthiv	United States
Makari	Doris	United States
Malhame	Melissa	United States
Malone	Robert	United States
Mansoura	Monique	United States
Masaquel	Anthony	United States
Mason	Dean	United States
Mazur	Marie	United States
McCauley	Mary	United States
McCubbins	Tom	United States
MCLAUGHLIN	JEFFREY	United States
McLoughlin	Sean	United States

Medea	William	United States
Meehan	Judith	United States
Mehrdady	Rosemina	United States
Meigs	Wendy	United States
Meissner	Cody	United States
Mendenhall	Heather	United States
Mergler	Michelle	United States
Middleman	Amy	United States
Miller	Sarah	United States
Miller	Jacqueline	United States
Milley	Frankie	United States
Modi	Raken	United States
Moline	Heidi	United States
Moore	Kelly	United States
Morgan	Devon	United States
Muhammad	Riyadh	United States
Mullette	Michael	United States
Mulligan	Mark	United States
Murphy	Linda	United States
Murphy	Ann T.	United States
Myers	Martin	United States
Narasimhan	Vasant	United States
Naumann	Lisa	United States
Neal	John	United States
Netoskie	Mark	United States
Neuman	William	United States
Neuzil	Kathleen	United States
Norman	James	United States
Offit	Paul	United States
Owens	Jack	United States
Paradiso	Peter	United States
Patel	Jaymin	United States
Penrod	Deborah	United States
Peters	Martin	United States
Peterson	Diane	United States
Petrucelli	Michael	United States
Pina	Liza Miriam	United States
Pisani	Amy	United States
Poland	Gregory	United States
Polino	Pamela	United States
Porter	Cathy	United States
Powell	Delories	United States
Pugh	Pearl	United States
Quandelacy	Talia	United States
Quinn	Jane	United States
Rai	Saroj	United States
Rall	Kristen	United States
Randall	Lisa	United States
Ray	Jill	United States
Redd	John	United States

Rennels	Margaret	United States
Richards	Steve	United States
Richardson	Vesta	United States
Richmond	Heather	United States
Roark	Jill B	United States
Robertson	Jeff	United States
Roche	Corleen	United States
Rosenbaum	Sara	United States
Ross	David	United States
Rousculp	Matthew	United States
Ryan	Kellie	United States
Ryan	Nessa	United States
Saah	Alfred	United States
Sanders	Courtney	United States
Sawyer	Mark	United States
Schaffner	William	United States
Schechter	David	United States
Schmader	Kenneth	United States
Schuchat	Anne	United States
Scott	Laura	United States
Scott	Daniel	United States
Seifert	Harry	United States
Shawen	Elizabeth	United States
Shelton	Jerry	United States
Sievert	Alan	United States
Silsbee	Jeffrey	United States
Silverstein	Leonard	United States
Singer	Andy	United States
Skjeveland	Eric	United States
Smalling	Delores	United States
Smith	Stephen	United States
Smith	Parker	United States
So	Phillip	United States
Sorrells	Keira	United States
Stanley	Jennifer	United States
Steinberg	Nina	United States
Stephens	David	United States
Stewart	Lorrie	United States
Stinchfield	Patsy	United States
Stobbe	Mike	United States
Stoddard	Jeffrey	United States
Strikas	Raymond	United States
Strutton	David	United States
Stuerke	Stacy	United States
Suárez Castaneda	Eduardo	United States
Sumaya	Ciro	United States
Sun	Wellington	United States
Swain	Chris	United States
Sylvester	Gregg C.	United States
Talarico	John	United States

Talkington	Kathy	United States
Tedesco	Francesca	United States
Temte	Jonathan	United States
TenEyck	Carolyn	United States
Thomas	Lonnie	United States
Thomas	Shannon	United States
Thompson	Bradley	United States
Toyer	Sheryl Ann	United States
Tsai	Theoldore	United States
Tucker	Miriam E.	United States
Turner	James	United States
Umscheid	Craig	United States
Vaupel	Christine	United States
Via	Christina	United States
Vigliarolo	Peter	United States
Waldapfel	Christopher	United States
Wallace	Fred	United States
Walters	Jean	United States
Wassil	James	United States
Welch	Verna	United States
Werzberger	Alan	United States
Wexler	Deborah	United States
Whitley-Williams	Patricia	United States
Whitney	Ellen	United States
Wighton	Timothy	United States
Wolfe	Antoinette	United States
Wood	Laurel	United States
Wu	Lauren	United States
Wyble	Lance	United States
Xu	Fujie	United States
Zimmerman	Richard	United States

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