

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

**Advisory Committee on
Immunization Practices (ACIP)**



**Summary Report
October 21-22, 2009
Atlanta, Georgia**

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Thursday, October 22

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Acronyms

AAFP	American Academy of Family Physicians
AAN	American Academy of Neurology
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core surveillance system
ACHA	American College Health Association
AOA	American Osteopathic Association
ACIP	Advisory Committee on Immunization Practices
ADEM	Acute Disseminated Encephalomyelitis
AGS	American Geriatrics Society
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AIN	Anal Intraepithelial Neoplasia
ALS	Amyotrophic Lateral Sclerosis
AOM	Acute Otitis Media
ARDS	Adult Respiratory Distress Syndrome
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
CAIS	Childhood / Adolescent Immunization Schedule
CAIV-T	Cold-Adapted Influenza Vaccine
CBER	Center for Biologics Evaluation and Research
CCID	Coordinating Center for Infectious Diseases
CDC	Centers for Disease Control and Prevention
CSF	Cerebral Spinal Fluid
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
CNS	Central Nervous System
COI	Conflict of Interest
COID	Committee on Infectious Diseases
DBD	Division of Bacterial Diseases (of NCIRD)
DGMQ	Division of Global Migration and Quarantine
DHQP	Division of Healthcare Quality Promotion
DMSS	Defense Medical Surveillance System
DoD	Department of Defense
DSMBs	Data Safety Monitoring Boards
DSTDP	Division of Sexually Transmitted Diseases Prevention [of NCHHSTP]
DtaP-IPV	Diphtheria, tetanus, and pertussis with inactivated poliovirus vaccine
DVA	Department of Veterans Affairs
DVBID	Division of Vector-Borne Infectious Diseases
DVD	Division of Viral Diseases (of NCIRD)
DVH	Division of Viral Hepatitis (of NCIRD)
DVRD	Division of Viral and Rickettsial Diseases
ED	Emergency Department
EIP	Emerging Infections Program
EIS	Epidemic Intelligence Service
EMR	Electronic Medical Records

EMS	Emergency Medical Services
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
GBS	Guillain Barré Syndrome
GID	Global Immunization Division
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GSK	GlaxoSmithKline
HAART	Highly Active Antiretroviral Therapy
HCP	Healthcare Personnel
HCUP	Healthcare Cost and Utilization Project
HICPAC	Healthcare Infection Control Practices Advisory Committee
HepA	Hepatitis A
HepB	Hepatitis B
HHS	Department of Health and Human Services
Hib	<i>Haemophilus influenzae B</i>
HM	Heterosexual Men
HMO	Health Maintenance Organization
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
ICER	Incremental Cost-Effectiveness Ratios
ID	Influenza Division (of NCIRD)
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	Indian Health Services
IHR	International Health Regulations
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IND	Investigational New Drug
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division (of NCIRD)
ISO	Immunization Safety Office (of CDC/OD/Office of the Chief Science Officer)
ITT	Intent to Treat
JE	Japanese Encephalitis
JORRP	Juvenile Onset Recurrent Respiratory Papillomatosis
KD	Kawasaki Disease
LBGT	Lesbian, Gay, Bisexual, and Transgender
MCO	Managed Care Organization
MedDRA	Medical Dictionary for Regulatory Activities
MenACYW-CRM	Meningococcal Conjugate Vaccine
MCV4	Meningococcal Conjugate Vaccine
MMR	Measles, Mumps, Rubella
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NCHHSTP	National Center for HIV, Hepatitis, STD, and TB Prevention (of CDC/CCID)

NCI	National Cancer Institute
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NCPDCID	National Center for Preparedness, Detection, and Control of Infectious Diseases
NCZVED	National Center for Zoonotic, Vector-Borne, and Enteric Diseases (of CDC/CCID)
NHFS	National 2009 H1N1 Flu Survey
NIH	National Institutes of Health
NIS	National Immunization Survey
NNDSS	National Notifiable Diseases Surveillance System
NREVSS	National Respiratory and Enteric Viruses Surveillance System
NSFG	National Survey of Family Growth
NVAC	National Vaccine Advisory Committee
NVICP	National Vaccine Injury Compensation Program
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
OCSO	Office of the Chief Science Officer
OD	Office of the Director (of CDC)
PBNA	Pseudovirion-Based Neutralization Assay
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PHER	Public Health Emergency Response
PEP	Post-Exposure Prophylaxis
PI	Principal Investigator
PRAMS	Pregnancy Risk Assessment Monitoring System
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
QALY	Quality-Adjusted Life Year
MCV4	Quadrivalent Meningococcal Conjugate Vaccine
RCA	Rapid Cycle Analysis
RHC	Rural Health Clinic
RRP	Recurrent Respiratory Papillomatosis
RSV	Respiratory Syncytial Virus Immunoprophylaxis
RTIMS	Real Time Immunization Monitoring System
SAEs	Serious Adverse Events
sBLA	Supplemental Biologics License Application
SCCS	Self-Controlled Case Series
SHEA	Society for Healthcare Epidemiology of America
SMC	Safety Monitoring Committee
SMEs	Subject Matter Experts
Tdap	Tetanus and Reduced Diphtheria Toxoids
TNWG	Tribal Nations Working Group
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
VZV	Varicella-Zoster Virus
WG	Work Group
WHO	World Health Organization
YF	Yellow Fever
YEL-AND	Yellow Fever Vaccine-Associated Neurologic Disease
YEL-AVD	Yellow Fever Vaccine-Associated Viscerotropic Disease

Wednesday October 21, 2009 - continued

3:00	<i>Break</i>		
3:15	<u>Respiratory Syncytial Virus (RSV)</u> <ul style="list-style-type: none">▪ New ACIP Work Group: RSV Immunoprophylaxis Work Group	Information	Dr. Lance Chilton (ACIP, WG Chair)
3:20	<u>Vaccine Supply</u>	Information Discussion	Dr. Jeanne Santoli (CDC/ NCIRD/ISD)
3:35	<u>Meningococcal Vaccines</u> <ul style="list-style-type: none">▪ Introduction▪ Immunogenicity and safety of Hib-MenCY-TT combination vaccine (<i>Haemophilus influenzae</i> type b and <i>Neisseria meningitidis</i> serogroups C and Y-tetanus toxoid conjugate vaccine combined)▪ Epidemiology of meningococcal disease in infants and young children▪ Considerations in the use of meningococcal conjugate vaccines in infants	Information Information Information Information Discussion	Dr. Cody Meissner (ACIP, WG Chair) Dr. Jacqueline Miller (Director, Clinical Research and Development and Medical Affairs, GSK) Ms. Jessica MacNeil (CDC/ NCIRD/DBD) Dr. Amanda Cohn (CDC/ NCIRD/DBD) Dr. Cody Meissner (ACIP, WG Chair)
5:15	<u>Public Comment</u>		
5:30	<u>Adjourn</u>		

Thursday, October 22, 2009

8:00	<u>Unfinished Business</u>		Dr. Carol Baker (Chair, ACIP)
8:30	<u>Agency Updates</u> (CDC, CMS, DOD, DVA, FDA, HRSA, IHS, NIH, NVAC, NVPO)	Information	ACIP <i>Ex Officio</i> Members
8:45	<u>Yellow Fever Vaccine</u> <ul style="list-style-type: none">▪ Introduction▪ Revised recommendations for the use of yellow fever vaccine in U.S. travelers	Information Information Discussion Vote	Dr. Carol Baker (ACIP, WG Chair) Dr. Erin Staples (CDC/ NCZVED/DVBID)
9:20	<u>Rotavirus Vaccines</u> <ul style="list-style-type: none">▪ Introduction: update on rotavirus vaccines▪ Post-licensure monitoring of intussusception▪ Update on 2009 rotavirus season	Information Information	Dr. Umesh Parashar (CDC/ NCIRD/DVD) Dr. Chris Mast (Merck) Dr. James Baggs (CDC/NCPDCID/ISO) Dr. Jennifer Cortes (CDC/NCIRD/DVD)
9:50	<i>Break</i>		

10:10	<u>13-Valent Pneumococcal Conjugate Vaccine (PCV13)</u>	Information Information Discussion Information Discussion Information Discussion	Dr. Mike Marcy (Chair, ACIP) Dr. Peter Paradiso (Vice President, Scientific Affairs, Wyeth) Dr. Mark Messonnier (CDC/ NCIRD/ISD) Dr. Pekka Nuorti (CDC/ NCIRD/DBD)
	<ul style="list-style-type: none"> ▪ Introduction ▪ Update on PCV13 licensure status and immunogenicity ▪ Cost-effectiveness of PCV13 (routine & catch-up program) ▪ PCV13: draft recommendations and immunization schedules 		

12:10 *Lunch*

Thursday, October 22, 2009 - continued

1:10	<u>Influenza Vaccines</u>	Information and Discussion	Dr. Anthony Fiore (CDC/NCIRD/ID) Dr. Lyn Finelli (CDC/NCIRD/ID) Dr. Nancy Cox (CDC/NCIRD/ID) Dr. Weigong Zhou (CDC/NCIRD/ID) Dr. Pascale Wortley (CDC/ NCIRD/ISD)
	<ul style="list-style-type: none"> ▪ Introduction and Work Group discussions ▪ Update: influenza epidemiology ▪ Update: influenza virology ▪ Influenza vaccine safety ▪ Update: 2009 influenza vaccine implementation 		

4:15 **Public Comment**

4:30 **Adjourn**

October 21, 2009

Welcome and Introductions

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Carol Baker
Chair, ACIP

Dr. Pickering called the meeting to order. He introduced Dr. Carol Baker as the new ACIP Chairperson beginning with the current meeting. Dr. Baker is a Professor of Pediatrics and Molecular Virology and Microbiology at Baylor College of Medicine in Houston, Texas. Dr. Pickering also introduced Dr. Jonathan Temte as the new Vice Chair. Dr. Temte is a Professor of Family Medicine at the Wisconsin School of Medicine and Public Health. Dr. Pickering welcomed these members to their new roles, emphasized their importance, and expressed appreciation for their service. Dr. Baker extended her welcome to everyone and requested that Dr. Pickering make the meeting announcements.

After adding his welcome to everyone attending the October 2009 ACIP meeting, Dr. Pickering announced that all future ACIP meetings would be broadcast via The World Wide Web due to the success of the initial webcast in July 2009, and in the interest of making the ACIP meeting accessible to as many people as possible. The proceedings will now be available to the following people who are not in attendance: any liaison representatives, members of state health departments and immunization programs in the United States (US), members of federal agencies, professional societies and international agencies, and others who have an interest in the meeting deliberations.

Dr. Pickering recognized several people in the room who were to be in attendance throughout the duration of the ACIP meeting to assist with various meeting functions: Antonette Hill, Committee Management Specialist for ACIP; Natalie Greene; Tamara Miller; Tanya Lennon; and Suzette Law. 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 also 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 recognized and welcomed a new liaison representative Mark Netoskie, who previously served as an interim representative. Dr. Netoskie is from Humana Houston Dallas / Fort Worth and has been selected to represent America's Health Insurance Plans (AHIP) as its liaison to the ACIP.

Those unable to attend the meeting included Dr. Norman Baylor (FDA), with Dr. Wellington Sun attending on his behalf. Dr. Kevin Ault (ACOG) was in attendance in Dr. Stanley Gall's place. Dr. Sandra Fryhofer (ACP) was in attendance on Dr. Greg Poland's behalf. Dr. David Salisbury from the Department of Health United Kingdom and Dr. Kenneth Schmader (AGS) were unable to attend.

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 corner 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 can issue 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 ACIP Provisional Recommendations slide was shown on the screen, which reflected the current seven provisional recommendations on the ACIP website. Several questions have been received regarding the length of time it takes to publish new recommendations. In order to answer this question, Dr. Pickering reviewed both tracks a recommendation could take. Recommendations with minor changes are published directly in CDC's *Morbidity and Mortality Weekly Report (MMWR)* generally within one month of an ACIP vote. The full statements take a second track and begin by being posted as provisional recommendations on the ACIP website within three weeks of an ACIP vote. The full recommendations are published in the *MMWR* under the Recommendations and Report series within six to eight months of an ACIP vote. The

ACIP is working diligently to determine how the timeline could be decreased; however, the recommendations go through a significant amount of clearance before being published.

The ACIP Secretariat solicits applications throughout the year for candidates to serve on ACIP. Detailed instructions for submissions of name of potential candidates may be found on the ACIP website. Applications may be submitted at any time of the year. Materials in support of the next cycle of applications for ACIP membership (beginning July 2010) are due no later than November 15, 2009. Interested parties were encouraged to complete an application and submit it by the deadline.

Dr. Baker welcomed and introduced a new member to the advisory committee, Dr. Wendy Keitel, who is Professor of Medicine and Molecular Virology and Microbiology at Baylor College of Medicine in Houston. Dr. Keitel completed her Medical Degree, her Internal Medicine Residency, and Infectious Disease Fellowship at Duke University and then went to Houston where she completed an Infectious Disease Influenza Research Fellowship. She currently serves as Principal Investigator (PI) of the Vaccine Treatment and Evaluation Unit in Houston. She brings more than 25 years experience in the design and implementation of clinical trials in diverse adult populations, and extensive experience in the science of vaccine safety. She has also served on numerous DSMBs. Her major research interests include the development of new and / or improved vaccines, particularly those relating to influenza. Dr. Baker mentioned that there would be another new ACIP member attending the next meeting.

The following conflicts of interest were declared:

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

Dr. Wendy Keitel: Research support from Novartis

Dr. Cody Meissner: Payments made to Tufts Medical Center by MedImmune and Wyeth for participation in clinical trials

The remainder of the ACIP members declared no conflicts.

Human Papillomavirus (HPV) Vaccines

HPV Vaccine Session Introduction

Janet Englund, MD
Chair, ACIP HPV Vaccine Work Group

As the Chair of the HPV Work Group, Dr. Englund acknowledged the support she and the group received from the CDC participants, as well as the insightful sessions provided by Merck, GlaxoSmithKline (GSK), and many academic colleagues throughout the country.

During this session, two main issues were addressed: 1) Use of bivalent HPV (types 16,18) vaccine for females; and 2) Use of quadrivalent HPV (types 6,11,16,18) vaccine for males.

Indications for bivalent HPV vaccine in females as licensed is for prevention of the following conditions caused by HPV types 16 and 18: cervical cancer, cervical intraepithelial neoplasia grade 2 or worse and adenocarcinoma in situ, and cervical intraepithelial neoplasia grade. This vaccine is now licensed for use in females ages 10 through 25 years [<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186957.htm>]. Indications for quadrivalent HPV vaccine in males is based on the prevention of genital warts caused by HPV type 6 and 11. This vaccine is now licensed for use in males aged 9 through 26 years [<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm>].

The current ACIP recommendations for use of quadrivalent HPV vaccines were approved in June 2006 and were published in the *Morbidity and Mortality Weekly Report (MMWR)* in March 2007. The quadrivalent HPV vaccine is recommended by ACIP for routine vaccination for females ages 11 to 12 years, with catch-up at the ages of 13 through 26 years.

Throughout the past four months, the ACIP HPV Vaccine Work Group has heard numerous speakers and discussions on many issues. There have been extensive discussions regarding bivalent HPV vaccine in females, including the mechanisms of action of ASO4 adjuvant / meta-analysis of adverse events, final phase III efficacy results and cross protection data, comparative immunogenicity of the bivalent and quadrivalent vaccines, co-administration of HPV vaccines with other recommended adolescent vaccines, use during pregnancy, and recommendations to bring forward to the full ACIP. With respect to the use of quadrivalent HPV vaccine in males, the working group's discussions have focused on safety and efficacy, acceptability of male vaccination, cost-effectiveness, HPV epidemiology and disease in men who have sex with men (MSM), and potential recommendations to be brought forward to the full ACIP.

A wide range of issues remain to be considered in terms of next steps. With regard to the bivalent HPV vaccine for females brings, there are now two licensed products with some different indications. Consideration must be given to how to harmonize these recommendations, and how to update recommendations for females. Use of quadrivalent HPV vaccines in males also must be addressed in terms of cost-effectiveness, and the options being considered for recommendations given the data currently available.

Following a review of the outline for this session, Dr. Englund acknowledged the extensive work by multiple Work Group members.

Bivalent HPV Vaccine and Comparative Quadrivalent HPV Vaccine Data

Lauri E. Markowitz, MD
National Center for HIV / AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

With respect to background, Dr. Markowitz pointed out that there are over 100 different HPV types, about 40 of which are sexually transmitted. The low risk types, such as HPV 6 and 11, cause genital warts and recurrent respiratory papillomatosis. The high risk types, such as HPV 16 and 18, cause cervical and other anogenital cancers and a subset of oral cavity and oropharyngeal cancers.

Most cervical cancers, as well as other HPV-associated cancers, are caused by HPV 18. With respect to the percentage of cervical cancers attributed to the most frequent HPV types in all regions of the world, 16 (54.4%) and 18 (15.9%) account for about 70% of all cancers, with each of the other types accounting for a smaller percentage [Smith et al. Int J Cancer 2007].

With licensure of the bivalent vaccine, there are now two HPV vaccines available for use in the United States (US). The quadrivalent vaccine produced by Merck was licensed in 2006. This HPV vaccine is directed against two low risk types, 6 and 11, and two high risk types, 16 and 18. The bivalent vaccine produced by GSK was licensed in 2009. This HPV vaccine is directed against two high risk types, 16 and 18. Both of these vaccines are L1, virus-like particle (VLP) vaccines. The antigen for the quadrivalent is produced in a yeast system. For the bivalent vaccine, antigens are expressed in a baculovirus expression vector system in insect cells.

The adjuvants for the vaccines differ. The quadrivalent vaccine contains an alum adjuvant, which is used in other licensed vaccines in the US [225 µg aluminum hydroxyphosphate sulfate]. The bivalent vaccine contains AS04, which includes aluminum hydroxide salts and monophosphoryl lipid A, and is shown to enhance immune responses to the VLP in early clinical development of this product [500 µg aluminum hydroxide 50 µg 3-O-deacyl-4'- monophosphoryl lipid A]. This is the first vaccine licensed in the US with the AS04 adjuvant. Both vaccines are given as a three-dose schedule over a period of six months, with the timing of the quadrivalent being 0,2,6 months and the bivalent being 0,1,6 months.

Both manufacturers have conducted large clinical development programs. The Phase II efficacy trials were conducted in females 16-23 or 15-25 years, and these were powered to detect virologic endpoints such as persistent infection. The larger Phase III clinical trials were conducted in similar ages of women and were powered to detect histologic endpoints such as cervical intraepithelial neoplasia and adenocarcinoma in situ. Bridging immunogenicity and safety trials were conducted in younger adolescents, and efficacy and immunogenicity studies have been or are being conducted in older age groups. For the quadrivalent, the mean follow-up time for the Phase II trial is 5 years and for the Phase III trial is 3.5 years in the per protocol populations. For the bivalent, the mean follow-up time for the Phase II trial is 5.9 years and for the Phase III trial is 2.9 years in the per protocol populations. While the trials by the two companies were similar in many respects, there are some important differences including the study populations, baseline eligibility criteria, control groups, analytic approaches, and the serologic and polymerase chain reaction (PCR) assays used to detect infection and the colposcopy algorithms and evaluations.

For the bivalent vaccine, there have been numerous ACIP presentations between 2005 and 2009. At the June ACIP meeting, Dr. Dubin presented the pivotal Phase III end of study trial results and the comparative bivalent and quadrivalent immunogenicity study. Both of these studies have been published and copies of these were distributed to the ACIP members before this meeting.

The Bivalent Phase III trial enrolled over 18,000 women in 14 countries. It was a double blind randomized trial in which subjects received either the HPV vaccine or hepatitis A vaccine as a control. The primary objective was to determine efficacy against 16/18 related CIN2, 3, or adenocarcinoma in situ, referred in this presentation as CIN2+, in the According to Protocol (ATP-E) cohort. A variety of secondary and exploratory objectives were examined as well (e.g., efficacy against persistent infections, CIN2+ lesions associated with non-vaccine oncogenic types, and others).

The primary endpoint in the According to Protocol analysis included women who received all three doses, were DNA and seronegative to the vaccine type at baseline and DNA negative through month 6, and had normal or low grade cytology at baseline. For the bivalent vaccine, overall efficacy was 93%; efficacy was high for types 16 (96%) and 18 (87%) individually. For the Per Protocol Analysis for the quadrivalent vaccine, overall efficacy was 98% against CIN 2+ and it was 98% and 100% effective for HPV 16 and 18 related CIN2+ lesions, respectively. For the quadrivalent vaccine, there were also Per Protocol Analyses for other endpoints for which very high efficacy found: vulvar and vaginal intraepithelial neoplasia grade 2 and 3 (100%), and condyloma or genital warts (99%).

In the Total Vaccinated or Intent to Treat analyses, as they are called in the two different programs, all women who had at least one dose of vaccine were included, regardless of whether they had preexisting vaccine type HPV infections at enrollment. Efficacy was lower for the HPV16/18 related CIN2+ for both vaccines at 53% for the bivalent vaccine and 52% for the quadrivalent vaccine. This is not unexpected since many of the CIN2+ lesions in these analyses included lesions associated with preexisting infections at the time of enrollment. In both of these analyses for the vaccines, efficacy increases with time as more infections accrue in the control group, but plateau in the vaccine group. [Paavonen et al. Lancet 2009; Kjaer et al. Cancer Prev Res 2009. Dillner et al 2009 in press].

Cross-protection has been evaluated for both vaccines, examining both composite and specific non-vaccine oncogenic HPV type endpoints. These are difficult analyses for a variety of reasons. The analysis of CIN2+ endpoints are difficult to interpret because of co-infections which make it difficult to assign causality. With respect to efficacy using composite endpoints for a number of oncogenic non-vaccine HPV types in analyses performed among women who were naïve to all of the types tested (e.g., 14 types for of the bivalent and 12 oncogenic types for the quadrivalent) at baseline, cross-protection against some types in the A9 species (the types that are phylogenetically related to HPV 16) was observed for both vaccines at 66% for the bivalent and 35% for the quadrivalent vaccine, respectively. For some types in the A7 species, the types related to HPV 18, efficacy was observed for the bivalent vaccine, but efficacy was not statistically significant for the quadrivalent vaccine. For a composite endpoint of 10 non-vaccine types, there was an efficacy of 68% for the bivalent and 33% for the quadrivalent [Skinner et al, presented at IPC, Malmo Sweden (May 2009); Brown et al, JID 2009;199].

Analyses have also been conducted to assess specific non-vaccine types such as 31 and 45. For the bivalent vaccine, 100% protection was observed against CIN2+ and persistent infection due to types 31 and 45. Protection was also observed against 6-month persistent infection of 78% for 31 and 81% for 45. For the quadrivalent vaccine, protection was observed against type 31-related CIN2+ (70%) and persistent infection (46%), but not for type 45. Type 31 is related to HPV 16 and type 45 is related to type 18 [Paavonen et al, presented at IPC, Malmo Sweden (May 2009); Brown et al, JID 2009;199].

One of the limitations of these analyses is that some of these lesions also had HPV 16 or 18 co-infection, so the observed efficacy could have been due to protection provided by the vaccine HPV type. For the bivalent vaccine, further analyses were conducted to explore efficacy against CIN2+ due to 12 oncogenic non-vaccine types, both including and excluding lesions that were co-infected with HPV 16 or 18. For a composite endpoint of 12 combined non-vaccine types, the efficacy against CIN2+ was 54%. In the analysis excluding lesions that had co-infection with HPV 16 or 18, efficacy was 37% [Paavonen et al. Lancet 2009].

Both vaccines are highly immunogenic and induce antibody titers higher than natural infection after the third dose. The minimal protective antibody threshold is not known because of the high efficacy observed in the vaccine trials. Bridging immunogenicity studies show the geometric mean titers (GMTs) are non-inferior and higher in adolescents (10-14 or 9-15 years) compared to the older females in the efficacy trials. Different antibody assays were used by the two companies in the vaccine trials and because of this, one cannot directly compare the antibody results from the different vaccine trials. A comparative trial conducted by GSK measured antibody after both vaccines using a pseudovirion-based neutralization assay (PBNA), which does allow a direct comparison between the two vaccines. In the Phase II trials at month 7, one month after the third dose, all vaccinees had detectible antibody for both vaccines. While almost all vaccinees had detectible antibody in the bivalent vaccine trials at month 36, in the quadrivalent trial, HPV 18 seropositivity was 74%. Importantly, loss of antibody for HPV 18 was not associated with breakthrough infections in the quadrivalent vaccine trials and was felt to be possibly due to low sensitivity of the assay used [Villa et al. Vaccine 2006; Harper et al. Lancet 2006 ; Paavonen et al. Lancet 2009]. For the bivalent vaccine, follow-up through month 76 shows good persistence of antibody as measured both by enzyme-linked immunosorbent assay (ELISA) and the PBNA assay. Titers are higher after vaccination than after natural infection.

In the comparative trial of the bivalent and quadrivalent vaccine conducted by GSK, the HPV 16 neutralizing antibody GMTs at month 7 were 3.7- and 7.3-fold higher in the bivalent vaccine group for HPV 16 and 18 respectively. HPV 16 and 18 antibodies measured in cervical vaginal secretions, circulating antigen-specific Memory B cells and CD4 T-cell responses were also higher in the bivalent vaccine group [Einstein et al. Human Vaccines 2009]. The clinical significance of these data are unclear, given that both vaccines have shown excellent efficacy for the duration of the follow up time. In the pre-licensure trial, safety evaluations of the bivalent vaccine included a variety of outcomes (e.g., solicited symptoms, unsolicited symptoms, medically significant conditions, new onset autoimmune disorders and chronic diseases, serious adverse events, and pregnancy outcomes). There was an integrated safety analysis, which was a pooled safety database including 11 trials of bivalent vaccine involving approximately 30,000 women, and a meta-analysis of autoimmune diseases from trials of vaccines containing the AS04 adjuvant involving 68,000 subjects.

In the Phase II and III trials, detailed data were collected using diary cards for 7 days following each injection and unsolicited events were collected for 30 days after vaccination in a subset of women. Data on all the other outcomes were collected from all women in the trials during the study period. Solicited local and general adverse events (AE) 7 days post-vaccination were analyzed in the pool safety database. The control groups differed in the study in that some received a hepatitis A vaccine, some received an investigational formulation of the hepatitis A vaccine, and some received a placebo. A larger proportion of persons reported injection site symptoms in the group that received bivalent HPV vaccine compared with those in the other groups. Pain, redness, and swelling were all reported more frequently in the bivalent vaccine group. There was no difference in unsolicited symptoms that occurred within 30 days of vaccination between the vaccine group and any of the control groups. In this analysis of severe adverse events and potential new autoimmune disorders, there were no differences between the rates in over 12,000 women who received the bivalent vaccine and over 10,000 women in the pooled control groups.

The meta-analysis, which was presented previously to ACIP, was done because of concerns regarding potential autoimmune disorders. The meta-analysis of all trials with AS04-containing vaccines assessed disorders of potential autoimmune etiology. There was no difference in the occurrence rate of potential autoimmune disorders among those receiving the AS04-containing vaccine and the control groups for any of the outcomes evaluated. An updated meta-analysis with longer follow-up showed an elevated relative risk for neuroinflammatory outcomes, but this did not reach statistical significance. The additional cases, which occurred 2 to 6 years after vaccination, were not believed to be supportive of a relationship to vaccination [Verstraeten, Vaccine 2008].

In the comparative trial of the bivalent and quadrivalent vaccine, the incidence of solicited symptoms was higher after the bivalent vaccine than the quadrivalent vaccine. The percentage of women reporting any pain after vaccination was 93% in the bivalent group and 72% in the quadrivalent group, and grade 3 pain was reported by 17% of the bivalent and 3% of the quadrivalent recipients. Fatigue within 7 days of vaccination was also reported more frequently in the bivalent than the quadrivalent group (49.8% versus 39.8%), as was myalgia (27.6% versus 19.6%). All of these symptoms were transient and resolved. Unsolicited symptoms, including serious adverse events, occurred at similar rates in the two groups [Einstein M. et al. Human Vaccines 2009].

Although pregnancy was an exclusion criterion for the trials and pregnancy testing was done before each dose, there are over 6,000 pregnancies in the clinical trials. There were no differences, including no differences in congenital anomalies or spontaneous abortions, between the vaccine group and the pooled control group. A sub-analysis to examine outcomes among women who became pregnant around the time of vaccination was also performed. This was defined as the last menstrual period minus 3 to 45 days after vaccination. In this analysis, limited to women who were 15 through 25 years of age, the only imbalance observed between the two groups was for spontaneous abortion, which occurred in 13.4% in the vaccine group and 8.8% in the control group

[www.fda.gov/AdvisoryCommittees/CommitteesMeetingsMaterials/BloodVaccinesandOther Biologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm181365.htm](http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingsMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm181365.htm)].

When the interim analysis was found to have this imbalance, the National Cancer Institute (NCI) was asked to conduct independent combined analysis of data from the GSK Phase III trial, and the NCI Phase III trial, which is being conducted in Costa Rica. The trial in Costa Rica has a very similar study design as well as a similar control group as the GSK trial (e.g., hepatitis A). In the primary analysis of this combined independent analysis, there was no evidence of any subset of pregnancies that had an increased risk of miscarriage using a pre-specified statistical approach to assess a variety of different intervals during pregnancy. Other analyses were conducted to examine specific time intervals. Among pregnancies conceived within the 90 days of vaccination, spontaneous abortions occurred in 15.4% of the HPV group and 9.6% of the control arm. There were no differences in pregnancies conceived later. NCI currently plans to follow up pregnancies in the control group after crossover to the HPV vaccine arm in Costa Rica [Wacholder et al. submitted].

There are some issues to consider with regard to these data. There was an imbalance in the spontaneous abortions observed in the Phase III trial among 15 through 25 year olds from women who became pregnant around the time of vaccination. The clinical trials were not designed to study spontaneous abortions and the rates, both in the vaccine group and the

control group, were all within expected background rates (9% to 21%). There was no difference in time to spontaneous abortion in the vaccine or the control groups, and there are no other data from the trials to suggest a possible mechanism of action. For example, no teratogenic effect was observed and there was no dose effect with an increased rate of spontaneous abortions after increasing number of doses. The pre-clinical reproductive toxicology studies did not show any signal. The bivalent vaccine is classified as a Category B on the basis of animal studies in rats showing no evidence of impaired fertility or harm to the fetus in doses that are about 47 times the human dose.

With respect to post-marketing data, the bivalent HPV vaccine is currently licensed in over 100 countries, including 27 countries in the European Union (EU), and about 7 million doses have been distributed worldwide. This vaccine has been used in the routine immunization program in the United Kingdom (UK) since September of 2008, with over one million doses distributed there. The company has tabulated reports of 1,680 adverse events reported during a 2-year period ending in May 2009. Of these, 7% were serious, 93% were non-serious, and there was one death that was not related to vaccination during that time period (e.g., 12-year old girl related to Group A streptococcal septicemia at 3 weeks after dose 2)

[www.fda.gov/AdvisoryCommittees/CommitteesMeetingsMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm181365.htm]; and <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm183835.htm>].

The most common adverse events in the world wide post-licensure safety database include headache, injection site pain, and fever. Frequency of the 10 most reported adverse events from 5/07 to 5/09 included the following:

Event	Number of Events	Reports 100,000 doses distributed
Headache	249	3.65
Injection site pain	246	3.61
Pyrexia	223	3.27
Dizziness	188	2.76
Nausea	163	2.39
Pain in extremity*	162	2.38
Malaise	119	1.75
Rash	115	1.69
Product quality issue	110	1.61
Syncope	101	1.48

GSK has a large pharmacovigilance plan post-licensure, which includes assessment of autoimmune disease in a Phase IV trial in US as well as in Finland. Pregnancy outcomes will be evaluated in a US trial, which is a post-marketing requirement for the company. There are registries in the US and the UK. Other studies are on-going as well that examine co-administration, vaccination HIV positives, long-term immunogenicity, and safety and efficacy.

In summary of the current understanding of these two vaccines in females, both appear to provide excellent protection against HPV 16- and 18-related CIN2+. The quadrivalent vaccine has also demonstrated efficacy against vaginal and vulvar pre-cancer lesions. The quadrivalent also provides high protection against HPV 6 and 11 genital lesions. In terms of cross protection against CIN2+ due to high risk types other than 16 or 18, there appear to be data showing that both vaccines provide some protection. The quadrivalent may provide protection against types

phylogenetically related to 16, and the bivalent may provide protection against types phylogenetically related to HPV 16 and 18. Seroconversion to vaccine types is very high for both vaccines. GMTs after vaccination are higher for the bivalent than the quadrivalent, although the clinical significance of this is unclear. Local reactogenicity is higher for the bivalent than the quadrivalent, but both vaccines are very well-tolerated. The costs of the vaccine in the private sector are \$130 for the quadrivalent and \$128 for the bivalent. The cost for the CDC contract for the quadrivalent is \$106 CDC, but is unknown for the bivalent [<http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm>].

Overview of Cost-Effectiveness of Quadrivalent and Bivalent HPV Vaccination

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During this session, Dr. Chesson discussed the health and cost burden of genital warts and juvenile onset recurrent respiratory papillomatosis (JORRP), particularly published cost-effectiveness studies of female HPV vaccination in the US that present results with and without inclusion of HPV 6 and 11 related health benefits, and those studies that assessed the impact of duration of protection on vaccine cost-effectiveness. He also presented published and unpublished estimates of the impact of cross-protection on vaccine cost-effectiveness.

Health economic studies have shown that HPV vaccination of 12-year old females is a cost-effective public health strategy for the bivalent or quadrivalent vaccine. However, the cost-effectiveness estimates of the two vaccines might vary due to potential differences in the benefits of each, such as protection against HPV 6 and 11 or related outcomes, cross-protection in terms of efficacy against non-vaccine oncogenic HPV types, duration of protection, and vaccine cost.

There are an estimated 500,000 incident cases (range 250,000 to 1 million cases) of genital warts each year in the US, with a cost per case of approximately \$460 (range: \$390 to \$530). It is believed that perhaps 90% of these cases are attributable to HPV types 6 and 11, with an annual burden of HPV 6/11 attributable genital warts of approximately \$210 million (range \$87 million to \$480 million). The burden of JORRP is subject to uncertainty because of the variability in the incidence and cost per case estimates. The number of new cases each year could be between 80 to 3200, while the cost per case is estimated to range from \$60,000 to approximately \$350,000. It is thought that most or all of these cases are attributable to HPV 6 and 11. A base case estimate has been suggested of approximately \$100 million for the burden of HPV 6/11 attributable JORRP, with a wide range of \$5 million to \$1.1 billion [Hu & Goldie, *Am J Obstet Gynecol* 2008]. When including HPV 6/11 attributable CIN1, the burden of HPV 6 and 11 outcomes is about \$330 million each year. In contrast, the burden for HPV 16/18 attributable outcomes is \$1.1 billion. Thus, the bulk of benefits, in terms of offsetting medical costs, would be achieved by preventing HPV 16 and 18.

Across the studies of published estimates of the cost per quality-adjusted life year (QALY) gained by HPV vaccination of 12 year-old girls, inclusion of the HPV 6 and 11 outcomes reduces the cost per QALY by approximately \$3,000 to \$10,000 in absolute terms and by approximately 10% to 50% in relative terms.

Two studies have provided estimates of the vaccine price differential that would offset the benefits of preventing genital warts. These studies estimated that a vaccine that does not prevent genital warts would have to cost about \$77 to \$125 less per series [Jit 2008, UK] or \$50 to \$140 less per series [Brisson 2007, Canada] than a vaccine that does protect against genital warts. However, both of these analyses assume that there were no other differences between the vaccines except for the benefits of preventing genital warts.

Regarding the impact of duration of protection, across five studies that show the cost-effectiveness of HPV vaccination of 12 year-old girls with and without lifelong duration of vaccine protection, in absolute terms the waning immunity increases the cost per QALY by \$15,000 to over \$100,000 and by about 50% to over 500% in relative terms.

A number of key themes emerge from published studies. If the vaccines differ only in protection against HPV 6 and 11, then the vaccine that protects against HPV 6 and 11 will be more cost-effective. This is because of the chance to offset substantial health and economic burden of HPV 6 and 11-related outcomes. There is an uncertain degree of impact that prevention of JORRP would have on the vaccine cost-effectiveness because of the uncertainty in the cost and incidence of this outcome. Finally, the cost-effectiveness estimates are sensitive to the duration of vaccine protection.

There are four estimates available of the impact of cross protection on vaccine cost effectiveness. In the recently published study by Kim & Goldie (2008), a scenario was examined in which the bivalent vaccine would provide efficacy of 27% against all other high risk HPV types besides HPV 16 and 18. The inclusion of this cross-protection reduced the estimated cost per QALY from \$43,000 to about \$33,000. In an adaptation of the published Merck model [Dasbach et al], the cost-effectiveness impact of cross-protection was estimated assuming that there would be 16% efficacy against infection and 33% efficacy against disease associated with five HPV vaccine types (31, 33, 45, 52, 58). This cross-protection was estimated to reduce the cost per QALY gained by quadrivalent vaccination from \$4,200 to \$3,500.

Using the GSK model, Kruzikas and colleagues examined the cost-effectiveness of HPV 16 and 18 vaccine with cross-protection compared to an HPV 6/11/16/18 vaccine without cross-protection. They assumed that the HPV 16/18 vaccine would provide 37% efficacy against the 12 non-vaccine oncogenic types. They found that in this scenario, the bivalent vaccine would have a lower cost per QALY; that is, it would be more cost-effective at \$1,500 per QALY versus \$7,200 per QALY for the quadrivalent vaccine without cross-protection.

Chesson et al also updated their published model to compare these two vaccines under different assumptions about cross protection. They examined three scenarios: 1) assuming no cross-protection for either vaccine; 2) assuming cross-protection for both vaccines, but with a greater degree of cross protection for HPV 16 and 18; and 3) assuming that cross-protection would only apply for the HPV 16/18 vaccine. Across these three scenarios, the cost per QALY estimates were similar for the two vaccines. In the first two scenarios, the HPV 6/11/16/18 vaccine had a lower cost per QALY at \$7,100 versus \$10,500 for the HPV 16/18 vaccine for Scenario 1 and \$5,300 versus \$7,100 for Scenario 2. For Scenario 3, the cost per QALY estimates were \$7,100 each.

To summarize, the prevention of cervical disease is the most important benefit of HPV vaccination. Given that both vaccines offer this benefit, the cost-effectiveness estimates of the

two vaccines are similar. However, if the vaccines differ only in regard to protection against HPV 6 and 11, then the quadrivalent vaccine would be more cost-effective because of the potential to offset the health and economic burden of genital warts and possibly RRP. However, the protection against HPV 6 and 11 is just one of the factors that influence the cost effectiveness. Many other factors can impact these estimates, such as duration of protection and degree of cross protection. There is no evidence of a difference in the bivalent and quadrivalent vaccine in terms of duration of protection. Cross-protection data are difficult to interpret, but differences may exist.

Discussion

Dr. Cieslak inquired as to how good a predictor serology is of immunity and how important that would be. To some degree, the GSK data seemed to be trying to suggest that titers were of major importance. Thus, he wondered whether it was serologic response that correlated with immunity or something else, and how much that should be weighing into ACIP's considerations.

Dr. Markowitz replied that both vaccines have shown excellent efficacy and there is no evidence of waning protection, so serology has not been considered to be a major indicator of immunity. At this point, the assumption is that there is no indication that there is any difference in duration of protection.

Dr. Temte expressed curiosity regarding the persistence of immunity and whether that was also taken into consideration in terms of changes in behavior and changes in risk over time and how that was modeled.

Dr. Chesson responded that none of the models, to his knowledge, took into account any changes in behavior as a result of vaccination.

Dr. Neuzil pointed out that if this vaccine was being given at 11 years of age and there were 5 to 6 years of duration, this would just reach into the 16- to 17-year old age group. The committee would obviously like to see duration for longer and would in the future. While she understood that antibody titers could not be compared directly between the Merck and GSK assays, she wondered whether they could feel comfortable comparing antibody titers with any studies (e.g., the Merck assay is consistent across studies and the GSK assay is consistent across studies).

Dr. Markowitz replied that even within studies, the assays could not be compared because they have not been standardized. For example, the antibody titer for HPV type16 in the Merck trial cannot be compared to the antibody titer for HPV type18 in the Merck trial.

Dr. Neuzil clarified that she was referring to comparing HPV 16 antibody in girls at age 11 and then10 years later. That is, are the companies consistently using the same assay over that 10 year duration such that ACIP members could feel comfortable that the assay have not changed?

Dr. Markowitz responded that she would have to ask the companies. There has been some tweaking of the assay that Merck is using, although she was unaware of any change in the assay GSK is using.

Dr. Haupt (Merck) indicated that while there have been minor revisions to the Merck assay, it is essentially the same assay that being used to follow people over time. It is a competitive assay that measures just one neutralizing antibody against a known neutralizing epitope on the different types. Each assay is a completely different assay. Each assay has different standards, so the amount of antibody measured for type 16 is not comparable to the amount of antibody measured against type 18. There is no evidence that long-term antibodies are required for long-term protection. For type 18, Merck has observed that a number of women have become seronegative over time, but continue to experience 100% efficacy against any HPV type 18 clinical disease.

Dr. Dubin (GSK) indicated that GSK uses the same assays longitudinally. There are two assays that GSK has used to measure immune responses, one of which is an enzyme-linked immunosorbent assay (ELISA)-based format for 16 and 18, and the other of which is a pseudovirion neutralization assay based on methodology developed by the National Cancer Institute (NCI). The immunogenicity was assessed over a 6.4 year period of time using the same assay. GSK is confident that early time points can be compared to late time points and that the kinetics can be examined. GSK believes the kinetics may be important to help predict what might be observed in the future, at least in terms of levels of antibody over time. They will follow this even beyond the 6.4 years.

Ms. Ehresmann noted that based on Dr. Markowitz' presentation, there appeared to be some level of cross-protection efficacy. However, in her summary slide in trying to compare these two vaccines, there were question marks as if there was some uncertainty. She wondered whether that was because the efficacy rates were relatively lower.

Dr. Markowitz responded that those analyses are difficult to do and there are still some questions. There does appear to be cross-protection, but questions remain: How long will that last? Will it be as durable as the protection against the vaccine types?

Dr. Keitel found the differences in the titers elicited by the two vaccines to be impressive, and she wondered if there was any information regarding antibody responses to the non-vaccine types and whether that cross protection could be associated with just a higher level of homotypic antibody spilling across.

Dr. Dubin (GSK) responded that GSK has limited information on cross-protective antibody responses from the comparative trial. It is important to note that the mechanism of cross-protection is not known. It appears that a close phylogenetic relationship is important because the highest level of cross-protection is observed with closely related types phylogenetically. GSK believes that induction of cross-reactive responses, which could potentially be cross-reactive antibody responses or cross-reactive T-cell responses, potentially could play a role. There is some evidence that vaccination does induce cross-reactive T-cell responses. With regard to the duration of cross-protection, GSK has assessed cross-protection in two studies. One was the study referred to by Dr. Markowitz in which GSK assessed subjects over 6.4 years, specifically studying incident infection. This study showed evidence of efficacy over the entire 6.4 year period against incident infection with types 45 and 31. Those were the two types for which there were enough endpoints to draw conclusions. The pivotal Phase III study showed 37% to 54% protection against 12 non-vaccine types, which is considered as a composite endpoint. That was assessed over the entire duration of the Phase III study, so that estimate represents efficacy throughout the approximately 3 to 3.5 years of follow-up in that trial.

Dr. Haupt (Merck) indicated that Merck has evidence from its clinical trial that cross-reactive antibodies to non-vaccine types are generated through vaccination with Gardasil®. Certainly, the levels of those antibody responses are not at the same magnitude as the vaccine type responses that are seen. He concurred with Dr. Durban that the mechanism of cross protection, if it exists, is not clear. However, there are some cross reactive antibodies.

Regarding safety, it appeared to Dr. Pickering that local reactions were somewhat higher with the new vaccine, but that no serious adverse events had been reported.

Dr. Markowitz replied that that local reactions were, indeed, somewhat higher. With respect to the post-licensure data, there appeared to be no serious adverse events of concern based on what CDC had heard.

Dr. Judson noted that since immunogenicity seemed to be related, at least in some part to the adjuvant's reactogenicity, one would expect if the two adjuvants were similarly reactogenic on a microgram basis, that the GSK product would be more reactogenic, which it is, and probably more immunogenic since it has 500 micrograms versus 225 micrograms.

Dr. Neuzil commented that it is a different aluminum salt and while she did not claim to be an expert on adjuvants, she pointed out that the type of aluminum salt does matter. Therefore, it did not seem that there could be a direct comparison.

Dr. Baker clarified that the amount of virus-like protein is actually less in the bivalent. Thus, the increased reactogenicity could be assumed to be related to the AS04.

Dr. Duchin (NACCHO) requested information about access to pharmacovigilance data following licensure with respect to whether this would be public data, whether it would be reviewed by independent bodies, and what the timing of review would be by independent agencies such as the FDA.

Dr. Markowitz responded that the manufacturers are required to make periodic reports on the specific Phase IV studies (e.g., autoimmune disorders; pregnancy outcomes) to the FDA and the Vaccine Adverse Event Reporting System (VAERS). While she did not know who would have access to international VAERS data, VAERS data are provided to CDC when there are reports from the US.

Dr. Dubin (GSK) added that the Phase IV studies are going to be part of the pharmacovigilance plan. GSK will be making periodic reports according to its post licensure commitments to FDA. Data will be published and make data available in a timely manner as per other pharmacovigilance activities for other vaccines. The details of the protocols for the Phase IV studies are being developed, and GSK is engaged in discussions with the Center for Biologics Evaluation and Research (CBER) about the designs and timeframe for conducting those studies. Data about those studies will be made available to CBER through periodic reports.

Regarding side effects, Dr. Temte noted that the two cases from the current quadrivalent receiving attention are amyotrophic lateral sclerosis (ALS)-like. Out of the approximately 7 million doses of Cervarix®, he wondered whether anything similar was occurring in other countries.

Dr. Dubin (GSK) responded that in the clinical trials of Cervarix®, there are no reports of ALS. Neither was he aware of any reports through post-licensure or post-marketing surveillance.

Dr. Meissner commented that RRP is a very difficult disease to treat, and that pediatricians are aware of the difficulty of this illness. Given that it is such a rare occurrence, he understood that it was very difficult to address the impact of the quadrivalent vaccine on this disease. However, he wondered whether there was any expectation in the future that there may be some evidence of the ability of this vaccine to reduce the frequency of RRP.

Dr. Markowitz responded that there have been active discussions at CDC about how to set up monitoring for RRP. When the quadrivalent vaccine was rolled out, Canada initiated nationwide monitoring for RRP. There is an RRP registry in the US and there have been discussions regarding if and how that should be re-instituted. Merck has also engaged in efforts to determine whether administrative data can be used to follow trends in RRP.

Dr. Haupt (Merck) added that Merck is very interested in the potential of Gardasil® to impact RRP. This cannot be addressed through an efficacy study, so Merck is considering long-term observation or epidemiologic evaluations to make assessments over time. It will take some time before that data would be available, given the range of the coverage rates of vaccination, the rarity of RRP, and the potential impact on children who then have to develop disease over some years to determine whether there is prevention. Merck is certainly hopeful.

Recommendations and Vote for Bivalent HPV Vaccine and HPV Vaccines in Females

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Dr. Markowitz discussed the specific recommendations for bivalent and for the use of HPV vaccine in females. As discussed earlier, she indicated that in addition to making recommendations for the specific use of the bivalent vaccine, issues related to the availability of two licensed products in the US must be considered (e.g., preference, harmonization, and interchangeability of the vaccines). At the same time, current recommendations and proposed changes must be considered. The Work Group, to date, had addressed changes in variety of sections including the routine and catch-up, age ranges, dosing intervals, minimal intervals, and interchangeability. Given time constraints, consideration of special situations was deferred until the February 2010 ACIP meeting. The Work Group also discussed precautions and contraindications.

The indications for the bivalent vaccine in females for the prevention of diseases caused by 16 and 18 including cervical cancer, CIN grade 2 or worse and adenocarcinoma in situ, and CIN grade 1. This vaccine is approved for females aged 10 through 25 years
[<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186957.htm>] .

The quadrivalent vaccine in females is for prevention of cervical, vulvar, and vaginal cancer caused by 16 and 18; and genital warts caused by HPV 6 and 11 and diseases caused by 6,11,16, and 18 (e.g., CIN grade 2/3 and adenocarcinoma in situ, CIN grade 1, and vaginal intraepithelial neoplasia (VaIN) and vulvar intraepithelial neoplasia (VIN) grade 2 and 3). This vaccine is approved for females aged 9 through 26 years
[<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm>].

The Work Group discussed the approach to making a recommendation for two licensed products and whether a statement of preference should be made for one vaccine or the other. Their proposed approach to having two licensed vaccines, which have different attributes, was to: state non-preference for one vaccine over the other; state that there are differences between the two vaccines with regard to protection against 6 and 11; state the differences in other attributes and data available for the two vaccines; encourage providers to understand the differences between the two vaccines; indicate that for protection against 16 / 18 related cervical cancer, females should be vaccinated with either the bivalent or the quadrivalent vaccine; and indicate that for protection against 16 / 18-related cervical cancer / genital cancers and HPV 6 / 11-related genital warts, females should be vaccinated with quadrivalent vaccine.

In the ACIP statement, the background will provide data from the clinical trials, including data regarding potential cross protection. A rationale section will summarize the data and provide the rationale for non-preference. This will be followed by the recommendations. The rationale will include the following statements:

- Both vaccines have high efficacy against HPV 16/18-related cervical pre-cancers and duration of protection through at least 5-6 years is excellent.
- In addition to an indication for prevention of HPV 16/18-related cervical cancer, precancers and dysplastic lesions, the quadrivalent vaccine has indications for prevention of HPV 6/11/16/18-related vaginal and vulvar cancer, precancers and dysplastic lesions, and genital warts.
- HPV 16 and 18 antibody titers after vaccination with the bivalent vaccine are higher than those after the quadrivalent vaccine; the clinical significance of this finding is uncertain.
- Injection site reactions and general solicited symptoms are generally higher after the bivalent vaccine but both vaccines are well tolerated.
- There might be other differences between the vaccines that are only apparent with longer term use of these vaccines in larger numbers of persons.

The current section for routine vaccination with quadrivalent HPV Vaccine states the following:

“ACIP recommends routine vaccination of females 11 or 12 years of age with three doses of quadrivalent HPV vaccine. The vaccination series can be started as young as 9 years of age.”

The proposed recommendation states the following:

“ACIP recommends routine vaccination of females aged 11 or 12 years with 3 doses of HPV vaccine. The vaccination series can be started as young as 9 years of age. Two different HPV vaccines are licensed for use in the United States: the quadrivalent HPV (types 6, 11, 16, 18) vaccine and the bivalent HPV (types 16, 18) vaccine. Both vaccines are recombinant vaccines made from the L1 surface protein of the virus. The vaccines are 93-100% effective against cervical pre-cancers caused by HPV 16 and 18. The quadrivalent vaccine is also more than 99% effective against genital warts caused by HPV 6 and 11. ACIP does not express a preference for either vaccine. ACIP recommends vaccination with either the bivalent or the quadrivalent HPV vaccine 3 dose series for prevention of HPV 16 or 18-related cervical cancers, precancers and dysplastic lesions. ACIP recommends vaccination with the quadrivalent HPV vaccine 3 dose series for prevention of cervical, vulvar and vaginal cancers, precancers and dysplastic lesions due to HPV 16 or 18 and for prevention of genital warts due to HPV 6 or 11.”

Discussion

Ms. Ehresmann expressed her surprise with the lack of a preference, particularly given that one vaccine protects against four types. She wondered whether something dramatic that occurred amongs Work Group members with respect to how they decided upon a no preference option.

Dr. Markowitz responded that there was nothing dramatic. The feeling was that as a general rule, ACIP has expressed non-preference when there is more than one vaccine. Part of the reason for the last statement being the rationale is that there may be differences between the two vaccines that remain unknown currently, which is another reason for not expressing a preference at this time.

Dr. Sawyer also expressed concern with the non-preference statement. In the overall recommendations, language was included to encourage providers to understand the differences between the two vaccines. However, separate recommendations are included to state that in order to prevent genital warts one vaccine must be given, but to prevent cancer, the other vaccine should be administered. Given that he was often in the position of helping physicians understand the differences between vaccines, he was having difficulty thinking what he would say about why he would not want to prevent genital warts. There must have some discussion in the Work Group about the relative lack of morbidity from genital warts, or the relative lack of impact from a cost point of view, that led the Work Group to conclude that providers should have the choice to decide whether to prevent warts.

Dr. Baker pointed out that when there is a single manufacturer of a vaccine, there sometimes are vaccine shortages. Therefore, in principle, she thought it was beneficial to inform physicians that during shortages, there is another company from which they can order.

Dr. Markowitz responded that in general, she believed theWwork Group wanted to express non-preference and acknowledge that there may be differences between the two vaccines because many Work Group members thought that the quadrivalent would be attractive to many providers because it prevents genital warts. Conversely, some providers may review the data for the bivalent vaccine and decide to use it. It was a matter of allowing the decision to be made by providers.

Dr. Marcy added that he had been bouncing around on this issue for the better part of a year. It seemed to him that a middle ground ACIP could take would be to simply eliminate the sentence, "ACIP does not express a preference for either vaccine" and let practitioners decide. That may assuage everybody. He was convinced that third party payers would have a preference for the lower priced vaccine. If GSK comes in at a much lower price, there could be a problem. Dr. Marcy's recommendation was to eliminate that sentence and then let the practitioner decide.

Dr. Judson thought that almost everyone acknowledged that the reasons these vaccines were developed was to prevent cervical cancer, which should be first and foremost in the recommendations. While he did not object to going further to state that there are additional attributes of one vaccine or another, for the healthcare provider who wants to prevent cervical cancer in children, ACIP should offer no preference in either vaccine.

Drs. Ehresmann, Sumaya, and Chilton supported Dr. Marcy's suggestion.

Dr. Keitel noted that one reason had already been indicated with regard to why they might not want to state a preference. She wondered if there was a thorough discussion of the potential impact of making a preference recommendation or not.

Dr. Markowitz responded that they were concerned about making a preference recommendation because they wanted to ensure a market for both vaccines.

Dr. Chilton pointed out that depending upon the recommendation made for females versus males, it could appear that they were saying that genital warts do not matter in females but they do matter in males.

Dr. Englund reported that the Work Group engaged in a very thorough discussion with input from multiple academic and public health-related officials, not manufacturers, regarding the consequences of a preference at this point when a vaccine was licensed only for a week. The decision was based on the fact that cervical cancer is a potentially a preventable and lethal disease. While they all respected and had considerable input from many physicians about the social and psychological consequences of genital warts, the overall impact at \$400 a case or less pales in comparison to the impact of cervical cancer and the fact that cervical cancer is being acquired by many of the least socially advantaged population groups. The Work Group discussions were by no means uniform, were often heated, and included significant input from other advocates with various viewpoints.

It was not clear to Dr. Cieslak that the language as written reflected that the primary consideration should be prevention of cervical cancer. He suggested that this be made more clear.

Dr. Markowitz suggested that this could be addressed in the rationale statements preceding the recommendation.

Dr. Duchin (NACCHO) suggested that if they were actually making a recommendation for prevention of cancer, perhaps the title of the recommendation should reflect that. Discussion could then be included with respect to the added benefits of the quadrivalent vaccine. He also expressed concern about the payer market driving the choice if they did not express a preference and the implications of that. That is, if one vaccine is priced significantly less than

another, there is no preference expressed by ACIP, and there is no clear indication that the primary purpose of the recommendation is cervical cancer prevention, the least expensive vaccine will be the one available to most people because that is what will be covered by payers.

Dr. Middleman supported Dr. Marcy's comments about a preference. From the adolescent medicine point of view, genital warts is a tremendous burden and a very important issue to the physical and emotional health of youth. Having been on the Work Group, she thought they had delineated the difference between indications for cervical cancer and indications and other advantages of preventing genital warts.

Dr. Grogg (AOA) also suggested that the committee support Dr. Marcy's recommendation.

Dr. Keyserling (SHEA) pointed out that for the VFC vote, at least in states that do not have a choice, these vaccines clearly are not biological equivalents like hepatitis A and hepatitis B vaccines. In certain states, the VFC providers are not allowed a choice. He thought it should be clearly stated that these two products are not biologically equivalent and cannot necessarily be the only products available for VFC in a state.

Dr. Turner (ACHA) supported Dr. Marcy's comment as well. He pointed out that 30% of the HPV-related disease seen in college health is genital warts and it is a major issue. Though a benign disease physiologically, it has an enormous impact on relationships and self-esteem. ACHA feels that preventing the genital warts is equally important.

Dr. Kimberlin (AAP) said that from a pediatrician's standpoint, JORRP would be a greater concern than cervical cancer simply because cervical cancer occurs later in life. He pointed out that if the sentence was dropped as Dr. Marcy suggested, the following two sentences would be that ACIP recommends vaccination with either product to prevent cervical cancer and that ACIP recommends vaccination with the quadrivalent to prevent cervical cancer, dysplasia, and genital warts. That appears to be a preference.

Dr. Dubin (GSK) clarified that because Cervarix® was just licensed at the end of the previous week, the final approved label had just become available. Some of the information on cross-protection to which Dr. Markowitz referred is included in the US label (e.g., 37% to 54% protection against composite endpoint of 12 non-vaccine oncogenic types, CIN2+ endpoints).

Dr. Snider thought there had been a healthy discussion about whether to include a sentence about preference. In reflecting upon his last 15 years of association with this group, he was not comfortable with the notion of preference in that there had not been a consistent approach to deciding whether to indicate a preference, state that there was no preference, or be silent about a preference. It seemed to him that there should be a more general discussion at some point within ACIP about what the triggers and scientific basis should be for expressing preferences, particularly given that there did not appear to be a standard logic behind why preferences have been stated for any particular case.

Dr. Sawyer pointed out that based on the discussion, it would appear that ACIP would be silent with respect to preventing genital warts. With Dr. Marcy's suggestion, the recommendation would basically say that ACIP does not have a preference in the vaccines, and would simply states the obvious that one prevents warts and the other does not. He did not think that would be doing a service to providers.

Dr. Baker responded that providers are typically pretty smart and that the educational material should be sufficient to point out the differences in the two vaccines.

Motion: Bivalent HPV Vaccine and HPV Vaccines in Females

Dr. Marcy made a motion to approve the HPV vaccine recommendations as presented, with the elimination of the sentence "ACIP does not express a preference for either vaccine" and keeping the following two statements:

"ACIP recommends vaccination with either the bivalent or the quadrivalent HPV vaccine 3 dose series for prevention of HPV 16 or 18 related cervical cancers, precancers and dysplastic lesions.

ACIP recommends vaccination with the quadrivalent HPV vaccine 3 dose series for prevention of cervical, vulvar and vaginal cancers, precancers and dysplastic lesions due to HPV 16 or 18 and for prevention of genital warts due to HPV 6 or 11."

Ms. Ehresmann seconded the motion. The motion carried with 13 affirmative votes, 0 abstentions, and 1 negative vote.

With respect to harmonization, Dr. Markowitz pointed out that the age ranges in the clinical trials and the ages for licensure of the vaccine are slightly different. The bivalent is licensed for females aged 10 through 25 and the quadrivalent vaccine is licensed for females aged 9 through 26. With regard to background information, GSK has bridging immunogenicity trials in females both older and younger than the ages in the efficacy trials, which show that the GMTs are higher in younger females. In addition, 9-year olds are not the target age group for the vaccination program in the US and very few girls are being vaccinated at this age. If the age ranges are harmonized to the quadrivalent ages, this could facilitate communications for recommendations; however, it also could cause confusion with label and marketing. GSK is not permitted to market outside their licensed age groups. Biologically, there does not appear to be any difference between the 9- and 10-year olds and the 25- and 26-year olds. The immunobridging data for the bivalent vaccine show higher antibody titers in the 10- to 14-year olds than the 15- to 25-year olds for both types 16 and 18.

With respect to recommendation options, if there is not harmonization, the recommendation will state that the quadrivalent vaccine should be given routinely at age 11 or 12, but can be given as young as 9 and given as catch-up from 13 to 26 years. Routine bivalent vaccine would be recommended at 11 to 12 years, but can be given as young as 10 and given as catch-up from 13 to 25 years. In harmonization, the same age range would be included for both vaccines.

A second harmonization issue pertains to the dosing schedules and intervals. The clinical trials were slightly different in this regard as well. The quadrivalent vaccine was given at 0, 2, and 6 months and the bivalent vaccine was given at 0, 1, and 6 months. Data are available from the bivalent vaccine trial showing that the GMTs in females were similar if the second dose was administered 15 to 45 days after the first dose or if it was given 46 to 75 days after the first dose, which would correspond to the 0, 2, 6 schedule. Also from the trial, there are data showing that the GMTs in females are similar if all three doses are given within 5, 6, 7, 8, or 9 months.

The current recommendation states,

“Quadrivalent HPV vaccine is administered in a 3-dose schedule. The second and third doses should be administered 2 and 6 months after the first dose.”

“The minimal interval between the first and second doses is 4 weeks.”

The proposed dosing schedule, which would be harmonized, would state,

“The quadrivalent HPV vaccine and bivalent HPV vaccine are each administered in a 3-dose schedule.”

“The second dose should be administered 1-2 months after the first dose.”

“The third dose should be administered 6 months after the first dose.”

Another harmonization issues is minimal dosing intervals, which is important for the general recommendations and other tables that are published by ACIP. The minimal intervals could be harmonized as well, or they could be based on minimal ranges in the respective efficacy trials. The current minimal intervals are as follows:

	Minimum Dosing Intervals (weeks)		
	<u>Doses 1-2</u>	<u>Doses 2-3</u>	<u>Doses 1-3</u>
Quadrivalent	4*	12	24
Bivalent	3*	12	20

*Lower interval range in efficacy trials

The alternative is to have a harmonized minimal interval which would say for either vaccine, the minimal interval is 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 24 weeks between the first and the third doses. Thus, everything would be harmonized to the current recommendation for the quadrivalent vaccine.

There is no change for interruption of schedule, which currently states:

“If the vaccine schedule is interrupted for either the quadrivalent or bivalent HPV vaccine, the vaccine series does not need to be restarted.

If the series is interrupted after the first dose, the second dose should be administered as soon as possible. The second and third doses should be separated by an interval of at least 12 weeks, with a minimum interval of 24 weeks between the first and third doses. If only the third dose is delayed, it should be administered as soon as possible.”

The important issue of interchangeability of vaccines has arisen for other vaccines and ACIP has had to deal with this in the absence of data. Currently, there are no data pertaining to interchangeability, so the Work Group has proposed the following wording,

“ACIP recommends that the HPV vaccine series be completed with the same HPV vaccine product whenever possible. However, if vaccination providers do not know or have available the HPV vaccine product previously administered, either HPV vaccine product can be used to continue or complete the series to provide protection against HPV 16 and 18.”

“No studies address the interchangeability of the two HPV vaccines. It is possible that effectiveness of a series including both products might be reduced compared with a series completed with one product for protection against HPV 16 or 18-related cervical cancers and precancers.

“For protection against HPV 6 or 11-related genital warts, a vaccination series with less than three doses of the quadrivalent HPV vaccine might provide less protection against genital warts than a complete three dose series.”

The following table reflects available data and on-going studies for each vaccine:

<h3 style="text-align: center;">HPV Vaccine Co-Administration Immunogenicity and Safety Studies</h3>		
	Available Data	Ongoing/Planned Studies
Quadrivalent vaccine*	HepB (RECOMBIVAX HB) DTaP-IPV (REPEVAX) Tdap, MCV4 (MENACTRA, ADACEL)	Tdap (BOOSTRIX), MenACWY (Menveo)
Bivalent** vaccine	Tdap-IPV (BOOSTRIX Polio) MCV4, Tdap (MENACTRA, BOOSTRIX)	HepA/HepB (TWINRIX) Hep B (ENGERIX B)

No significant difference in reactogenicity or antibody response to any antigen with co-administration

*Wheeler, et al. Vaccine 2008; Vesikari, et al. PIDJ, in press; Reisinger, et al. PAS-SPR 2009
**Schwartz, et al. ESPID, 2009. Wheeler, et al. To be presented at IDSA 2009



Of note, there are now data for code administration with tetanus and reduced diphtheria toxoids and acellular pertussis vaccine (Tdap) and quadrivalent meningococcal conjugate vaccine (MCV4) for both the HPV vaccines. For all of the studies for which there are data, there were no significant differences in reactogenicity or antibody response with co-administration. For simultaneous administration, the proposed statement will be the same for the bivalent and the quadrivalent:

“HPV vaccines are not live vaccines and can be administered either simultaneously or at any time before or after a different inactivated or live vaccine. Specifically, HPV vaccine (either the quadrivalent vaccine or the bivalent vaccine) can be administered at the same visit as other age appropriate and routinely recommended vaccines, such as Tdap and MCV4. Available data indicate that when these vaccines are administered at the same visit, there is no adverse impact on safety or immune response to any of the vaccines. Data are also available for simultaneous administration of quadrivalent HPV vaccine and hepatitis B vaccine.

Discussion

Dr. Marcy suggested replacing the dash with “to” in the statement, “The second dose should be administered 1-2 months after the first dose” because then the minimum interval would be the same as for the bivalent vaccine. Having the statement as suggested would mean a discrepancy between ACIP’s recommendations and the package insert. There is good precedent for that with anthrax and rabies vaccine, so it would not be the first time ACIP handled a recommendation in this way. For both vaccines the schedule should be 0, 2, and 6 months.

Dr. Judson suggested eliminating the comment on the speculation that effectiveness might be reduced by mixing the two vaccines, given that this is not known.

Dr. Chilton strongly suggested harmonization, noting that there is a precedent for doing so with the rotavirus vaccines.

Dr. Temte agreed that harmonization is very user-friendly for busy clinicians. He indicated that they were hoping eventually to attach an evidence-based review onto recommendations like this, which should be helpful. He asked whether there had been any assessment of immunization registries to determine how commonly HPV vaccines are provided to 9- and 10-year olds. His experience has been that it is sometimes difficult to administer it to 11-year olds.

Dr. Markowitz replied that coverage in 9-year olds is very low. The National Immunization Survey starts with 13- to 17-year olds. There are data from some other surveys, some of which are national and some of which are from specific localities, which show very low coverage at that age.

Regarding the dosing schedule, Dr. Englund agreed that harmonization is important. She thought they should keep in “1 to 2 months” because it is easier to get people to return at one month than at two months.

Ms. Ehresmann agreed with Dr. Marcy's suggestion because it looked like the only data in terms of other time frames for dosing and the GMTs was for the bivalent vaccine. She wondered whether the same information was available for the quadrivalent vaccine.

Dr. Markowitz responded that the reason she did not show that was because the current recommendation states that the minimal interval between the first and second is 4 weeks for the quadrivalent, which was the allowable range in the clinical trial.

Dr. Haupt (Merck) responded that Merck has data down to four weeks between the first and second dose. In fact, the GMT response is somewhat higher at one month after the second dose as opposed two, so there is data to support the minimum interval of four weeks.

Dr. Cieslak agreed with removal of the dash, but also supported just using "1 month."

Dr. Lett pointed out that there was precedent for the "1 to 2 month interval" such as that for hepatitis B, which allows flexibility.

Dr. Marcy clarified that using "1 to 2 months" would mean that the recommended interval is also the minimum interval for quadrivalent, which was what concerned him.

Dr. Englund noted that this would align with the FDA licensed recommendations, which is beneficial because people do read labels.

It was not clear to Dr. Duchin (NACCHO) how a minimum could be both greater than one and greater than two months.

Dr. Markowitz responded that the minimum is not two. It is not the minimum—it should be administered one to two months following the first dose. There is a recommendation and there are also the minimal intervals that are published in other recommendations. This addresses when a dose is counted as valid. There is always recommended timing for dosing, but separately minimal intervals are published. It is somewhat confusing, but that is how minimal intervals work—they are separate from when vaccine should be administered.

Dr. Baker clarified that the second bullet pertained to the dosing schedule, "The second dose should be administered one to two months after the first dose." A different issue regarded the minimum interval, which is four weeks. She thought that practitioners who give these vaccines would certainly understand the statement.

Dr. Markowitz reminded everyone that for the minimal dosing intervals, there was a non-harmonized version and a harmonized version. The primary difference in these was for the bivalent, down to three weeks would be permitted because that was the minimal in the trial. The first and third doses are slightly different intervals. The harmonization would have the same minimal intervals for both. There would be no change in the schedule interruption recommendation. The statement that the effectiveness of the series might be less if the two vaccines are used interchangeably basically indicates a preference for completion of the series with the same vaccine product. However, if the clinician does not know which vaccine was previously used or does not carry the same product, they can use a different HPV vaccine.

Dr. Baker suggested using "not known" rather than "reduced" or "increased." Dr. Meissner agreed.

Given that there are data to support a minimum interval for the bivalent vaccine of down to three weeks, Dr. Wharton noted that if a proposed harmonized minimum interval of four weeks was accepted for purposes of catch-up schedules, it may be reasonable to allow doses that occur after three weeks but before four weeks for the bivalent vaccine.

Dr. Markowitz indicated that she spoke with Bill Atkinson who explained to her that with a minimal interval, there are really several days of leeway below that minimal interval.

Dr. Baker said she believed the window was four days.

Dr. Katz said that it was somewhat “apples and oranges.” There are a number of examples of other products for which there is more than one producer, so he thought interchangeability should be left alone.

Dr. Atkinson (CDC) indicated that there is a caveat in general recommendations that the so-called “grace period” allows a four-day leeway less than the minimum interval. That would not completely capture the three weeks that is in the label, or at least that there are data to support. However, there are a couple of examples. For instance, for diphtheria, tetanus, and pertussis vaccine (DTaP) three and four, there are two minimum intervals: one that is the stated minimum interval and another that is a base date no repeat interval. For DTaP, the minimum interval is six months, but there is a footnote in the statement that says if it is given at least four months after the previous dose, it does not have to be repeated. In theory, this could be captured with a footnote that states that if HPV2 was given at least three weeks after the first dose, it would not be necessary to repeat it. This could be done without necessarily endorsing that as a minimum interval.

Dr. Baker stressed the importance of trying to make this evidence-based, but simple enough for implementation because it would have been a nightmare if that work hadn't been done. Dr. Cieslak, last comment.

Dr. Cieslak said that while he understand the notion of four days leeway, as former chairman of a large pediatrics department, all of the immunizations in his department were given by immunization nurses. When it says minimum interval, that is minimum interval and if it has been less, they give it again. Immunizations are typically being given by nurses who interpret the guidelines very strictly, so three weeks and six days would mean another dose of vaccine to a lot of people.

**Motion: Harmonization / Interchangeability of
Bivalent HPV Vaccine and HPV Vaccines in Females**

Dr. Chilton made a motion to accept the language as written regarding harmonization and interchangeability, except that effectiveness is not known for a series that includes both products and dashes should be replaced with “to” or “through” where appropriate. Dr. Sumaya seconded the motion. The motion carried with 14 affirmative votes, 0 abstentions, and 0 negative vote.

Regarding modifications to the precautions and contraindications section, in the current ACIP statement for HPV vaccine pregnancy is in its own section. Subsequent to development of that ACIP statement, the ACIP Policy on Breastfeeding Work Group was formed, which set guidelines for where pregnancy should be included. Proposed modifications to precautions and contraindications were to move pregnancy into the precautions section, make no change to the wording for acute illness, update the preventing syncope section, and update the hypersensitivity and allergy to vaccine components with bivalent HPV vaccine information.

It was discussed in the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting that an imbalance in spontaneous abortions was observed in the Phase III trial in 15- to 25-year old females who became pregnant at approximately the time of vaccination at 13.4% (50/374) versus 8.3% (28/319) [LMP -30 days to +45 days from day of vaccination. Presented at VRBPAC meeting, Sept 9,2009 www.fda.gov/AdvisoryCommittees/CommitteesMeetingsMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm181365.htm].

The rates in the vaccine and the control group were within the expected background rate (9% to 21%). It is very difficult to determine a reliable rate for spontaneous abortions. In pregnancies that occurred around the time of vaccination, there was no difference in the mean time to spontaneous abortion and there were no other reasons to suspect a causative effect. The vaccine is classified as Category B based on animal studies in rats showing no evidence of impaired fertility or harm to the fetus, as is the quadrivalent vaccine. Pregnancy is not a contraindication or precaution in the label, but it is mentioned in the Patient Counseling and Information section, which states that the vaccine should not be given to women who are pregnant or planning to become pregnant.

The Work Group proposed to maintain the same basic statement for the quadrivalent and the bivalent vaccine, including it within the precaution section and adding statements regarding pregnancy testing and registries. The current statement reads as follows, with proposed additions underlined:

“HPV vaccines are not recommended for use in pregnant women. The vaccines have not been causally associated with adverse outcomes of pregnancy or adverse events in the developing fetus. However, data on vaccination during pregnancy are limited. Until additional information is available, initiation of the vaccine series should be delayed until after completion of the pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed. Pregnancy testing is not needed before vaccination.

Two vaccine in pregnancy registries have been established. Patients and health-care providers should report:

Any exposure to quadrivalent HPV vaccine during pregnancy to telephone: 800-986-8999

Any exposure to bivalent HPV vaccine during pregnancy to telephone: 888-452-9622”

For preventing syncope after vaccination the same basic statement will be included. This statement will be updated with recent information from the Vaccine Adverse Event Reporting

System (VAERS), given that outdated information is currently included. The Work Group proposed to update the last sentence indicating that vaccine providers should consider observing patients for 15 minutes after they receive vaccine with a stronger statement consistent with the current statement in the general recommendations. The current wording reads as follows:

“Syncope (i.e., vasovagal or vasodepressor reaction) can occur after vaccination, most commonly among adolescents and young adults. Among reports to VAERS for any vaccine that were coded as syncope during 1990–2004, a total of 35% of these episodes were reported among persons aged 10–18 years. Through January 2007, the second most common adverse event reported to VAERS following receipt of HPV vaccine was syncope. Vaccine providers should consider observing patients for 15 minutes after they receive HPV vaccine.”

“Syncope (i.e., vasovagal or vasodepressor reaction) can occur after vaccination, most commonly among adolescents and young adults. Among reports to VAERS for any vaccine that were coded as syncope during 1990–2004, a total of 35% of these episodes were reported among persons aged 10–18 years. Through January 2007, the second most common adverse event reported to VAERS following receipt of HPV vaccine was syncope. Vaccine providers should consider observing patients for 15 minutes after they receive HPV vaccine.”

The proposed revision to the syncope section reads as follows:

To avoid serious injury related to a syncopal episode, vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. Adolescents and adults should be seated during vaccination and the observation period to decrease the risk of injury should they have a syncopal episode.”

For hypersensitivity or allergy to vaccine components, the wording for the quadrivalent vaccine will remain the same and a paragraph will be added for the bivalent vaccine. The statement would read as follows, with the addition underlined:

“Quadrivalent HPV vaccine is a recombinant vaccine produced in *Saccharomyces cerevisiae* (baker’s yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast or to any vaccine component. Data from passive surveillance in Vaccine Adverse Event Reporting System (VAERS) indicates that recombinant yeast derived vaccines pose a minimal risk for anaphylactic reactions in persons with a history of allergic reactions to *Saccharomyces cerevisiae*.

“The bivalent HPV vaccine is contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. The prefilled bivalent vaccine should not be used in persons with an anaphylactic latex allergy because syringes have latex in the rubber stopper. Bivalent HPV vaccine single dose vials contain no latex.”

Discussion

Dr. Baker clarified that the wording about pregnancy was consistent with the guidelines in terms of moving this section into a separate section and the specific wording.

Dr. Marcy stressed that the phrase “should strongly consider” is a prelude to thought, not a prelude to action. Therefore, he proposed changing this phrase to “vaccine providers should observe patients for 15 minutes.”

Dr. Judson added that while syncope could occur up to 15 minutes or even longer following vaccination, the vast majority would be immediate. In order to prevent damage from falls, children should be immunized lying down. Sitting up would be the next best choice, while standing without any support would be the least desirable option.

Regarding hypersensitivity to vaccine components, Dr. Meissner expressed concern that providers may be somewhat confused given that the first sentence seems to say that the vaccine is contraindicated for anyone with an allergy to baker’s yeast, but the next sentence reports on VAERS and says that this is a very rare event.

Dr. Markowitz replied that the wording was borrowed from the general recommendations. The first sentence was intended to distinguish immediate hypersensitivity, while the second sentence pertained to people who have an allergy. There is a minimal risk for an anaphylactic reaction in someone who has an allergic reaction to yeast.

Dr. Baker clarified that the proposed change was underlined, while the remainder of the recommendation would remain unchanged. Given that this was consistent with the general recommendations, which was voted upon and approved, she did not believe they should rewrite history.

Regarding the latex statement and having done something similar with rotavirus vaccine, Dr. Chilton wondered whether the statements were consistent throughout the recommendations about latex and the chance of reactions, both in people who have demonstrated anaphylaxis to latex and in those who are at high risk (e.g., spina bifida).

Dr. Baker responded that to her knowledge, they had been consistent.

With respect to the general recommendations regarding avoiding injury related to a syncope episode, Dr. Kroger indicated that the recommendation states, “should consider observing patients for 15 minutes after they are vaccinated.” Allergy refers to anaphylactic allergy, which is typically thought of regardless of what component is being considered. There is not a specific reference to a particular type of yeast with respect to HPV in the general recommendations.

Dr. Temte inquired as to whether there was any evidence of allergies to cabbage looper, the component used for producing the vaccine. This is a similar question to the beer yeast in the Merck product.

Dr. Dubin (GSK) responded that there is no evidence of allergies in the clinical program to any of the components of the vector system used.

Dr. Markowitz indicated that the statement regarding latex allergy was exactly the same as in the rotavirus statement.

Dr. Chilton thought in the rotavirus statement ACIP stated a preference for the non-latex containing vaccine on the basis that infants would not yet have demonstrated anaphylaxis to latex. Therefore, those patients with bladder extropy and spina bifida would be possibly subject to anaphylaxis with the first dose.

Dr. Marcy suggested checking the statement regarding *Saccharomyces cerevisiae* to ensure that it was consistent with hepatitis B.

Dr. Markowitz replied that this would be checked. She believed this was taken from the hepatitis B statement.

Dr. Baker pointed out that all of the comments pertaining to details and similarities could be reviewed without delaying a vote on these issues.

Dr. Keitel suggested rephrasing the statement to read, “poses a minimal risk for anaphylaxis in persons with no history of immediate hypersensitivity.”

Dr. Markowitz pointed out that the change in the syncope statement regarding “should consider” was used in order not to conflict with the general recommendations.

Dr. Neuzil replied that she thought the committee believed that Dr. Marcy’s suggestion that “vaccine providers should observe patients for 15 minutes” was better than the general recommendations.

Regarding the general recommendations, it was not clear to Dr. Cieslak that what ACIP voted on for HPV in terms of a concern about syncope should be reflected in considerations for every other vaccine. HPV may be an exception.

Dr. Sumaya pointed out that the general recommendations would be reviewed later in the day, at which time several new revisions to existing voted on activities would be brought forth. He suggested that at that time they reconsider the terminology “strongly considered” to make it more action-oriented.

Motion: Pregnancy and Preventing Syncope

Dr. Neuzil made a motion to accept the language as written regarding pregnancy and preventing syncope, with the minor revisions suggested throughout the discussion, including Dr. Marcy’s recommendation to change the syncope statement to read, “vaccine providers should observe patients for 15 minutes.” Dr. Marcy seconded the motion. The motion carried with 14 affirmative votes, 0 abstentions, and 0 negative votes.

Post-Licensure Safety Monitoring

Frank DeStefano, MD, MPH
Director, Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention

Dr. DeStefano indicated that a significant amount of information is taken into consideration in the development of post-marketing surveillance plans, including review of pre-licensure data that are available internationally; review of identified or uncertain risks from Phase III trials; review of any available post-marketing data; development of a VAERS monitoring plan; development of a VSD plan to include key outcomes for Rapid Cycle Analysis (RCA) and other planned studies; identification / creation of key case definitions; identification of candidate CISA protocols; and identification of the need for special studies.

VAERS is a national, passive surveillance system for reporting adverse events. This system is co-managed by CDC and the FDA and accepts reports from physicians, other healthcare providers, and the public. The advantages of the VAERS system are that it is voluntary, it is easy to report an adverse event, and it has nationwide reach. Although subject to incomplete reporting given that the system is national, it tends to receive reports in a timely fashion and is usually the first system that alerts CDC and the FDA to potential problems. Its primary use is for signal detection of previously unrecognized and / or rare reactions related to a particular vaccine. This system is also used for monitoring known reactions, identifying pre-existing risk factors that may promote reactions, and vaccine lot surveillance.

Specifically for monitoring reports after receipt of CERVARIX®, aggregate summaries of VAERS reports will be reviewed periodically for reporting patterns and potential signal identification. These safety profiles will be compared with the profiles of other vaccines that are used in similar aged populations. Reports of serious adverse events, including deaths and other medically important conditions, will be reviewed in detail by medical officers in collaboration with the FDA. VAERS defines “serious adverse events” as those events involving death, hospitalization, life-threatening illness, persistent or significant disability / incapacity, or certain other medically important conditions

The Vaccine Safety Datalink project is the primary system utilized to obtain population-based data on rates of adverse events including comparison groups, so that relative risks can be determined. This is a collaboration that CDC has with eight participating managed care organizations (MCOs). The current population is 9.2 million members, with an annual birth cohort of over 90,000. The advantages of the VSD system for vaccine safety research is that it is comprised of a large, well-defined population; it has computerized, linkable administrative data files; and it is a powerful tool for controlled population-based studies. CDC has been able to implement this system in the last few years for several newly administered vaccines. Analysis can be conducted beginning shortly after a vaccine is licensed and begins to be used in these eight MCOs. This provides a mechanism to identify potential problems, and to follow-up on signal safety in VAERS or other sources, in a fairly timely manner.

VSD post-marketing safety surveillance activities for CERVARIX® specifically will include RCA as an alternative to traditional post-licensure vaccine safety study methods, which generally take years to complete. Analysis of pregnancy outcomes following vaccination will also be monitored. Pregnancy is not a condition that lends itself to weekly analyses. It would not be known that a woman was pregnant until she initiated prenatal care or after she delivered or there was some other pregnancy-related outcome.

One of the primary considerations for the VSD rapid cycle analyses is to specify, in advance, some conditions that are of interest or potential concern. These will be identified from the Phase III and IV studies conducted by the manufacturer, the literature, and VAERS. Final outcomes are under consideration and may include GBS, VTE and stroke, and syncope.

The VSD RCA allows for real time monitoring of new vaccines, which typically includes weekly data regarding vaccinations and outcomes for the previous two weeks. The study design will be women who received the CERVARIX® vaccine and the exposure window will vary depending upon the outcome and what is biologically plausible for that outcome. If there is any indication of an association, automated outcomes data will be substantiated with chart validation. A variety of comparison groups could be use for analyses (e.g., historical background rates, females who have received Gardasil®, and concurrent preventative care or other vaccination visits). Sequential statistical testing will be employed.

The objective for monitoring pregnancy outcomes following CERVARIX® vaccination is to conduct an analysis to evaluate the risk of adverse pregnancy outcomes after inadvertent vaccination of pregnant women. The outcomes of interest include spontaneous abortion, elective termination, still births, and live births for congenital anomalies.

VFC Resolution Update: Human Papillomavirus Bivalent

Lance E Rodewald, MD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

With respect to choice, Dr. Rodewald indicated that in the Vaccines for Children (VFC) Program, accountability is by doses not dollars. Thus, a state is able to acquire the same number of doses of a more expensive vaccine than a less expensive vaccine. However, the problem arises with respect to the discretionary side where accountability is by dollars. States will have limited 317 dollars and limited state dollars, so they may be able to stretch their doses further by selecting a less expensive vaccine on the discretionary side. The VFC program promotes and supports, but does not mandate, choice in the states. Many states have advisory committees, which permits stakeholders to offer input on selection of vaccines. An attempt is made to remove logistical barriers to choice. For example by utilizing centralized distribution, the states no longer have to stock all products. All products can instead be stocked in the VFC line.

ACIP is the sole authority for adding or removing vaccines from the VFC program. The language in this VFC resolution must match the language just approved and voted upon. For example, 10 years ago, the eligible age range would have been 10 through 18 years of age, but will now be 9 through 18 years of age. The recommended schedule for bivalent HPV vaccine is 0, 1, and 6 months. Other components of the resolution will include the following:

- ❑ Minimum age and dosage intervals for bivalent HPV vaccine
 - Minimum age: 9 years old
 - Dose 1 to 2:
 - Dose 2 to 3:

- ❑ Catch-up vaccination: no change
 - Vaccination is recommended for females 13 through 18 years of age who have not been previously vaccinated or who have not completed the full series.

- ❑ Other vaccination:
 - Eligible females as young as 9 years of age can be vaccinated.

- ❑ Interrupted vaccination schedule: no change
 - If the bivalent HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be given as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks. If only the third dose is delayed, it should be administered as soon as possible.

- ❑ Recommended dosage for bivalent HPV vaccine
 - Recommended dosage can be found in the package insert, available at
 - <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186957.htm>

- ❑ Precautions and contraindications
 - Precautions and contraindications can be found in the package insert, available at:
 - <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186957.htm>

The resolution will also likely be harmonized into one statement that will cover both vaccines.

The following statement regarding updates based on published documents will also be included:

“If an ACIP recommendation or notice regarding bivalent HPV vaccine 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.”

Motion: VFC Resolution for HPV Bivalent Vaccine in Females

Dr. Temte made a motion to accept the language as written regarding the VFC resolution for HPV bivalent vaccine in females. Dr. Keitel seconded the motion. The motion carried with 14 affirmative votes, 0 abstentions, and 0 negative votes.

Considerations for Quadrivalent HPV Vaccine in Males Background Information

Eileen Dunne MD, MPH

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)

Dr. Dunne presented ACIP considerations for quadrivalent HPV vaccine in males, offering a summary of the background information reviewed over the last year by the ACIP HPV Work Group. The ACIP HPV Work Group considerations for HPV vaccine in males was a process that began in preparation for FDA's possible licensure of the quadrivalent HPV vaccine in males. For this overview, Dr. Dunne reviewed the epidemiology of HPV; the burden of HPV associated diseases and cancers among men; the efficacy, safety, and immunogenicity of the HPV vaccine in males; and programmatic issues relevant to vaccine use for males.

As a reminder, much of these data were previously presented to the ACIP. In June 2006, ACIP recommended routine vaccination of girls 11 and 12 years of age with the quadrivalent HPV vaccine, and catch-up vaccination of 13 through 26 year old females. These recommendations emphasized immunizing girls at 11 and 12 years of age, as many in this age group had not yet had sex and were likely to have the full benefit of the vaccine. On October 16, 2009, FDA approved the quadrivalent HPV vaccine for boys and men 9 through 26 years of age for prevention of genital warts caused by HPV types 6 and 11.

With regard to the epidemiology and burden of diseases and cancers in men, HPV infection is commonly acquired through sexual contact. Available studies show that men have similar prevalence of HPV infection, and possibly higher acquisition of HPV, compared to women. The burden of diseases and cancers in men include genital warts; recurrent respiratory papillomatosis; and anal, penile, and some oral cavity and oropharyngeal cancers. Available data on HPV transmission suggests high transmission rates between sex partners. Based on cumulative incidence of HPV infection among males participating in a longitudinal study in Seattle, Washington, there is rapid acquisition of HPV infection similar to what is observed for females. By two years from enrollment, over 60% of the young men had acquired HPV infection [Partridge, et al. 2007 JID].

Sexual contact is the primary means by which HPV infection is acquired, so it is useful to describe the sexual behavior of adolescents from the National Survey of Family Growth (NSFG), a survey in which adolescents report vaginal sex. Based on this survey, for both females and males, there is an increasing prevalence by age of ever having vaginal sex. At age 18, a time when many teens are entering college, approximately 70% of females have had vaginal sex. About 25% of young men 15 years of age and about 70% of young men by age 19 years will have had vaginal sex [Mosher et al. 2005; Vital and Health Statistics: No. 362].

The burden of diseases attributed to HPV 6 and 11 in men includes over 90% of genital warts and most cases of recurrent respiratory papillomatosis. The burden attributable to HPV 16 and 18 is approximately 30% to 90% for anal, penile, and some oropharyngeal and oral cavity cancers. In terms of the burden of HPV-related cancers in women and men, there are 17,350 cancers in females and about 7,500 cancers in males that are possibly attributed to HPV [Watson M et al. *Cancer* 2008. Data source: National Program of Cancer Registries and SEER, covering 83% coverage of US population. Watson M et al. *Cancer* 2008. Data source: National Program of Cancer Registries and SEER, covering 83% coverage of US population]. Cancers related to HPV 16 and 18 specifically in men are a subset of these HPV related cancers. They are likely on the order of approximately 4,600 cancers every year [Gillison ML, et

al. Cancer 2008 National Program of Cancer Registries and SEER, covering 83% coverage of US population].

Data were previously provided to ACIP to offer an overview of genital warts. There are an estimated 500,000 new cases of genital warts each year. This disease can result in considerable costs, estimated at over \$200 million every year. Although genital warts are usually benign, there are frequent recurrences and sometimes expensive treatments that can result in adverse effects. Genital warts can also result in significant reductions in quality of life [Chesson H, et al. *Perspect Reprod Health* 2004, Insigna R, et al. *Pharmacoec* 2005, Chesson H, et al. *ISSTD* 2007, Woodhall, et al. *Sex Transm Infect* 2008, Hoy T et al. *Current Med Research Opin* 2009, Chesson H, et al. *Perspect Reprod Health* 2004, Insigna R, et al. *Pharmacoec* 2005, Chesson H, et al. *ISSTD* 2007, Woodhall, et al. *Sex Transm Infect* 2008, Hoy T et al. *Current Med Research Opin* 2009].

National Claims Data demonstrate that the peak prevalence of genital warts occurs in young men 25 to 29 years of age, while the peak in the genital warts diagnoses for women is in the early 20s. Specific populations, such as men who have sex with men (MSM), have a greater burden of HPV-related conditions including genital warts, anal pre-cancers, and anal cancers [Insinga RP, et al. *CID* 2003]. The estimates for anal cancers are 17-fold higher for HIV-negative MSM at 35 per 100,000 in HIV-MSM. Currently, there are no national recommendations for anal cancer screening as there are for cervical cancer screening. It is important to note that immunization of females would likely have minimal impact on these diseases and cancers in MSM. It is anticipated that there would be high acceptability of vaccine in these men [Hong PV, et al. *Clin Infect Dis* 2002. Johnson LG, et al. *Cancer* 2004, Simatherai, et al. *Sex Transm Inf* 2009].

The efficacy trial in males is referred to as Protocol 20, which was a randomized, double-blind, placebo-controlled trial that was conducted in 18 countries on multiple continents. Vaccine or placebo was administered on day 1, month 2, and month 6. Subjects included 3,463 heterosexual men (HM) 16 to 23 years of age and 602 MSM 16 to 26 years of age. The exclusion criteria included: history of genital warts, genital lesions possibly HPV-related, and greater than 5 or less than 1 lifetime sex partner. The objectives of Protocol 20 were to measure the efficacy, immunogenicity, and safety of the quadrivalent HPV vaccine in males. The primary study was of HM and MSM with the objective of measuring the efficacy for the outcome of HPV 6/11/16/18-related external genital lesions and other external lesions including penile, perianal, and perineal intraepithelial lesions. A sub-study was conducted in MSM on anal intraepithelial neoplasia (AIN). This study had not yet met the required number of endpoints for analysis at the time of submission to FDA. These data will be available in early 2010.

Dr. Dunne summarized only the data on efficacy for prevention of external genital warts at this time, given that there were too few outcomes of the other external genital lesions to include as an outcome. In addition, she provided efficacy data on prevention of persistent infection, immunogenicity, and safety.

The baseline information on HPV DNA and HPV seropositivity provided a measure of exposure to HPV at the beginning of the study. Of the subjects in this study, 12.2% of the men were PCR DNA positive to HPV 6/11/16/18 and 7.6% were seropositive. The baseline DNA positivity and seropositivity were higher for MSM when compared to the HM [BLA, Haupt R, June 2009 ACIP]. Based on the main efficacy data from the per protocol in the full analysis set, the efficacy was high for prevention for HPV 6/11-related genital warts. The per protocol assessment was an evaluation of men who were HPV DNA and seronegative at baseline to the type considered in the evaluation and also had the full vaccine series and no protocol deviations. Case counting began at month 7. The efficacy was 89% for the per protocol assessment for prevention of HPV 6/11-related genital warts. The full analysis set, which is similar to an intent to treat (ITT) analysis, included all men with at least one vaccine dose and case counting started at day 1. The efficacy for the full analysis set was 67%.

In terms of the efficacy against persistent infection by HPV type in Protocol 20, there was also high efficacy against persistent HPV 6/11/16/18 infection in this per protocol assessment [Presentation for VRBPAC Meeting, Sept 9, 2009]. The assessment of antibody titers at month 7 by age group of males receiving quadrivalent HPV vaccine found that geometric mean titers (GMTs) of the 9- to 15-year olds were non-inferior to those of the 16- to 26-year olds, and that the GMTs were over two-fold higher for the younger males ages 9 to 15 years. A higher proportion of subjects had injection site adverse experiences in the HPV vaccine group compared to placebo. Most were mild or moderate in intensity, and the most common reported experiences were pain, swelling, and erythema. The proportion who reported a systemic adverse experience was similar between the two vaccination groups. Most were judged to be mild or moderate in intensity. The most common systemic adverse experiences were headache (12.3% in vaccine and 11.2 in placebo) and pyrexia (8.2% in vaccine and 6.5% in placebo).

In summary, the vaccine trials demonstrate high efficacy for prevention of HPV 6/11-related genital warts in males 16 to 26 years of age. Safety evaluations of over 3,000 males receiving vaccine from different clinical trials demonstrated that the most common adverse events were injection site reactions. Immunogenicity post-vaccination was high, and was greater than two times higher in males 9 to 15 years of age compared to males 16 to 26 years of age.

There are a number of programmatic issues relevant to HPV vaccine in males, including acceptability of the vaccine, vaccine supply, cost, and programmatic challenges to immunizing adolescents. There is high vaccine acceptability reported in a variety of studies among providers, parents, and males. There is a sufficient supply of vaccine for males 11 and 12 years of age in the US. The vaccine cost per dose is \$106 for the public and \$130 for the private sector, which includes price and excise tax only. Important challenges to immunizing adolescents with the HPV vaccine series must be considered, including low use of preventive visits, barriers to completion of the vaccine series, and missed opportunities by providers to vaccinate [<http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm>].

The results of a recent National Immunization Survey (NIS) Teen Survey generally highlight the challenges of immunizing adolescent females with the HPV vaccine. Overall, in 2008, 37.2% of 13 to 17 year old girls had initiated the vaccine series and 17.9% had completed the series and received all three doses. The vaccine coverage by age did not appear significantly different, which overall in the 2007 survey was 25.1% of 13 to 17 year old girls who had initiated the vaccine series [MMWR Sept 18, 2009;58(36):997-1001].

Given that there are questions pertaining to whether males would also access an adolescent vaccine, coverage was evaluated for another adolescent vaccine (MCV4) for females and males. Data from the 2008 NIS Teen Survey show no overall differences in vaccine uptake by sex, but it is important to note that there are differences between the HPV vaccine and meningococcal vaccine, making it unclear whether vaccine coverage for this vaccine is the best indicator what might occur for male HPV vaccination [MMWR Sept 18, 2009;58(36);997-1001].

In summary of the cost-effectiveness data, there is a high burden of genital warts and HPV-related cancers in men. This burden is greater in females than males. Quadrivalent HPV vaccine has high efficacy for prevention of genital warts in males, and HPV acquisition is high in males. The vaccine would be most effective if administered prior to sexual debut.

Overview of Cost-Effectiveness of Male HPV Vaccination

Harrell Chesson, PhD

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)/CDC

Dr. Chesson reminded everyone that, as reviewed earlier in the morning, vaccination of 12-year old girls is cost-effective by the usual standards (< \$0 to \$50,000 per quality-adjusted life year (QALY)). This result was consistent across a wide range of models. There is more uncertainty and less precision regarding the cost-effectiveness of vaccinating females over 12 years of age and vaccination of males.

There are four published and two unpublished studies of the cost-effectiveness of adding male HPV vaccination to a female-only vaccination program. The first published study was by Taira and colleagues, who included the outcomes of cervical intraepithelial neoplasia (CIN) and cervical cancer in their study and assumed a total vaccine cost per series of \$300 + \$100 for a booster. In their base case assumptions of 70% coverage, male vaccination costs \$442,000 per QALY gained. However, at lower coverage, the cost per QALY was \$41,000 [Taira et al., 2004].

In the second study, Elbasha and colleagues found that when beginning with a vaccination program for 12-year old girls, adding catch-up vaccination of females was more cost-effective than adding vaccination of 12-year old boys. They calculated the cost-effectiveness of adding vaccination of 12-year old boys to a female only vaccination program for ages 12 to 24 years. Under this scenario, when including the outcomes of CIN, cervical cancer, and genital warts for males and females and using and assumed total vaccine cost per series of \$360, the cost per QALY of male vaccination ranged from \$24,000 at 50% coverage up to \$128,000 per QALY at 90% coverage. The reason for this is that as coverage of females increases, the burden of HPV is reduced not only in females, but also in males. This leaves little room for improvement that could be gained by male vaccination [Elbasha et al. (Merck), 2007].

The third published, by Jit and colleagues, examined vaccination in the UK. These investigators included CIN, cervical cancer, and genital warts for males and female—the same outcomes that were included in the published Merck study. They assumed a total vaccine cost per series of about \$440. They found that vaccination of males would cost about \$1,000,000 per QALY at 80% coverage [Jit et al. (UK), 2008].

A recently published study by Kim and Goldie (2009), the preliminary results of which Dr. Kim presented during the June 2009 ACIP meeting, included the most comprehensive set of potential health outcomes of any of the studies of male vaccination published to date (e.g., CIN, cervical and other cancers, genital warts, and JORRP). They assumed a total vaccine cost per series of \$500. Under the most optimistic scenarios they presented, in terms of vaccine efficacy in males, the cost per QALY gained was \$62,000 at 50% coverage and \$91,000 at 75% coverage.

The primary themes of these four studies are that within a given study, as coverage increases, the cost per QALY of male vaccination increases as well. Also, there is a difference across studies, even when the same coverage is assumed. While the published studies show that male vaccination has less impact and is less cost-effective as vaccine coverage of females increases, there is considerable uncertainty in these estimates because of the uncertain factors that go into these analyses. As such, there is a wide range of cost-effectiveness ratios across models and also within models as key assumptions are varied.

With regard to the two unpublished studies, the Merck model assumes a lower vaccine cost per series of \$400 versus \$500 in the Chesson model. Both of the models included cervical cancer, CIN, genital warts, non-cervical cancers, and RRP. Both models used a 100 year time horizon of analysis and indirect effects were included. The Merck model used a much more complex dynamic transmission model. There is no evidence to date of vaccine efficacy against RRP or all non-cervical cancers included in the analyses (e.g., penile cancer, oropharyngeal cancer). Both models included juvenile-onset RRP (JORRP), while the Merck model also included adult-onset RRP. Cervical cancer screening was incorporated directly into the Merck model, and the annual probability of receiving screening varied by age. In Chesson et al's simpler model, the cervical cancer screening was not modeled directly, but was assumed to be reflected in the observed rates of cervical cancer used in the model. Both models included the impact of CIN on quality of life, which the published study by Kim and Goldie did not include. The quality of life impact of all of the HPV-related health outcomes varied across the models.

For example, in the Merck model there was a greater loss of utility associated with genital warts for a greater duration of time than in the Chesson et al model. The Merck modelers assessed the cost-effectiveness of adding vaccination of 9 to 26 year old males to the current vaccination program for females 9 to 26. The Chesson et al model assessed the addition of vaccination of 12-year old males to females aged 12 to 26.

The Merck model projections of the long-term impact of HPV vaccination on cervical cancer in women and anal cancer in men were presented. Male vaccination had a relatively greater incremental impact on anal cancer in men than on cervical cancer in females. However, it is worth noting that the majority of the reduction in anal cancer in men that can be achieved by vaccinating both sexes could be achieved by vaccinating females only, with sufficient coverage. [Erik Dashbach, unpublished Merck model result].

This table shows the estimated cost per QALY of male vaccination based on which HPV diseases are included in the analysis. When including only cervical outcomes, the cost per QALY gained by male vaccination was over \$200,000. However, as more and more outcomes are included in the analysis, the cost per QALY decreases. When including all potential outcomes, the cost per QALY was about \$25,000 as shown on the bottom row. The top three outcomes are those for which there is evidence of vaccine efficacy. If the focus is placed only on these indicated outcomes, the cost per QALY of male vaccination is about \$72,000:

Merck model: Estimated cost per QALY gained based on HPV diseases included

HPV diseases included	Female-only vaccination (ages 9-26 years)	Adding male vaccination (ages 9-26 years)
Cervical	\$16,800	\$218,600
+ vulvar and vaginal	\$15,400	\$200,300
+ genital warts	\$7,400	\$72,800
↑ Indicated outcomes ↑		
+ anal	\$5,900	\$53,100
+ oral cavity & oropharyngeal	\$4,000	\$29,600
+ penile	\$3,900	\$27,500
+ RRP	\$2,100	\$25,200

Chesson et al examined the estimated cost per QALY of male vaccination under three female coverage scenarios: 30%, 45%, and 70%. They found that the cost per QALY increases as female coverage increases: \$37,700 at 30% coverage; \$47,500 at 45% coverage; and \$93,700 at 70% coverage, when including all health outcomes (e.g., CIN, cervical and other cancers, genital warts, RRP). The following chart reflects the estimated cost per QALY gained by male vaccination based on the HPV diseases included. It is important to note that when including only cervical outcomes, the cost per QALY of male vaccination was above \$100,000. When including all outcomes, the cost per QALY of male vaccination was \$47,500:

Estimated cost per QALY gained by male vaccination based on HPV diseases included

Chesson et al. model, scenario of 45% female coverage by age 18 years*

	Female-only vaccination (ages 12-26 years)	Adding male vaccination (ages 12 years)
Cervical outcomes only	\$19,700	\$105,700
+ genital warts	\$16,100	\$80,100
+ other cancers	\$11,500	\$48,400
+ JORRP	\$10,500	\$47,500

*In this scenario, coverage of 12-year-old males and females is 30%. With catch-up vaccination, coverage of females reaches about 45% before age 18 years and 53% at age 26 years.

JORRP: juvenile-onset recurrent respiratory papillomatosis. QALY: quality-adjusted life year. Cost per QALY estimates show the incremental cost per QALY of adding vaccination of 12-year-old males to a female-only vaccination program for ages 12-26 years. Results preliminary, not for citation.

The following table summarizes the published and unpublished studies. The studies are grouped by row according to the outcomes that were included in the study. The Taira study examined only the cervical outcomes; whereas, the Jit and published Merck studies examined cervical outcomes and genital warts. The studies on the bottom three rows include a wider range of health outcomes. Within each study, as coverage increases, the cost-effectiveness of male vaccination decreases. For a given coverage assumption, the cost-effectiveness estimates can vary substantially across studies, particularly in the high coverage scenarios:

**Incremental cost per QALY of male vaccination
Summary of published and unpublished* results**

Outcomes included	Study	Coverage (male & female): 20% - 40%	Coverage (male & female): ≈ 50%	Coverage (male & female): 70% - 90%
Cervical outcomes	Taira, 2004	\$41,000	-	\$442,000 (70%)
Cervical outcomes, genital warts	Jit (UK), 2008	-	-	≈ \$1,000,000 (80%)
	Elbasha (Merck), 2007	-	\$24,000	\$42,000 (70%) \$128,000 (90%)
Cervical outcomes, genital warts, non-cervical cancers, JORRP	Kim 2009**	-	\$62,000	\$91,000 (75%)
	Merck'	\$25,000	-	\$38,000 (70%)
	Chesson'	\$37,700	\$47,500	\$93,700 (70%)

QALY: quality-adjusted life year. *Indicates preliminary, unpublished estimates (not for citation). **Kim (2009) estimates are from the most optimistic scenarios reported; the cost per QALY of male vaccination is higher in many other scenarios presented in that study (such as with lower efficacy in males). Cost per QALY estimates show the incremental cost per QALY of adding male vaccination to female-only vaccination. UK results were converted to US dollars. Merck model also includes adult-onset JORRP. Coverage headings apply to approximate female coverage (not male and female coverage) by age 18 years in the Chesson model results; coverage of 12-year-old males in the three scenarios was 20%, 30%, and 50%, respectively. Results not updated for inflation.

To summarize, the cost-effectiveness of male vaccination is subject to considerable uncertainty. There are differences in the cost per QALY estimates within one model when key assumptions are changed, such as coverage, and across different models due to differences in the model structure and / or assumptions in the models. The cost effectiveness of male vaccination depends critically upon the vaccine coverage of females. The most favorable scenario for male vaccination is when coverage of females is low. As coverage of females increases, cost per QALY gained by male vaccination increases. The cost effectiveness of male vaccination depends on what health outcomes are included in the analyses. As more potential health benefits of vaccination are included, the cost-effectiveness of vaccination becomes more favorable. In most scenarios examined by the models, adding male vaccination to female-only vaccination is not the most cost-effective use of public health resources. Improving vaccination coverage of females is likely to be a more effective and cost-effective strategy to reduce the overall burden of HPV associated conditions.

Discussion

Dr. Neuzil pointed out that coverage in adolescent girls should really affect how ACIP judged the decision pertaining to HPV vaccines in males. Current coverage in adolescent girls is approximately 40% for one dose and perhaps half that or somewhat less for 3 doses. She wondered whether there were any data to suggest whether female coverage was expected to increase.

Dr. Dunne responded that this information was not available. She thought that while there seemed to be sentiment by many members that absent policies to encourage coverage, it would likely remain low.

Dr. Neuzil stressed that it was known that increases in new vaccination programs tended to take time to reflect increases, but she wondered whether this could be put into perspective in terms of other adolescent vaccination programs and how they were accepted and changed over time.

Dr. Rodewald responded that the goal for vaccines with universal recommendations for adolescents is 90% coverage. Tdap is currently at about 72%, which is not satisfactory. Reaching adolescents is challenging. It is true that new vaccine uptake generally takes approximately 8 to 10 years to increase from 0% to 90%. His sense was that because HPV

vaccine experienced a 12% jump in first dose coverage between 2007 and 2008, they were on track to make great progress. Whether uptake would reach 90% remained difficult to predict; however, it was likely to reach the 70%.

Dr. Baker pointed out that another difference was that Tdap and meningococcal vaccines require a single dose; whereas, HPV requires three doses for protection.

In view of the fact that after three years of fairly aggressive campaigning, Dr. Meissner pointed out that fewer than 20% of females have completed the three-dose series for a very serious illness, cervical cancer. With that in mind, he wondered why males would be more likely or even as likely to acquire all three doses of this vaccine. Moreover, there is not quite the degree of disease burden in males.

Dr. Dunne responded that it was unclear what could be expected. She was referring to some studies conducted with males that generally showed high acceptability.

Dr. Judson suggested that one experience with a three-dose adolescent vaccine would be hepatitis B. Even with a universal recommendation for adolescents and mandatory school immunization laws, within a couple of years the targeted age groups are at approximately 80% to 90% uptake, even in inner city school districts like Denver.

Dr. Temte wondered what results were anticipated as increasing numbers of adolescent girls received more bivalent vaccine. His assumption was that the quadrivalent in boys would become more cost-effective.

Dr. Chesson responded that there certainly is potential for that. However, this particular issue has not been addressed in any of the models he is aware of.

Dr. Lett inquired about the status of evaluating cost-effectiveness in MSM and how that might also fit into these other models.

Dr. Chesson responded that they hope to present these data during the February 2010 ACIP meeting.

Ms. Ehresmann wondered whether they were to assume that they could not use the data regarding the non-licensed indications. There is quite a significant difference in terms of the cost-effectiveness between the licensed and non-licensed indications. If cervical, vulvar, and vaginal cancer and genital warts were included, when males were added it was \$72,800. If all of the other cancers were added, it dropped to \$25,200. It was not clear to her how this should be interpreted.

Dr. Chesson responded that one of the benefits of models is that they help to address the unknown. Therefore, models can show what the outcomes would be if there was efficacy against all of the outcomes or some of them.

Dr. Sumaya wondered whether more states were instituting policies to require HPV in females and if so, whether that was affecting the rates of immunization.

Dr. Englund pointed out that there has been uniform reluctance to make HPV mandatory at state levels. The majority of the Work Group members, in most cases, were not willing to approach the word “mandate.” That is a state prerogative.

Dr. Judson stressed that ACIP does not have the authority to mandate anything. All they can do is recommend.

Referring to the Watson M et al and the Gillison et al data presented by Dr. Dunne, Dr. Marcy noted that male disease is fairly high at 34% of female disease. He thought a large portion of that could be attributed to MSM. Therefore, he wondered whether they should address MSM in terms of recognizing the fairly significant burden of these conditions in men.

Dr. Dunne clarified that it was really not clear for the 4,600 cancers in men how many were attributable to MSM. Nevertheless, it is believed that there is a larger burden in that population.

Dr. Meissner inquired as to whether there were any data regarding transmissibility of HPV among men or women who have been vaccinated.

Dr. Dunne replied that there are limited data on transmission of HPV between men and women. Some models suggest that there is very high transmission. To her knowledge, there is only study from Dr. Hernandez’s group at University of Hawaii which examined men and women dyads. That study found very high transmission between men and women, and higher transmission from men to women than women to men. However, that is one study and it is limited because it has small numbers. She had not seen any data pertaining to the efficacy for prevention of transmission among the vaccinated, but agreed that it was an important consideration.

Dr. Sawyer found it encouraging that the coverage rate in women throughout the teenage years was very similar. He had thought previously that it would drop off in the later teen years—the later years being those during which more men will begin to engage in that activity. He suggested that it would be a potentially viable strategy to consider focusing on that population, recognizing that they might be targeting middle to later adolescents.

COL Cieslak expressed serious concern about some of Dr. Dunne’s data, pointing out that he was stuck by the difference in incidence of oropharyngeal and oral cavity cancer between men and women. It appeared that the incidence was much higher in men than women, which he would not have expected logically. He was worried that if these data were being used for cost-effectiveness of the vaccine, it would play a significant role in slanting the cost-effectiveness data for men. He also requested clarification regarding whether these were cancers believed to be attributable to HPV, or whether these data represented all oropharyngeal cancers that might be due to smoking. If smoking played a major role, he could understand a much higher male incidence, but if it did not and these were believed to be HPV-associated, he would expect similar rates in men and women.

Dr. Dunne responded that these data were assembled by Dr. Saraiya from the Division of Cancer Prevention. They represent a sub-set of specific cancers that are HPV-related. The oropharyngeal and oral cavity cancers include the lingual and palatine tonsil base of tongue and oralpharynx, so it is a subset of all head and neck cancers. These are possibly attributable to HPV, so she emphasized possible HPV based on the anatomic site of the cancer and whether it was squamous.

Dr. Saraiya clarified that the anatomical sites selected for oropharyngeal and oral cavity were where the attributable fraction of HPV tends to be higher than 50%. The outcomes that are HPV 16/18-associated are based on specific studies. The FDA indication for the HPV vaccine is to prevent genital warts, and AIN is being considered. Currently, there are no efficacy outcomes for penile cancer or for oropharyngeal and oral cavity cancers. These are just potential benefits.

Dr. Turner (ACH) inquired as to what gold standard ACIP was using for cost-effectiveness.

Dr. Pickering responded that there is no gold standard. Economists state that there is no defined standard of QALY that should be utilized. He noted that the economist would be presenting in the afternoon about QALYs.

Dr. Wharton added that while there is not a “rule” about this, CDC hoped that the committee would make decisions that represented good investments for public health dollars.

Dr. Baker stressed that they must keep in mind that these other cancers in men were not part of the new label that was approved by the FDA because there were insufficient data. When sufficient data become available, they certainly could then consider this. Under consideration for this discussion was prevention of male genital warts.

Dr. Judson’s understanding was that ACIP should not be considering information about, or making recommendations on, indications that had not been sought by the company yet or approved by the FDA. Regarding whether 100% of these cancers are actually caused by the virus, he thought it was important to realize these viruses are necessary, but not sufficient to explain cancer. There is a reason that perhaps only 1 out of 100 with an HPV 16/18 CIN 2/3 actually goes on to develop invasive cancer. There are clearly co-factors that can drive these equations in very different ways. Smoking in women increases the rate of cervical cancer by 2. Herpes simplex virus was initially thought to be a co-factor. Oropharyngeal cancer is in another realm for which there is far less basic information than needed.

Dr. Haupt (Merck) clarified that the male efficacy study was designed to show efficacy against the most common HPV-related disease, which was 6/11 genital warts. Merck previously demonstrated very high immunogenicity in adolescent boys and wanted to show that there was efficacy against disease. That study was not powered to show efficacy against prostatic intraepithelial neoplasm (PIN). In the end, there were 0 in 3 cases, or 100% efficacy with very small numbers. PIN is a more rare condition that occurs in older men, and would be very difficult to study. An expectation that there would be efficacy against penile cancer is unlikely. The AIN study, for which the results are not yet available, was also not powered to show efficacy against AIN 2/3. Therefore, Merck will not report to ACIP information about disease efficacy with a pre-cancer endpoint in the AIN sub-study. Discussion is underway regarding how Merck could potentially address the efficacy against HPV-related head and neck cancers.

Considerations for HPV Vaccine in Males: ACIP Options

Eileen Dunne MD, MPH

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)

Dr. Dunne presented highlights of the deliberation of the ACIP HPV Work Group on ACIP options for male vaccination. There was widespread participation and active discussions about male vaccination among the members. As previously described, there have been discussions over the last year about male HPV vaccine, as well as discussions about additional data that may be available soon.

There is an important burden of male HPV-related disease and cancers, and there is a greater HPV-related burden in females than males. It is important to note, as Dr. Chesson highlighted, that based on cost-effectiveness models, improving vaccine coverage of females is likely to be a more effective and cost-effective strategy to reduce the overall burden of HPV-associated diseases and cancers. HPV vaccination in males does offer opportunities to reduce the burden in males as well as females, and the vaccine would be the most effective when given to males prior to sexual debut.

The Work Group discussed specific populations, such as men who have sex with men (MSM), who have a significantly higher burden of HPV-related diseases and cancers. However, Work Group members felt a targeted approach to vaccinate this group would be difficult and could be stigmatizing. Many Work Group members thought the targeted approaches, as in other experiences, would also have limited success. The Work Group engaged in discussions about outstanding data that would be informative to discussions of male vaccination of this group.

The ACIP HPV Work Group outlined some next steps, including review of information as it becomes available. This includes outstanding data from efficacy trials on anal intraepithelial neoplasia (AIN) and MSM, cost-effectiveness in MSM, and other data related to vaccines for males and females.

With regard to the HPV vaccine for male options proposed by the Work Group members, most members supported permissive use of the HPV vaccine in males 9 to 26 years of age at this time. Some Work Group members supported routine vaccination of males 11 or 12 years of age.

Regarding the Work Group's rationale for routine vaccination, there was high efficacy for prevention of genital warts in the clinical trials, a stigmatizing and common condition in adolescents. There would likely be high efficacy for prevention of anal and other cancers in males, although there are no data available at this time. Vaccination of males provides the opportunity to reduce the HPV burden in males and females, as well as the resulting diseases and cancers. There was interest by Work Group members supporting this routine vaccination recommendation in equity by a provision of vaccine to both sexes. Current coverage for females is low and cost-effectiveness of male vaccination improved greatly in scenarios of low female coverage. Many Work Group members felt that vaccine coverage in females would remain low in the absence of policies supporting widespread vaccination, such as mandates. Although there are no data to support this; however, some Work Group members thought that adding males to a female vaccination program could have the added benefit of increasing overall immunization rates among females. In addition, the current gender-based immunization

policy is similar to targeted or risk-based approaches, which have limited success. In past experiences, these approaches were not as successful as universal vaccination strategies.

With respect to the majority opinion of the Work Group to support permissive HPV vaccine for males and the rationale for doing so, there are significant programmatic challenges at the state and local levels in terms of constraints due primarily to limited resources. These Work Group members believed that the focus of the HPV vaccine program should be reduction of cancers. It is also clear that most of the burden of diseases and cancers is in females, and cost-effectiveness studies demonstrated additional costs for adding male HPV vaccination to female vaccination, with minimal benefits, except in certain scenarios. There was interest in prioritizing the vaccination coverage of females and improving coverage to reduce the overall burden of HPV-related diseases and cancers. There were also outstanding issues that some Work Group members felt were important to consider, including forthcoming data on the efficacy of a vaccine for prevention of AIN in MSM and cost-effectiveness in MSM. In addition, many Work Group members felt vaccine price would be an important parameter to consider, especially given cost-effectiveness estimates for males.

Because most Work Group members supported the permissive vaccination option, the current draft statement to be voted upon reads as follows:

“Quadrivalent HPV vaccine may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. Quadrivalent HPV vaccine would be most effective when given before exposure to HPV through sexual contact.”

ACIP Recommendations and VFC Resolutions: Considerations for a Permissive Recommendation

Lance E Rodewald, MD
Director, Immunization Services Division
National Center for Immunization and Respiratory Diseases

Dr. Rodewald reported that he had recently presented new information to the Work Group regarding how the VFC program operates under a permissive recommendation, and that during this session he would distinguish ACIP recommendations from VFC resolutions, and describe the function of permissive resolutions.

The purpose of ACIP recommendation is to offer advice and guidance to the federal government (e.g., the Secretary of HHS, the ASH, and the Director of CDC) regarding the most appropriate selection of vaccines and related agents for effective control of vaccine-preventable diseases in the civilian population; and to make evidence-based recommendations to providers and programs regarding how the vaccine should be used. The evidence used includes burden of disease, vaccine efficacy, vaccine safety, and cost-effectiveness. In contrast, the purpose of a VFC resolution is to offer a means for ACIP and CDC to support ACIP's vaccine recommendations by reducing cost as a barrier to financially vulnerable children. Cost to the VFC program should not be the primary consideration, but should be considered in the context of overall public health priorities. The VFC entitlement is to the child.

There are several types of ACIP vaccine recommendations. A routine recommendation is most commonly for a specific age group. For example, "All 11 and 12 year olds should be vaccinated with Meningococcal Conjugate Vaccine (MCV4)." Catch-up recommendations are usually for defined cohorts and periods of time. For example, "All females aged 13 to 18 should be vaccinated if they have not been previously vaccinated with HPV vaccine." There are also risk-based recommendations. For example, "All 19 to 49 year old adults should be vaccinated with influenza vaccine if they have asthma." Permissive recommendations basically signify that if someone would like to prevent a particular disease that is not otherwise recommended, it is permissible to do so.

In terms of how the VFC program operates under an affirmative recommendation, providers are expected to offer vaccine proactively to VFC-eligible children. Immunization programs are expected to promote such recommendations. Uptake is the measure of program and provider performance. In contrast, under a permissive recommendation, providers are not expected to offer vaccine proactively to VFC-eligible children, but they are expected to vaccinate VFC-eligible children on request if they stock the vaccine, and are expected to refer the child elsewhere if they do not stock the vaccine. Providers may offer vaccine proactively to VFC-eligible children. Immunization programs are not expected to promote such recommendations. Uptake is not used to measure of program or provider performance.

The impact of a VFC resolution on coverage for vaccine for children with insurance covering that vaccine is that vaccination generally takes place in the medical home. For children with insurance that does not cover vaccine, there is no coverage without a VFC resolution. With a resolution, these children have coverage in Federally Qualified Health Center (FQHC) / Rural Health Clinic (RHC). Children with Medicaid coverage, uninsured children, and American Indian / Alaska Native children are not covered without a VFC resolution; however, these children are covered in their medical homes with a VFC resolution.

Permissive VFC resolutions cover a vaccine in the VFC program for individuals not affirmatively recommended to be vaccinated, and vary by characteristics of the vaccine recommendation and by intent of the VFC resolution. For example, in 2006, ACIP passed a resolution that was permissive for influenza. The recommendation stated that all children up to 5 years of age should be vaccinated. At that time, the VFC program included coverage for all children through 18 years of age and eligible for the VFC program, regardless of whether they had risk factors. A permissive VFC resolution can be a means to allow equity in access to vaccines. It is not a mandate on children, parents, providers, or programs; it is not a de facto universal recommendation; it is not meant to be promoted by vaccine manufacturers.

Dr. Rodewald concluded that the VFC program is a large program that has saved tens of thousands of children's lives.

Discussion

Dr. Meissner requested further explanation regarding what it meant that a provider could be "proactive."

Dr. Rodewald replied that it basically meant that physicians seeing adolescent could suggest vaccines covered under permissive VFC recommendations. It is not an expectation that every time a physician sees an adolescent he or she is required to suggest such vaccines. A parent may initiate a conversation about vaccines in the VFC program. The entitlement is embodied in

the child. There is an expectation that if a doctor does not stock the vaccine requested and it is covered under a permissive VFC recommendation, the physician must at least refer the child to a place where he or she can receive the vaccine.

Dr. Sumaya inquired as to whether the VFC was operationally an entitlement or if there were specified levels of appropriations for the program.

Dr. Rodewald responded that it is mandatory for the federal government to provide enough funding to the VFC program to purchase the vaccines recommended by ACIP. A key phrase in the VFC statute is that the budget is in advance of appropriations, so it does not go through the appropriations process. The VFC program works directly with the Office of Management and Budget (OMB), which has been highly supportive of this program and has agreed that as long as strong evidence is provided regarding how many children need to be vaccinated, they will provide the appropriate level of funding.

Dr. Baker inquired as to whether every state's VFC providers are required to disperse vaccine supply.

Dr. Rodewald replied that for fully recommended vaccines, states are expected to offer the entitlement as immediately as possible following the recommendation. In general, almost all states implement VFC vaccine recommendations rapidly. There are exceptions. For example, one state waited nearly a year and a half before offering meningococcal conjugate vaccine (MCV).

Dr. Baker wondered about situations in which the recommendation was permissive.

Dr. Rodewald responded that there are existing contracts and providers, so this does not seem to be a barrier. Providers would merely have to indicate that they would like to begin vaccinating with a product for which there is a permissive recommendation.

Dr. Schaffner (NFID) inquired as to what impact a permissive recommendation would have on the private health insurance industry and their likelihood of covering vaccine under such a recommendation.

Dr. Rodewald replied that nobody really knows how to anticipate what private insurance plans will do. There is no mandate for them to cover any vaccines. It could be presumed that coverage would likely be less than for a full recommendation. The pathway through the VFC program is a circuitous one for those who are under insured, and it is not a very effective pathway. Vaccine uptake for permissive recommendation has typically been very low.

An unidentified participant thought there would be a lot of variability with coverage with a permissive recommendation. Certainly, a lot of the major players would fully cover routine vaccination. Coverage of a permissive vaccination may also be highly dependent upon the type of clients purchasing the plan.

Dr. Turner (ACHA) indicated that he had been involved in student health insurance plans for many years, and has always found that these plans are highly reluctant to cover any recommendation other than routine. He has also been involved in healthcare reform nationally and the Young Invincible Plan. Through this plan, it is hoped that 20 to 30 million young people under the age of 25 will be covered for ACIP-recommended vaccines and that this will not count

toward a deductible. Although this is years away, it is important to think about. However, it is doubtful that a permissive vaccine would be covered.

Dr. Campos-Outcalt (AAFP) inquired as to whether a state could decide not to cover or allow VFC vaccine to be used for a permissive recommendation.

Dr. Rodewald responded that because the entitlement belongs to the child, if a parent requests the vaccine for the child, that child is entitled to receive the vaccine under current law. It would place a state that did not allow a vaccine to be used for an entitled child in an awkward position. While there has never been a lawsuit in the VFC program for not offering a vaccine, even if there was a delay in the uptake, potentially a lawsuit could be brought over such a situation.

Dr. Whitley-Williams (NMA) expressed concern that a permissive recommendation would create a two-tiered system in the public or private sector. Children who are at the greatest risk may still not have access.

Dr. Rodewald responded that the resolution should not do the work of the recommendation. If ACIP wanted to recommend a vaccine, it would normally go into the VFC program. If the committee wants to offer a permissive recommendation, they can do so. Not having a VFC resolution to support a full or permissive recommendation would likely result in inequity because financially challenged and financially vulnerable children would not have access to the VFC program without a VFC resolution.

Dr. Middleman (SAM) urged the committee to make a meaningful public health effort to eradicate HPV disease among young people by making a universal recommendation for the use of quadrivalent HPV vaccine among males as well as females. The vaccine is both safe and effective, and the cost-effectiveness analysis indicates that it is cost-effective to immunize males when coverage among females is 50% or less. The data from the 2008 NIS has been mentioned and it reveals that coverage rate for the only longstanding, solely adolescent vaccines, Tetanus and diphtheria (Td) and tetanus, diphtheria and acellular pertussis (Tdap) coverage is about 72%. This is after a universal recommendation for a single injection for over 20 years with many state requirements to support it. The data for HPV vaccine, which includes a series of three injections, differentiating it from other vaccines, with few supportive requirements, was 18%. Dr. Middleman expressed great confidence that adolescent rates would rise, but that it would take time. Current coverage rates make a male recommendation cost-effective now and for the foreseeable future. Male youth deserve protection against a virus that costs them in terms of physical and mental health. SAM strongly supported and urged ACIP to support a universal recommendation to protect youth of both genders without disparity.

Dr. Cieslak expressed concern about the value of the vaccine, the wide variability in the cost-effectiveness studies, and the unknown uptake of vaccine among females. According to the graphs presented during this session, it appeared that the anticipated reduction in male anal cancer would be 2 per million per year, which was not a very substantial reduction for a fairly expensive vaccine. This was comparable to the consideration of Japanese Encephalitis (JE), which is a nasty disease preventable by vaccination, but so rare that it is entirely conceivable that the cost in terms of yet unknown but very rare side effects might exceed the burden of what it can prevent. Therefore, he said he was very uncomfortable recommending this vaccine for all males.

Dr. Baker clarified that ACIP would be making a recommendation only about preventing genital warts, not cancers in males.

Dr. Grogg (AOA) agreed with Dr. Middleman, pointing out that the most common question he hears raised by other practicing healthcare providers regards when HPV vaccine will be available for males. If the recommendation is permissive, the vaccine is unlikely to be readily available to men, especially with insurance.

Reflecting on what Dr. Wharton said about being good stewards for public funds, Dr. Temte noted that the VFC program had grown from about \$500 million in 1994 to about \$3 billion currently. He worried that in the current climate about cost cutting, this program would become a target for unregulated growth without congressional oversight. Therefore, he urged everyone to be very careful about using good evidence to support recommendations.

Dr. Campos-Outcalt (AAFP) pointed out that when these types of comparisons are made from year to year, remembering what was done in years past becomes a little difficult. He wondered what the cost-benefit analysis was of MCV4, second dose varicella vaccine, et cetera. It would be beneficial to have a table showing those analyses in order to compare and to be consistent.

Dr. Pickering suggested that they might also want to include the cost analysis of other preventative health services.

Dr. Katz (IDSA) indicated that he was very much in favor of the permissive approach for the reasons that had already been stated. Other vaccines for which permissive recommendations have been made have, by and large, worked. He wondered whether ACIP had ever offered encouragement rather than just a permissive recommendation alone, and encouraged the use of the vaccine in MSM. They have discussed this in the Work Group, but there was a very enlightening feature article in the Sunday *New York Times* titled “*Coming Out*” a few months ago which showed that the gender identification of many young people is at 12 and 13 years of age. He indicated that he would be more comfortable with a permissive recommendation with the inclusion of a clause to encourage vaccination for MSM. While it would likely be a departure for ACIP, at least they could be adventuresome and consider something different for a change.

Dr. Baker indicated that when there were data, they certainly had encouraged efforts in the past. An example would be encouragement before recommending influenza in young children.

Dr. Marcy agreed with the notion of strongly encouraging the use of HPV vaccine in MSM, and he preferred the terminology “strongly encourage” over “strongly consider.”

Dr. Judson suggested wording it “men who have not yet had sex with men, but think they may.”

Dr. Ault (AGOG), who was sitting in for Dr. Gall, expressed Dr. Gall’s very strong opinion that there should be a universal recommendation. Dr. Gall is a member of the Work Group.

Dr. Lett reminded everyone they would hear data on MSM in February 2010, so that particular language could wait until then.

Dr. Baker stressed that ACIP’s general principle has been to make recommendations based on data so that they are as evidence-based as possible.

Dr. Cieslak thought the argument would probably be a good one, but they had yet to see the data on warts in MSM. They did see data comparing incidence of anal cancers, which reflected a striking difference.

Dr. Neuzil indicated that given the discussion and evidence, and because it would likely affect the vote, she was uncomfortable with adding anything about MSM to the current statement.

At this point, Dr. Baker opened the floor to the general public to offer their comments prior to the HPV vaccine in males vote.

David Hastings (Oral Cancer Foundation) reported that 3.5 years ago he noticed a totally painless swelling in his neck as he was shaving one morning. He was a healthy, non-smoking individual, who had never been sick a day in his life. After 5 doctors and 4 weeks, it was confirmed that he had Stage 4 squamous cell carcinoma originating at the base of his tongue. After life-altering surgery, radiation, chemotherapy, he was given only a 60% chance of surviving 5 years. The treatment was brutal and barbaric and he permanently lost some of his ability to taste, to produce saliva, and to hear. Fortunately so far, his treatment has been successful, but in over 50% of the time, oral cancer results in a horrific death in which the cancer, despite this barbaric treatment, literally eats its way out from the oral cavity consuming the patient's face before a welcomed death. Throughout this horrific ordeal, he was told by everybody that his cancer was typically caused by heavy tobacco and alcohol use, which he did not do. A few weeks post-treatment, he was searching the web and discovered a connection between his cancer profile and HPV. He persuaded Moffitt to send his cancer slides to Johns Hopkins for testing, and the results came back HPV 16 positive. Mr. Hastings is also an unpaid volunteer and a single patient advocate for the Oral Cancer Foundation, which has had over 30,000 members, over half of whom are no longer alive because of oral cancer. As an organization that over the last 10 years has watched and had to deal with the rapid increase of incidents of oral cancers in those it serves and advocates for, specifically HPV positive oropharyngeal cancers, they are very aware of what is happening. They recognized the rapid ramp-up in cancers in 2001 and worked with CDC to try to develop tracking for this new etiology. Currently, this is the fastest growing segment of the oral cancer population, and many researchers believe that if the current trend in this disease continues, it will displace tobacco as a primary oral cancer cause in the next 10 years. More people in the US die from oral cancer than cervical cancer each year. While tobacco use has been on a constant decline for the last 15 years, the incidence rate of oral cancer has been on a steady increase for the last decade, with an 11% increase in 2007 alone. With the historic risk factors on the decline, obviously a replacement etiology is at play that has been firmly identified as HPV 16. Unlike cervical cancer, there is no HPV set site test in the oral cavity causing most, if not all, HPV positive oral cancers to be found late and staged as a 3 or a 4. It is known that the later cancer is discovered, the greater the chance of death. Mr. Hastings respectfully urged this committee to give this vaccine its strongest and broadest recommendation so that one day, HPV would be eliminated as an etiology of cancer and a killer of our children, their children, and their children.

Dr. Stephen Goldstone (Private Practice, Mt. Sinai) reported that he takes care of a largely MSM population, but also treats heterosexual men with HPV-related disease. When he went to medical school, they learned nothing about HPV-related disease. He learned a little about it during his residency. His entire practice is now devoted to HPV disease, so he stressed that he was talking from the front lines. While this disease may only cost an average of \$480 to treat, the end result lasts an entire lifetime. He sees patients who cry that they have not had sex in two years because they are worried that they will give a woman genital warts from their penis.

He thought it was absolutely absurd to minimize the cost of HPV-related disease in men even if it only pertained to genital warts. He expressed concern about a recommendation for MSM, given the potential for stigma. As an adolescent, he could not imagine the doctor saying to his mother, while he was in the room, that he needed a vaccine because he would be “a screaming queen someday.” While boys may identify or may know that they have sexual proclivities for other men, most of them are not going to tell their parents, especially if they are a person of color. Most of Dr. Goldstone’s young adult patients come from college health services or are employed and have their own insurance. During his entire career, in which he sees over a 100 patients a week for procedures, he has had only one referral from a pediatrician. He does not believe that most pediatricians are aware of this disease, and that it happens in college health. If a limit is set of 11 to 12 years of age for even an indication, all boys will be missed. Parents are not prepared to consider this and youth are not prepared to go against their parents’ recommendation. There must be a universal recommendation and there must be a catch-up recommendation. As part of a research project, his practice surveyed 250 men. They found that the number one reason people wanted to receive GARDASIL® was because they knew someone with HPV disease or they had HPV disease. The primary reason they did not want it was because they could not afford it. He requested that if ACIP passed a permissive recommendation, that they offer wording for clinicians to explain to patients and their parents why they will not be eligible to receive this vaccine and why their insurance company will not cover it.

Dr. Ellen Daily (University of South Florida, Moffitt Cancer Center) indicated that she is an Assistant Professor at the College of Public Health at the University of South Florida and a behavioral researcher with expertise in women’s health, cancer prevention, and reproductive health. From 2001-2006, she was a principal investigator on a CDC-funded study that examined the psychosocial impact of HPV in women. Currently, she is the principal investigator of a National Institutes of Health (NIH)-funded R01 study of psychosocial impact of HPV in men. Prior to her career in academic research, she started and directed 5 women’s health clinics in New York, Michigan, and Florida beginning in the early 1970s. The last clinic was started in 1983, the same year that Dr. Harald zur Hausen published an article connecting HPV with cervical cancer. At her clinic, many patients had abnormal paps and HPV. They spent many years engaging in patient education and support groups for those women, which was good start-up for them to conduct the CDC study. That study was conducted prior to the release of the HPV vaccine and in it, they found that being diagnosed with HPV created strong reactions of stigma, distress, anxiety, and fear. In her current study of HPV in males, they have found very positive vaccine intentions among the men who have been tested for HPV and they have also identified strong negative emotions, especially among participants whose test results are positive for HPV or among participants who are symptomatic for external genital warts. Dr. Daily indicated that she had come to speak to them not only as a public health researcher, but also as a women’s health advocate. While her comments may seem simplistic, she is not a bench scientist or a vaccine researcher, but she is someone who is concerned about the burden that women face related to HPV. She also raised a series of simple questions: If we know that HPV causes cervical cancer, and we know that HPV is sexually transmitted and that women can contract HPV from intercourse with men, why would they not approve the HPV vaccine for males with a strong recommendation for prevention of cervical cancer? That seemed to be a sufficient indication in and of itself. Given that the burden of genital warts, both physically and emotionally, is significant for both females and males, the vaccine could reduce that burden for both genders. Therefore, why would they not approve the HPV vaccine for both groups to equalize that burden? Her 16-year old son has grown up with a mother who conducts HPV research. He has heard about HPV his whole life and knows and is known by Dr. Harald zur

Hausen. Her son knows about the vaccine and fully expects to get it. She would like him to get the vaccine for several reasons. First, because women and girls should not bear the full burden of receiving the vaccine but should share it with males. Also, she would like her son and all sons to share the benefits of the vaccine having the advantage of preventing genital warts. She requested a full recommendation for males 9 to 26 years of age for the broadest possible indications.

Diane Solomon (NCI) clarified that she was voicing her opinion as a public health officer, but that her comments did not reflect any formal opinion of the NCI. She also disclosed that she is one of two medical monitors on an HPV vaccine trial in Costa Rica that is supported by NCI, but receives vaccine from GSK. She did not deny the emotional trauma of venereal warts or the horror of the diagnosis of oropharyngeal cancer and its treatment. She urged the committee to keep its eye on the goal, which was the responsible stewardship of public health funds. First and foremost, they should not be spending public health dollars on interventions that are not cost-effective. She also urged the committee not to rush to any conclusions. Within a couple of years there will be additional data on uptake in females. NCI is anticipating analyzing the protection provided by two doses of vaccine as opposed to three and will have more data on duration of protection. With regard to cost, she thought it was important to communicate to industry that they were not going to blithely accommodate excessive costs relative to public health gain. She expressed her personal hope and belief that if they sent this message, companies would respond responsibly with reasonable pricing.

John Ehrlich expressed his gratitude for the development of this vaccine. He was diagnosed with HPV and warts 20 years ago. In his 20 years of experience, he has had over 30 operational procedures. In the past year, he was diagnosed with anal cancer and had radiation and chemotherapy. He thought it would be fortunate for young children to be able to prevent this from ever happening to them because there is no turning back. He encouraged the committee to think about recommending that everybody be vaccinated.

Dr. Schneider (Gay and Lesbian Medical Association: GLMA) indicated that the GLMA is an organization dedicated to advocating for equity in healthcare for lesbian, gay, bisexual, and transgender patients and clients, and healthcare professionals. His clinical work is at Grady Hospital in downtown Atlanta, where he serves primarily an indigent African American population. The VFC program is critical for serving under-served youth in his patient population. He indicated that he was present to advocate for the needs of gay-identified youth, some of whom are people of color. Gay-identified youth face many barriers to accessing quality patient-centered healthcare. Healthcare disparities among gay youth, known and presumed, are oftentimes related to lack of access. A permissive recommendation for the HPV vaccine would create yet another barrier for gay youth trying to access care that is patient-centered. As they had heard during this session, the goal was to administer the vaccine well before sexual debut. The lesbian, gay, bisexual, and transgender (LGBT) community are the people who are most at risk, most disconnected and marginalized, least able to advocate for themselves, and also the least likely to have access or to be able to afford the out-of-pocket costs independent of coverage. He urged the committee members to approve a universal routine recommendation for the HPV vaccine for use in males.

Dr. Anna Giuliano thanked the committee for giving her an opportunity to speak. She indicated that she is the Chair of the Department of Epidemiology and Genetics at the Moffitt Cancer Center. By way of disclosure, she is also the principal investigator overall for Merck's protocol 20, the international male vaccine trial that they heard about during this session. She also

chaired their male advisory board. The reason for that was that her scientific expertise is in the epidemiology of HPV infection and cancer as it relates to men and women, having several large NIH and CDC funded studies and due to the publications over the past 20 years. She highlighted some of the issues that arose during the session. There is definitive evidence that HPV causes cancer at the sites discussed. The consensus statement was made at the World Health Organization (WHO) meeting in 2005. There was no question that the word "cause" could be used for those cancers. Since 2005, the attributable risk due to HPV infection has become increasingly clearer. It is now understood with better data that the proportion of those cancers caused by HPV is greater than originally thought. While the incidence of any particular cancer in men appears low, the total cancer burden related to HPV in men is quite high, as one of the committee members pointed out. It is not that dissimilar for females. The other fact that we was not heard during this session was that of particular importance is that certain cancers in men are actually increasing in incidence, including HPV-related oropharyngeal cancers and HPV-related anal cancers. This is not limited to MSM. The oropharyngeal cancers are 2-fold higher in men and 2- to 5-fold higher in men than in women. It is unlikely that this is all attributable to MSM behavior. Both cancers result in tremendous loss of quality of life both during and after treatment. Both cancers are costly to treat and both cancers ultimately result in mortality. Prevention of the HPV infection that causes cancers in men is the only viable option there is to reduce HPV related cancers in men to prevent unnecessary morbidity and mortality. Therefore, both men and women should have the opportunity to benefit from the newly licensed vaccine. It is also known that HPV is a shared infection between men and women. To achieve the public health benefit and opportunity this vaccine presents, both sexes should be vaccinated. This is especially true in the setting of the US where only 18% of females who received three doses and the estimates for uptake did not appear very optimistic. It is doubtful that the estimate of 75% of females completing the 3-dose sequence will be achieved. With such a low uptake of vaccine in females, male vaccination becomes an important part of establishing herd immunity and reducing infection and disease caused by HPV in females. HPV is a shared infection. The responsibility for preventing infection and decreasing the population burden should also be shared. She expressed her hope that ACIP would vote for a strong recommendation for this vaccine in males.

Motion: Quadrivalent HPV Vaccine in Males

Dr. Englund made a motion to approve the HPV vaccine recommendation for males as presented. Dr. Sawyer seconded the motion. The motion carried with 12 affirmative votes, 1 abstention, and 0 negative votes.

VFC Resolution Update:
Human Papillomavirus Quadrivalent Vaccine for Males

Lance E Rodewald, MD
National Center for Immunization and Respiratory Diseases

Dr. Rodewald indicated that the resolution for a permissive VFC recommendation would be identical to the current recommendation for quadrivalent HPV vaccine, with the two additions underlined:

- Eligible groups
 - Add: Males, 9 through 18 years of age
- Recommended schedule for quadrivalent HPV vaccine
 - Recommended schedule
 - Add: A 3-dose series is recommended for all females and males at age 11 to 12 years ...
 - Minimum age and intervals: no change
 - Catch-up vaccination: no change
 - Other vaccination
 - Add: Eligible females and males as young as 9 years of age can be vaccinated
 - Interrupted schedule: no change
- Recommended dosage for quadrivalent HPV vaccine: no change
- Precautions and contraindications: no change

The statement regarding updates based on published documents will read as follows:

“If an ACIP recommendation or notice regarding quadrivalent HPV vaccine for males 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. Englund wondered whether, in the interest of harmonization, consideration should be given to moving it one to two months for females.

Dr. Rodewald replied that they would ensure that any language that changed in the female recommendation in terms of intervals, et cetera would be consistent with the recommendations.

Motion: VFC Resolution for Quadrivalent HPV Vaccine in Males

Dr. Neuzil made a motion to approve the VFC resolution for quadrivalent HPV vaccine in males as presented, ensuring that harmonization is consistent. Dr. Judson seconded the motion. The motion carried with 13 affirmative votes, 0 abstentions, and 1 negative vote.

2010 Childhood & Adolescent Immunization Schedule

Introduction

Dr. Cody Meissner, Chair Childhood & Adolescent Immunization

Dr. Meissner reported that the approach to the 2010 childhood and adolescent schedule was to accurately reflect the existing ACIP recommendations. Changes to the schedule were carefully written so that there were no changes to the immunization policy. The version of the schedule that being presented to ACIP for approval represents input from several sources. Input was first obtained from Work gGoup members during monthly conference calls. ACIP recommendations published since January 2009 regarding the inactivated polio vaccine (IPV), revaccination with meningococcal conjugate vaccine (MCV), and changes to influenza immunization policy were added. The Work Group-revised schedule was then circulated among CDC subject matter experts (SMEs). Their comments were submitted to the Work Group and were discussed during monthly calls. A document that combined both Work Group revisions and the revisions of the CDC SMEs was submitted for internal clearance in September 2009.

The basic layouts of the 2010 schedules were unchanged from the 2009 schedules. There are three separate schedules, each with its own footnotes: 0 through 6 years, 7 through 18 years, and catch-up. In the three schedules, guidance is provided for immunization against 16 of the 17 vaccine preventable diseases.

In the past, because of changes made to the text by *Morbidity and Mortality Weekly Report (MMWR)* editors, the version of the schedule published in *MMWR* differed from that approved by ACIP and posted on the CDC website. Beginning in 2009, these edits have been incorporated into the early drafts of the schedules to minimize changes made by the *MMWR* editors, and help ensure that the published version closely matches the version approved by ACIP.

Numerous changes in wording have been made in the footnotes of all three schedules to make them as clear and unambiguous as possible. Words and phrases have been modified to accommodate space limitations, while maintaining a reasonable font size. For example, endashes have been removed because clinicians are not consistent in interpretation. Some interpret the endash as meaning “to” and others interpret it as meaning “through.” The endashes were replaced with words (to or through) to reduce misinterpretation. Symbols for “greater than” and “less than” are being replaced with words because clinicians frequently misinterpret the meaning of the symbols.

Proposed Changes to the Immunization Schedule For Persons 0 Through 18 Years of Age

Dr. William Atkinson, CDC Lead Centers for Disease Control and Prevention

Dr. Atkinson reiterated that the objective of the schedule is to accurately and succinctly reflect the recommendations made by this committee—not to create new policy. While there are a couple of minor exceptions, the goal is to shorten the 30 to 50 page documents generated by ACIP to two bullets.

A number of proposed changes have been made to the 2010 schedules. During the CDC internal clearance process, it was noted by an astute observers that a sentence about combination vaccines which appears at the beginning in a paragraph right under the 0 to 6 and the 7 to 18 schedule has been there since 1997. This sentence differs from the combination vaccine statement sentences ACIP voted on in June 2009 and has been changed.

Some clarifying sentences were added to the hepatitis B footnote (0-6 schedule) at the request of the Division of Viral Hepatitis. The wording of the rotavirus footnotes (0-6 and catch-up schedules) was modified to be consistent with the published ACIP statement. Hiberix® was added to the Hib footnote (0-6 schedule). Spacing of PCV7 and PPSV23 for high risk children (0-6 schedule) was clarified with a statement about the interval between pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine at the request of Bacterial Diseases.

A footnote for inactivated polio vaccine was added (0-6 schedule) and IPV footnotes were modified according to recommendations published in the *MMWR* on August 7, 2009 (7-18 and catch-up schedules). Reference was made to the August 29 H1N1 vaccine ACIP statement (0-6 and 7-18 schedules). There was some discussion about whether this should be done as a web link, or whether the ACIP statement should be referenced. The internal opinion was to actually reference the statement itself. The hepatitis A footnote was modified in all three schedules to allow vaccination of children "for whom immunity is desired." This was first attempted in 2008, but was not approved. It has been further vetted has now been included.

The meningococcal footnotes were modified to reflect the MCV4 revaccination recommendation published in the *MMWR* on September 25, 2009 (0-6 and 7-18 schedules). Throughout the document, most references to published ACIP statements have been deleted. These are mentioned in the introductory paragraph of the 0-6 and 7-18 schedules. References to ACIP recommendations published in the *MMWR* weekly were retained.

Changes were proposed to the combination vaccine statement (0-6 and 7-18 year schedules). The current and revised statements read as follows:

Current: Licensed combination vaccines may be used whenever any component of the combination is indicated and other components are not contraindicated and if approved by the Food and Drug Administration for that dose of the series.

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

The revised combination vaccine statement is verbatim from the provisional recommendation upon which ACIP voted in June 2009. While this does not offer the scope because the approved statement included a footnote to clarify exactly what “provider assessment” means, there is not room for the footnote in the schedules unless someone on the committee felt strongly that it should be included. The existing language will simply be replaced with the provisional recommendation posted on the ACIP website.

Dr. Atkinson offered further details about some of the most extensive revisions. Three changes were made specifically at the request of the Division of Viral Hepatitis to clarify some issues pertaining to the hepatitis B vaccine (0-6 year schedule). For Footnote 1, a sentence was added to state that Monovalent HepB vaccine should be used for doses administered before age 6 weeks. Testing for immune response 1 to 2 months after completion of at least 3 doses was specified, and a sentence was added to state that the 4th dose should be administered no earlier than age 24 weeks.

For the rotavirus vaccine footnotes (0-6 Year and Catch-Up Schedules), the two bullets were revised to match exactly the recommendation as it was published in the *MMWR*. It maintains the maximum age for the first dose and the maximum dose for any doses being 15 weeks and 8 months respectively. The revisions are depicted in the following illustration:

2. Rotavirus vaccine (RV). (Minimum age: 6 weeks)

- Administer the first dose at age 6 through 14 weeks (maximum age: 14 weeks 6 days). Vaccination should not be initiated for infants aged 15 weeks 0 days or older. (i.e., 15 weeks 0 days or older).
- Administer the final dose in the series by age 8 months 0 days. The maximum age for the final dose in the series is 8 months 0 days
- If Rotarix[®] is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

Three footnotes were modified for IPV. There is a new footnote for the 0 through 6 year schedule, the wording for which was taken nearly verbatim from the August 7 *MMWR* and is as follows:

6. Inactivated poliovirus vaccine (IPV) (Minimum age: 6 weeks)

- The final dose in the series should be administered on or after the 4th birthday and at least 6 months following the previous dose
- If 4 doses are administered prior to age 4 years an additional (fifth) dose should be administered at age 4 through 6 years. See *MMWR* 2009;58(No. 30):829-30

There was an attempt in 2008 to add a permissive statement for parents who wished their children to be vaccinated with hepatitis A vaccine. However, there was some objection because it had not been vetted through the Hepatitis Work Group, which was then newly constituted. The revised hepatitis A statement for all three schedules reads as follows, with the revision underlined:

10. Hepatitis A vaccine (HepA).
(Minimum age: 12 months)

- HepA also is recommended for older children who live in areas where vaccination programs target older children, who are at increased risk of infection, or for whom immunity against hepatitis A is desired.

This same wording was passed through the Hepatitis Work Group, who agreed that this was a reasonable addition to the schedule. The statement has been added to all three footnotes: 0 to 6, 7 to 18, and the catch up schedule.

These revised meningococcal footnotes are as follows:

10. 11. Meningococcal vaccine. (Minimum age: 2 years for meningococcal conjugate vaccine [MCV4] and for meningococcal polysaccharide vaccine [MPSV4])

- Administer **MCV4** to children aged 2 through 10 years with terminal **persistent** complement component deficiency, anatomic or functional asplenia, and certain other high-risk groups. See *MMWR* 2005;54(No. RR-7).
- Administer **MCV4** to children previously vaccinated with **MCV4 or MPSV4**. Persons who received MPSV-3 or more years previously and who remain at increased risk for meningococcal disease should be revaccinated with **after 3 years if first dose given at age 2 through 6 years**. See *MMWR* 2009;58(No. 37):1042-3.

This following is the analogous footnote that is in the 7 to 18 schedule, which contains the same information except that it also includes revaccination for children who remain at increased risk and whose previous dose was given at age 7 or older, indicating the interval for revaccination is 5 years. An additional sentence was included to address on-campus housing as a risk factor:

3. Meningococcal conjugate vaccine (MCV4).

- Administer **MCV4** is recommended for to children aged 2 through 10 years with terminal **persistent** complement component deficiency, anatomic or functional asplenia, and certain other groups at high risk. See *MMWR* 2005;54(No. RR-7).
- Administer to children **Persons who received previously vaccinated with MCV4 or MPSV4 at 5 or more years previously and who remain at increased risk for meningococcal disease should be revaccinated with MCV4 after 3 years if first dose given at age 2 through 6 years or after 5 years if first dose given at age 7 years or older. Persons whose only risk factor is living in on-campus housing are not recommended to receive an additional dose.** See *MMWR* 2009;58(No. 37):1042-3.

This is the 7 to 18 IPV schedule so it has the same footnote indicating the minimum age and interval for the last dose of the IPV series:

8. Inactivated poliovirus vaccine (IPV).

- For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.
- **The final dose in the series should be administered on or after the 4th birthday and at least 6 months following the previous dose.**
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

This change has been reflected in the grid that has all the values of minimum intervals to change the minimum interval for the dose 3 to 4 to 6 months rather than 4 weeks as it was prior to ACIP's new recommendation in both the 4 through 6 and the 7 through 18 year schedules:

CATCH-UP SCHEDULE FOR PERSONS AGED 4 MONTHS THROUGH 6 YEARS					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Inactivated Poliovirus ⁶	6 wks	4 weeks	4 weeks	4 weeks ⁶ 6 months	

CATCH-UP SCHEDULE FOR PERSONS AGED 7 THROUGH 18 YEARS					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Inactivated Poliovirus ⁶	6 wks	4 weeks	4 weeks	4 weeks ⁶ 6 months	

One thing not included in the *Notice to Readers* in the following footnote is the second bullet that was appended to address the 4th dose. The issue of individuals who began the series late was not directly addressed in the *MMWR*, so it was included in this footnote. A footnote was added to address minimum intervals in the first 6 months of life:

6. Inactivated poliovirus vaccine (IPV).
- For children who received an all-IPV or all-oral poliovirus (OPV) series The final dose in the series should be administered on or after the 4th birthday and at least 6 months following the previous dose.
 - A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months following the previous dose.
 - In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
 - If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

The HPV footnotes are currently specific to HPV4 manufactured by Merck. Based on the results of the ACIP deliberations and vote on the HPV2 vaccine, three to four additional footnotes would need to be added to HPV. Dr. Atkinson will work with Drs. Markowitz and Dunne to ensure that the footnotes clearly represent and reflect the HPV votes.

Discussion

Dr. Baker requested that a representative of the Meningococcal Work Group address the question regarding whether children with rheumatologic disease with deficiencies of C2 and C4 are at increased risk of meningococcal disease.

[Dr. Amanda Cohn] indicated that the word “terminal” could not be changed to “persistent.”

Dr. Baker pointed out that in the minds of pediatricians, “persistent complement deficiency” includes patients who have rheumatologic diseases with low levels of C4 and C2.

Dr. Cohn indicated that the Work Group discussed changing it from “terminal” to “persistent” to specifically include deficiencies in C3 and some other specific complement components that are not in the terminal pathway. In the meningococcal statement, complement deficiencies are listed that should be included. For space reasons, this was not done in the schedule.

Dr. Atkinson added that the *Notice to Readers* includes some examples, for which a reference is included.

Dr. Cohn noted that C2 and C4 are not included in those.

Dr. Baker stressed that pediatricians depend on the schedule and the schedule footnotes rather than the *Notice to Readers* and some of the longer documents.

Dr. Hosbach (sanofi pasteur) pointed out that because hepatitis B could be completed with either three or four doses, the footnote should state “the final dose” rather than “the fourth dose” because monovalent vaccine can be completed after three doses.

Dr. Atkinson responded that the first part of the fourth dose hepatitis B statement was in the context of presumably a birth dose plus a combination vaccine that included it, so it technically would be the fourth dose. To generalize more, it could be revised to state “24 weeks and final dose.”

Dr. Katz requested clarity regarding whether the specified testing for a response one to two months after completion of at least three doses of hepatitis B vaccine was only for the offspring of infected women or everyone.

Dr. Atkinson responded that it was primarily intended for children born to surface antigen-positive women.

Motion: 2010 Child and Adolescent Immunization Schedule

Ms. Ehresmann made a motion to approve the 2010 Child and Adolescent Immunization Schedule as presented, with the incorporation of the suggestions made during the discussion. Dr. Englund seconded the motion. The motion carried with 13 affirmative votes, 0 abstentions, and 0 negative votes.

Dr. Atkinson indicated that the new HPV footnotes would be revised based on the votes taken earlier in the day to reflect as closely as possible what ACIP voted on. Unless anyone felt the need to share it with the full committee, he indicated that he would submit the revised information to the Work Group and the HPV representatives to ensure that they are acceptable. Once the revisions are accepted, the documents will be submitted for simultaneous publication in the *MMWR*, *Pediatrics*, and *American Academy of Family Physicians*. The scheduled *MMWR* publication date is January 8, 2010.

2010 Adult Immunization Schedule

Introduction

Ms Kristen Ehresmann
Adult Immunization Work Group Chair

Ms. Ehresmann indicated that the Adult Immunization Work Group activities included monthly calls to discuss the schedule revisions. Separate calls were convened with the General Recommendations Work Group and the Influenza Work Group related to their adult sections. As the Adult Immunizations Work Group moves forward, the plan is to publish the recommended adult immunization schedule in January 2010, to continue to streamline and harmonize the schedule footnotes, and to complete the revision of the Healthcare Personnel Recommendations, with Healthcare Infection Control Practices Advisory Committee (HICPAC).

Proposed Changes to the 2010 Immunization Schedules For Person 19 Years of Age and Above

Dr. Carol Friedman
CDC, NCIRD, ISD

Dr. Friedman indicated that the Work Group was proposing to change the abbreviation for Human Papillomavirus from HPV to HPV4 to reflect that this is a quadrivalent vaccine and to harmonize with the adolescent immunization schedule. An abbreviation, if agreed upon by the HPV Work Group and others, would also be included for the bivalent vaccine, which would probably be HPV2. These changes will be made in the medical and other indications figure of the schedule. Figure 1 illustrates the proposed schedule:

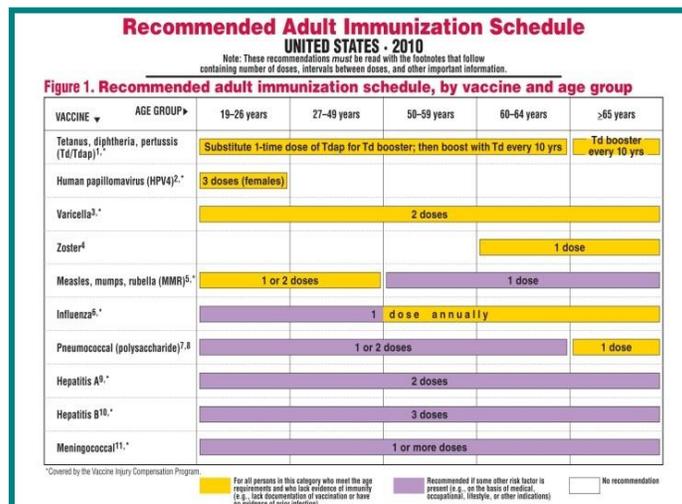


Figure 2 illustrates the vaccines that might be indicated for adults based on medical and other indications:

Figure 2. Vaccines that might be indicated for adults based on medical and other indications

INDICATION ▶	Pregnancy	Immu- compromising conditions (including human immunodeficiency virus (HIV)) ¹⁰	HIV infectant ^{10,11} CD4 ⁺ lympho- cyte count (≥200 cells/cc)	Diabetes, heart disease, chronic lung disease, chronic alcoholism	Asplenia ¹² (including elective splenectomy and persistent complement component deficiencies)	Chronic liver disease	Kidney failure, end-stage renal disease, receipt of hemodialysis	Health-care personnel	
Tetanus, diphtheria, pertussis (Td/Tdap) ¹	Td	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs							
Human papillomavirus (HPV) ^{2,*}		3 doses for females through age 26 yrs							
Varicella ^{3,*}	Contraindicated	2 doses							
Zoster ⁴	Contraindicated	1 dose							
Measles, mumps, rubella (MMR) ^{5,*}	Contraindicated	1 or 2 doses							
Influenza ^{6,*}		1 dose TIV annually							1 dose TIV OR LAVI annually
Pneumococcal (polysaccharide) ^{7,8}		1 or 2 doses							
Hepatitis A ^{9,*}		2 doses							
Hepatitis B ^{9,*}		3 doses							
Meningococcal ^{11,*}		1 or more doses							

Covered by the Vaccine Injury Compensation Program.

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of prior infection) Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications) No recommendation

*These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly indicated for adults ages 19 years and older, as of January 1, 2009. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/pubs/acip-04.htm).

For Figure 2, the Work Group also proposed to revise the column heading for asplenia by removing the word “terminal” from complement component deficiencies and replacing it with “persistent.” This change was supposed to have been made for the 2009 schedule, but was not included. Also, this would be to harmonize with the childhood and adolescent schedules as well.

One of the general enhancements that the Work Group made, in consultation with the SMEs, was to introduce each footnote with an introductory sentence. Just as an example, for the meningococcal footnote the introductory sentence would be, “Meningococcal vaccine should be administered to persons with the following indications.”

The Human Papillomavirus (HPV) Footnote #2 will be revised to indicate the licensure of a bivalent HPV (HPV2) vaccine for women ages 19 through 26 years; and indicate the new indication for use of HPV4 for men ages 19 through 26 years.

The Measles, Mumps, Rubella (MMR) Footnote #5 has been revised to delete sentences from measles and mumps components stating that adults born before 1957 generally are immune to reduce redundancy; and to add an introductory sentence stating that adults born before 1957 are generally considered immune to measles and mumps. This footnote has also been revised to clarify which adults born during or after 1957 do not need 1 or more doses of MMR for measles component, and reads as follows, “Adults born during or after 1957 should receive 1 or more doses of MMR unless they have a medical contraindication, or documentation of vaccination with 1 or more doses of MMR vaccine, or laboratory evidence of immunity, or documentation of physician-diagnosed measles.” The same clarification is made for the mumps component, which reads, “Adults born during or after 1957 should receive 1 or more doses of MMR unless they have a medical contraindication, or documentation of vaccination with 1 or more doses of MMR vaccine, or laboratory evidence of immunity, or documentation of physician-diagnosed mumps.” This footnote has also been revised to reword the recommendation for a dose of MMR for women whose rubella vaccination history is unreliable.

The rubella component reads, “1 dose of MMR is recommended for women who do not have documentation of rubella vaccination or lack laboratory evidence of immunity.”

MMR Footnote #5 was also revised to highlight recommendations for vaccinating healthcare personnel born before 1957 by deleting sentence from mumps component and moving to new section. This will now read, “For unvaccinated healthcare personnel born before 1957 who lack laboratory evidence of measles, mumps, and/or rubella immunity or laboratory confirmation of disease, healthcare facilities should consider vaccinating personnel with two doses of MMR vaccine at the appropriate interval (for measles and mumps) and one dose of MMR vaccine (for rubella), respectively.” The footnote was also revised to highlight recommendations for vaccinating healthcare personnel born before 1957 during outbreaks in new section, which reads, “During outbreaks, healthcare facilities should recommend that unvaccinated healthcare personnel born before 1957 who lack laboratory of measles, mumps, and/or rubella immunity or laboratory confirmation of disease, receive two doses of MMR vaccine during an outbreak of measles or mumps, and one dose during an outbreak of rubella.”

Influenza Footnote #6 has been revised to distinguish between seasonal influenza and pandemic influenza by adding the term “seasonal.”

Hepatitis A Footnote #9 was revised to include information regarding unvaccinated persons who anticipate close contact with an international adoptee as an indication for HAV vaccination. The language reads, “Unvaccinated persons who anticipate close personal contact (e.g., household contact or regular babysitting) with an international adoptee from a country of high or intermediate endemicity during the first 60 days following arrival of the adoptee in the United States. The first dose of the 2-dose hepatitis A vaccine should be administered as soon as adoption is planned, ideally 2 or more weeks before arrival of the adoptee.”

Hepatitis B Footnote #10 was revised to include dosing information for the hepatitis B vaccine, which reads, “Administer or complete a 3-dose series of HepB to those persons not previously vaccinated. The second dose should be administered one month after the first dose; the third dose should be administered at least two months after the second dose (and at least four months after the first dose).”

Meningococcal Disease Footnote # 11 was revised to clarify which formulation of meningococcal vaccine is preferred for certain age groups. The revision is “meningococcal conjugate vaccine (MCV4) is preferred for adults with any of the preceding indications who are age 55 years or younger; meningococcal polysaccharide vaccine (MPSV4) is preferred for adults age 56 years and older.” In addition, the meningococcal disease footnotes have been revised to clarify which formulations can be used for revaccination after 5 years and to also provide an example. The revision is “Revaccination with MCV4 after 5 years is recommended for adults previously vaccinated with MCV4 or MPSV4 who remain at increased risk for infection (e.g., adults with anatomic or functional asplenia).” Another revision is to include information regarding who does not need to be revaccinated with the meningococcal vaccine, which reads, “Persons whose only risk factor is living in on-campus housing are not recommended to receive an additional dose.” This is harmonize with the adolescent schedule as well.

Hib Footnote # 12 has been revised to clarify which high-risk patients can receive the Hib vaccine, which reads as follows, “However, studies suggest good immunogenicity in patients who have sickle cell disease, leukemia, or HIV infection or who have had a splenectomy.

Administering Hib vaccine to these high-risk persons, who have not previously received Hib, is not contraindicated.” This is also to harmonize with the adolescent schedule.

Discussion

Because it is unlikely that very many people currently know what measles look like, it was not clear to Dr. Marcy that physician diagnosed measles and mumps would be valid.

Dr. Amy Parker (Division of Viral Diseases) indicated that the general recommendations had not been updated for MMR, so this could be taken into consideration.

Dr. Judson agreed that it is currently difficult to make an accurate clinical diagnosis of mumps or rubella, much of which is sub-clinical and follows rash patterns and lymphadenopathy that are largely non-specific. He also expressed concern with Footnote #6 distinguishing between seasonal influenza and pandemic influenza at the very time any useful distinction between novel H1N1 and other seasonal influenza was being lost. If this footnote was looking forward, it probably ought to take into account perspectives or editorials in the *Journal of Infectious Diseases (JID)* from Warrens and others that National Institute of Health (NIH) stating what constitutes a pandemic. There really is no agreement on that.

Dr. Freidman responded that she would take this into consideration.

As a member of the Influenza Work Group, Dr. Neuzil indicated that for the trivalent and monovalent vaccines, there are different vaccines. This was trying to express what terminology to use.

Dr. Baker thought that novel H1N1 would be adequate for this year rather than putting in an identifier.

Dr. Katz inquired as to whether the chart signified that MMR could be given to HIV patients who have reasonable CD4 counts.

Dr. Friedman responded that the chart distinguishes between a less than 200 and greater than 200 T-cell count.

Pertaining to seasonal influenza, Ms Ehresmann pointed out that ACIP had just voted on including that language in the childhood schedule, so they should be consistent across all schedules.

Ms. Stinchfield suggested that another improvement which could be made in terms of consistency pertained to intervals. For example, the MMR footnote for healthcare personnel in an outbreak states two doses of MMR but does not indicate the interval.

Motion: 2010 Adult Immunization Schedule

Ms. Ehresmann made a motion to approve the 2010 Adult Immunization Schedule as presented, with the incorporation of the suggestions made during the discussion. Dr. Keitel seconded the motion. The motion carried with 14 affirmative votes, 0 abstentions, and 0 negative votes.

General Recommendations

Overview

Ciro Sumaya, MD, MPH, Chair General Recommendations Work Group

Dr. Sumaya reported that the General Recommendations Work Group has been working diligently. In the past, the *MMWR* has been published in 3 to 5 year intervals, but the Work Group is attempting to work on an expedited 3.5 year interval for the next publication. General recommendations address immunization issues that are relevant to all vaccines and are not necessarily attributable to a single vaccine. These recommendations are directed to a variety of providers (e.g., physicians, nurse-practitioners, nurses, pharmacists, medical assistants) who are administering many vaccines on a daily basis. The general recommendations include text, tables, and figures for quick reference. The sections and sub-sections which the Work Group has been revising include the following, with the status of the section or date of votes shown to the side of each section:

- Introduction **(NEW)**
- Timing and spacing of immunobiologics **(October 2008)**
 - Combination Vaccines **(June 2009)**
- Contraindications and precautions **(October 2008)**
- Preventing and managing adverse reactions **(October 2008)**
 - Benefit and Risk Communication **(October 2008)**
- Reporting adverse events after vaccination **(October 2008)**
 - The National Vaccine Injury Compensation Program **(Oct.2008)**
- Vaccine administration **(October 2008)**
- Storage and handling of immunobiologics **(February 2009)**
- Altered immunocompetence **(VOTE DEFERRED)**
- Special Situations **(June 2009)**
- Vaccination records **(June 2009)**
- Vaccination programs **(NEW)**
 - Child
 - Adolescent
 - Adult
- Vaccine information sources **(NEW)**

The discussion during this session focused on the three new sections (e.g., Introduction, Vaccination Programs, and Vaccination Information Sources); some sections that had already been voted on, but for which newer revisions were available (e.g., Timing and Spacing of Immunobiologics, Storage and Handling of Immunobiologics); and Altered Immunocompetence for which the vote was previously deferred, but revisions are now available to be added. Much of the information pertaining to Hematopoietic Stem Cell Transplant patients receiving vaccines is being developed by scientific and professional organizations, but has not yet come to closure and consensus.

There would also be some discussion dealing with the rotavirus and HIV settings, and some comments will probably be received on standard liquid-filled thermometers that require further discussion. More recently, the HPV discussion addressed syncope and harmonizing the general recommendations with the HPV recommendations.

Vaccination Programs

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

Dr. Kroger reported that the new content consisted of an introductory statement beginning on page 1, line 1; an extensive section on vaccination programs beginning on page 82, line 8; and the vaccination information sources section beginning on page 94, and line 4.

The Vaccination Programs section was extensively revised. This section deals with programmatic issues within the context of revising the entire general recommendations document. As a part of that process, the Work Group wanted to incorporate past ACIP standalone documents, specifically those dealing with general adult immunization principles published in 1991, general adolescent immunization principles published in 1996, some ACIP *MMWR* statements addressing combining vaccination programmatic activity with the women, infant and children program published in 1996, and a document regarding assessment feedback incentives and exchange published in 1996. Dr. Kroger indicated that the members should consider review of this in the context of general efforts within CDC to promote adolescent and adult immunization. Significant input into this section was provided by the ACIP Adult Work Group and others at CDC who have been a part of this process as well. The outline for this section is as follows:

- ❑ Child and adolescent immunization
 - Pediatrics Immunization Standards
 - Women/Infants/Children Program
- ❑ Topics specific to adolescent immunization
 - Definition of age range
 - Coverage rates
 - Linking immunization and primary care – avoiding missed opportunities
 - Immunization record retrieval
- ❑ Adult immunization principle
 - Burden of disease
 - Adult Immunization Standards
 - Cost-effectiveness of vaccines
 - Coverage rates – barriers to high coverage
- ❑ Evidence-based interventions
 - Assessment/Feedback/Information/Exchange
 - Other strategies
 - ★ Enforcing school requirements, etc.
- ❑ Other programmatic issues
 - Description of stakeholders in vaccine financing
 - Little to no discussion of mechanisms of financing

This section is divided by age group. A discussion for the immunization standards is carried over from the 2006 general recommendations document from the National Vaccine Advisory Committee (NVAC). The Work Group tried to update that section based on more recent NVAC documents that have been published, specifically in the area of adolescent immunization and ways to avoid missed opportunities. There is a discussion of coverage rates; a limited discussion of the cost-effectiveness of vaccine specifically in the adult immunization part of this section; a discussion of evidence-based interventions that includes discussion of Assessment / Feedback / Information / Exchange published previously; other strategies that have been published by the Task Force on Community Preventive Services, with language included from the Task Force and from the 2006 General Recommendations document on strategies (e.g., enforcing school requirements); and other programmatic issues such as stakeholders involved in vaccine financing, with a limited discussion of the VFC and a limited discussion regarding mechanisms of financing occurs. There is little included on the topic of financing, given that it is beyond the purview of ACIP.

Regarding new revisions to sections already voted on by ACIP, there was an ACIP vote on the Combination Vaccine sections during the June 2009 ACIP meeting. Provisional recommendations were placed on the website in August 2009. On page 13, line 12 of the document, a sentence was included based on the discussion indicating that administering extra antigens in a combination vaccine should be avoided in most situations. The context of that decision was primarily to avoid extra doses of diphtheria, tetanus toxoid when giving combination vaccines such as Pentacel® and Pediarix™.

A new minimum interval and minimum age is included for poliovirus vaccine. This was changed by the Polio SME to allow for adequate spacing so that a strong immune response will be generated following primary series, and a strong boost would be generated following the 4th dose or the fifth dose if using combination vaccine. The minimum interval between next-to-last and last dose is 6 months, the minimum age for dose 4 is 4 years, and providers who use Pentacel® might need to give five doses of polio vaccine. This section is less permissive about using minimum intervals. With regard to “spacing of multiple doses of same antigen” page 4 line 8, “simultaneous administration” now can only expedite three doses of IPV in infancy, (previously was four) page 8, line 2. New polio vaccine intervals are reflected in Table 1, page 134.

Regarding the storage and handling section, which was also voted on previously by ACIP, a sentence was added to discourage transport of vaccine over long distances from the pharmacy to the provider who administers the vaccine. This had to do with the issue of “brown bagging” with the Zoster vaccine. Informal surveys have indicated that 40% of providers who use Zoster vaccine permit transportation of the vaccine by patient from pharmacist. Zoster vaccine must be kept frozen, so this practice poses a problem. Thus, language was included on page 47, line 22 stating that vaccine transport between the storage site and the administration clinic is discouraged unless the cold chain is maintained, and vaccine transport by the patient (e.g., “brown-bagging” of zoster vaccine) is particularly discouraged.

In terms of the Altered Immunocompetence section, changes to the 2006 General Recommendations were submitted to ACIP for review in February 2009. A potential conflict was identified between recommendations and work occurring among other professional organizations (e.g., IDSA, CDC). Various topics were covered in these discussions, including vaccination of HIV-infected children, vaccination of hematopoietic cell transplant recipients, and general altered immunosuppression issues. The draft on Altered Immunocompetence begins

on page 49, line 1. It contains content identical to the 2006 General Recommendations versus what was submitted for ACIP's consideration in February 2009. During this session, ACIP must consider whether this section could be moved forward and whether certain revisions could be placed into the final version. The Work Group's proposed recommendations included the following:

- ❑ Revise Altered Immunocompetence Table 13 Page 173, Line 1 so that:
 - B-lymphocyte deficiency is a contraindication for yellow fever vaccine, BCG vaccine, and typhoid vaccine (these vaccines are currently not listed)
 - Harmonize the two complement category rows into one: persistent complement component deficiency, (since all cell values are identical anyway)
- ❑ Insert zoster language into section on "Vaccination with Live Attenuated Vaccines" INSERT at Page 55, Line 11:

"The incidence of zoster is increased in persons with altered immunocompetence. Adults with most types of altered immunocompetence are still expected to maintain residual immunity to varicella-zoster virus because of past infection that protects against primary varicella but offers incomplete protection against zoster. Zoster vaccine is contraindicated in individuals with primary or acquired immunodeficiency states (e.g. lymphoma, leukemia, tumors involving the bone marrow and patients receiving chemotherapy) and some AIDS patients. In some cases of altered immunocompetence such as AIDS patients with CD4+ lymphocyte counts greater than 200 cells/ul, there is no contraindication to zoster vaccine."

There is language on page 54, line 14 that states that infants born to mothers who are HIV-positive should not receive rotavirus vaccine unless identified as HIV-negative themselves. That language needs to be changed due to the recently published CDC NIH, IDSA document regarding the topic of opportunistic infections in HIV-positive individuals, which states that rotavirus vaccine would be recommended for an infant born to a mother who is HIV-positive.

Dr. Kroger pointed out that also important for ACIP to discuss during this session was a recent publication by Prymula in *The Lancet* regarding Acetaminophen, the active ingredient in Tylenol® [Prymula, R. *The Lancet*, Oct. 17, 2009; vol 374: pp 1339-1350]. This is based on a study from the Czech Republic in which 400 to 500 children received a combination vaccine containing pneumococcal components as well as tetanus, diphtheria, pertussis, and Hib vaccine. Based on the findings in children who received Tylenol® and those who did not, data suggested that there may be reductions in immunity in the children who received Tylenol®. This is relevant, given that the General Recommendations contain a brief section that discusses this topic. This is contained in the Administration section in which there is discussion of the methods for alleviating pain, and includes an allowance for the use of Tylenol® post-vaccination with diphtheria-tetanus-pertussis (DTP), but before the fever occurs.

Discussion

Dr. Marcy reiterated his previously stated concern regarding standard fluid filled thermometers as a means of monitoring vaccine temperature. In the winter, power outages occur frequently and it can be impossible to determine what may have occurred between a Friday night and Monday morning when no one is on-site. Given that fluid filled thermometers are not adequate, it was unclear to him why they kept recommending them.

Dr. Judson thought that with regard to altered immunocompetence, congenital and acquired immunodeficiency needed to be separated from a number of other autoimmune conditions that may or may not be associated with immune incompetence or inability to respond (e.g., lupus, HIV, rheumatoid arthritis).

Dr. Pickering indicated that there is a table. Pediatricians are used to dealing with that, and the table clearly separates primary from secondary immune deficiencies. Over 500 primary immunodeficiencies are seen in children, so not everyone is listed. However, the major categories are included and the table is fairly clear.

Dr. Kroger added that autoimmunity is not specifically grouped, nor was it grouped in 2006.

Dr. Baker clarified that the changes presented were consistent with the 2009 IDSA guidelines. A new guidelines committee was convened to specifically address altered immunocompetence, although this work has not been completed. However, the proposed language is consistent with the currently published language.

Dr. Keitel noted that the altered immunocompetence table did not include yellow fever vaccine which should be included.

Dr. Kroger responded that yellow fever vaccine would be included if ACIP preferred that it be added.

Dr. Grogg clarified that for typhoid, it was stated that lymphocyte deficiency is contraindicated for yellow fever and typhoid; however, it should say oral typhoid which is the live vaccine. Injectable is fine.

Dr. Neuzil requested clarification regarding whether ACIP would be voting on the entire document during this session.

Dr. Kroger responded affirmatively.

Dr. Neuzil pointed out that rotavirus conflicted with the new statement from the beginning of 2009 and needs to be edited.

Dr. Turner (ACHA) pointed out that page 16 of the General Recommendations included a statement about administering live vaccine simultaneously, particularly intranasal vaccines. His understanding was that currently the recommendation was that seasonal and monovalent H1N1 were not to be administered together. He suggested that a footnote inserted in Table 3, page 141 would correct this.

Dr. Englund inquired as to whether page 56, line 1 would be altered further with respect to Hematopoietic Stem Cell Transplants and beginning the vaccination at 12 months later because of the new information pertaining to starting at 6 months after with conjugate vaccines.

Dr. Sumaya responded that the section on recipients needed to be reviewed.

Dr. Englund indicated that she would be happy to work with Dr. Sumaya and others to further develop this section, pointing out that any issues could be solved by using more general language.

Regarding the MMR statement, Dr. Meissner pointed out that the statement on CDC website is a much stronger statement than the one reflected in the General Recommendations language. He wondered whether that would be reconciled.

Dr. Kroger responded that the Work Group was considering an editorial change and incorporation of content that is on the CDC website already. This involves the incorporation of language in the section on simultaneous vaccination in the Timing and Spacing section. This will be incorporated on about page 6, line 16. The issue regards incorporation of language to address simultaneous vaccination of MMR versus single antigen measles, mumps, rubella vaccine. The language, which is already on the CDC website, would specifically state that "Administering combined MMR vaccine yields safety and immunogenicity results similar to administering individual measles, mumps, and rubella vaccines at different sites; there is no scientific reason for or benefit to separating the antigens. No credible evidence exists that measles vaccine or MMR vaccine increases the risk of autism. Separating the doses puts children and pregnant women who may be exposed to them at increased risk for these diseases by extending the time children remain unvaccinated. Studies have shown that it is necessary for parents to schedule additional appointments for vaccinations and there is an increased risk that their children may not receive all the vaccines they need."

Dr. Feinberg (Merck) indicated that Merck greatly values the role CDC and ACIP play in putting forward recommendations and policies about the optimal use of vaccines to prevent important infectious diseases. Similarly, Merck takes its role very seriously in terms of developing and supplying vaccines that are optimally suited to meet those public health needs. With respect to the specific issues for optimal prevention of measles, mumps, and rubella infection, Merck appreciates the enhanced guidance that the CDC has come forward with in this regard. Based on discussions that took place during the last ACIP meeting and subsequent feedback Merck received from professional societies and scientific leaders, Merck has decided not to resume production of its monovalent measles, mumps, and rubella vaccines. The company will certainly focus attention on meeting current and emerging growing use for the global prevention of measles, mumps, and rubella with its combination MMR2 vaccine. When questions are received from parents or other interested parties, they will be referred to the useful information provided by CDC, AAP, AFP, and other professional organizations. Similarly, Merck encourages parents and physicians to seek guidance from these groups as well.

It was not clear to Dr. Marcy how / if the acetaminophen DTaP issue was fully addressed.

Dr. Baker responded that this has not been discussed yet. She noted that the serology, for pneumococcus, for example, suggests protective responses in the non-Tylenol® and the Tylenol® groups. To her, this did not appear to be a major issue.

Dr. Langley mentioned that there is a study in adults published in the *Canadian Medical Association Journal (CMAJ)* in 1993 by F. Y. Aoki et al in which healthcare workers. The objective of this prospective, randomized, double-blind placebo-controlled trial was to “evaluate the effects of acetaminophen on the incidence of adverse effects to, and the immunogenicity of, whole-virus influenza vaccine in healthcare workers.” These investigators found no difference in hemagglutinin-inhibition (HAI) antibody titers [Canadian Medical Association Journal, Vol 149, Issue 10 1425-1430, Copyright © 1993 by Canadian Medical Association].

Dr. Baker clarified that ACIP would be voting on the entire document, with the assurance that Drs. Sumaya and Kroger would revise anything voted upon in the language on the website regarding MMR would be incorporated into these general recommendations.

Dr. Sumaya inquired as to whether they needed to allude to the fact that there are emerging though variable data on acetaminophen.

Dr. Baker responded that they had not yet reviewed the evidence.

Dr. Englund pointed out that there was a single paper with a very small number of patients, all of whom received vaccine from one company. While there was some significance, the true clinical significance of having slightly lower antibody titers is not clear. Recent studies show that new vaccines are so much more immunogenic and much less reactogenic than old vaccines, giving every child prophylactic acetaminophen does not make sense anyway. Rates of fever are not common. Therefore, she was comfortable with stating that prophylactic use of acetaminophen with every dose of vaccine is not necessary, and did not think they should refer to the paper.

It seemed to Dr. Baker that because the full committee had not reviewed the evidence, and there was only one published paper related to children, perhaps a better course would be to address this issue on the website information. Questions were being raised because the media was talking about this study. While it was not clear to her how to respond to the media, in terms of the general recommendations she was personally uncomfortable including information about the article.

Dr. Neuzil agreed. For influenza, Q&As are included on the website. This is often how some issues are dealt with when a paper is published. She suggested that CDC take this into consideration.

Dr. Kimberlin (AAP) agreed that it would be wise to continue to evaluate this issue over time, keeping in mind that acetaminophen is also for pain and discomfort—not just fever. Any weighing of scientific evidence would have to take into account whether it is clinically meaningful, but that must be balanced with the definite benefits of minimizing discomfort in babies who cannot tell anyone they are uncomfortable.

Dr. Pickering noted that the general recommendations highlighted other ways to deal with pain aside from administering medication. He suggested removing the sentence about DTP since it is no longer used in this country.

Dr. Hahn (CSTE) pointed out that a major issue regarded the two live influenza vaccines and whether they need a four-week separation.

Dr. Baker agreed that this was a valid issue, but noted that it would be discussed the second day during the influenza session

Dr. Wharton reflected on the lack of harmony with the morning's syncope recommendation. With the stronger recommendation, she wondered what the committee's desire was regarding harmonization with the general recommendation.

Dr. Baker responded that the committee members did not seem to be very worried about that issue, given that there is greater association in adolescents with syncope specific to HPV vaccines. However, she did not believe they thought this required any changes in the general recommendations.

Dr. Curtis's (NCIRD / CDC) understanding was that adverse events have been observed in the vaccines that are generally recommended for adolescents, not just uniquely to HPV vaccine. Perhaps it would be appropriate to include language in the general recommendations that addresses adolescents rather than simply leaving the HPV recommendations to be different.

Dr. Baker also noted that if they get adolescents into the office, they are usually given three injections because they need them all.

Dr. Sawyer favored a statement specifically about adolescents, not about any specific vaccine that adolescents receive.

Dr. Lett thought that if they included a general statement like this about adolescents in the general recommendations, it would apply to mass influenza vaccination clinics. She has heard this type of push-back in attempting to develop state guidelines. That is, people feel that they would be held liable. There was also judgment about when to impose the 15-minute rule.

Dr. Baker agreed that there is a liability issue.

Dr. Zimmerman (University of Pittsburgh) had an HPV syncope case occur within two minutes of administering a dose of vaccine. The recipient was seated, was easy to catch, and recovered well. He expressed concern that imposing a 15-minute wait for every adolescent vaccine would be burdensome in the busy clinical setting. In many practices, there simply will not be enough space to watch every patient for 15 minutes.

Dr. Judson agreed, also noting the difficulty in getting adolescents to actually sit for 15 minutes.

Dr. Cieslak expressed concern that perhaps they were attempting to do too much "on the fly" without reviewing the data.

Dr. Katz inquired as to the current military experience in terms of whether sitting down to be vaccinated and waiting 15 minutes was permitted or possible, for in his day, the military basically pushed everyone through quickly.

COL Cieslak responded that there had been little change in the military, although when he last received his vaccines, he did sit down for them.

Dr. Middleman (SAM) noted that several *MMWRs* had been published on the topic of syncope. There was a death in the last 10 years, so she thought this should be considered a serious issue. This is specific to young adolescents and young adults, and probably has something to do with the way the cardiovascular system responds in this particular age group. Therefore, she expressed concern about not including this information in the general recommendations. While cases do occur in the first 5 minutes, approximately 88% probably occur in the first 15 minutes. She thought it was very important not to minimize this as an issue in this age group, and that the general recommendations should make a statement that it would be prudent to sit down and wait 15 minutes.

Dr. Judson pointed out that 15 minutes was completely arbitrary, and to create a potential liability from arbitrary recommendations was not a good idea.

Regarding the syncope issue, Dr. Kroger indicated that a change made to the recommendation when this section was presented to ACIP in October 2008. The recommendation was to leave the statement as it was in 2006, which stated that practitioners should “consider a 15 minute observation period.”

Dr. Middleman (SAM) disagreed that the 15-minute period was arbitrary. Data from an *MMWR* from the late 1990s, which was updated in 2007, indicated that about 60% percent of cases occurred in the first 5 minutes, while 88% occurred in the first 15 minutes.

Dr. Marcy wondered upon what criteria the decision should be based if the terminology “should consider” was used.

Dr. Hahn mentioned that it is very common in allergy practice to have the patient wait for 30 minutes. To address the issue of capacity, it has been her experience that this is not done while a patient is still in the exam room. They return to the main waiting room where typically a secretary watches them. While this was a compromise, it represented a practical solution.

Dr. Baker thought this was why they should leave such a decision up to the providers.

Alison Rue-Cover (ISO) indicated that CDC recently completed a syncope study. They reviewed the last few syncope reports from January to August 2009 for all vaccines. They found that most of the syncope occurred following HPV vaccine. However, this also occurs following other vaccines, especially if multiple doses of vaccines are given. Serious adverse events are occurring, so CDC contacted providers to ask them for further information about the cases that are not normally reported VAERS. They found that practitioners had a tendency to change their policies after they had just one serious syncope report.

Dr. Sumaya indicated that he was not uncomfortable with the use of the term “strongly consider.” Perhaps they could supplement this with emerging data and a discussion about the higher risk groups.

Dr. Baker pointed out that this might be a nice topic for AAP news, and it is clearly stated in the *Red Book*.

Dr. Bocchini agreed that this would be a good topic, pointing out that the *Red Book* uses Dr. Marcy’s interpretation and language of “should consider.”

Dr. Baker noted that this could also be added to the Q&A about HPV in the CDC website.

Dr. Marcy asked for clarity regarding what the criteria would be for waiting 15 minutes if “considering” it. There must be some implementation criteria for such a consideration.

Dr. Baker responded that adolescents who are at increased risk physiologically, those receiving HPV even if they are getting it alone, and those who are receiving multiple vaccines should be the criteria, given that they are all adolescents. They should definitely recognize that there is clearly a distinction for HPV.

Dr. Marcy thought that this should be clearly stated.

Dr. Curtis thought the concern about the potential liability of somebody falling post-vaccination and sustaining an injury should be the focus rather than the potential liability of observing someone for only 10 minutes rather than 15 minutes. An injury far outweighs any risk associated with a specified observation period.

Dr. Baker pointed out that no matter what ACIP recommended, this would be an implementation issue. Therefore, she thought the terminology “strongly considered” would assist with the caveat that HPV is a much stronger recommendation.

Dr. Iskander reminded the committee that the best data available were from the VSD. These data were presented during the October 2008 meeting by Dr. Julianne Gee, although an *MMWR* has not yet been published. These data show that there is, in fact, an overall secular trend for increased post-vaccination syncope in adolescents. However, no increased risk associated with the HPV vaccine was found. Therefore, consideration must be given to harmonization versus discrepancy in the recommendations.

Dr. Cieslak thought that as a matter of process, it might be better to vote on the package that was presented to them and the vote on some of these amendments as they arose. They seemed complex and there did not appear to be consensus about any of them.

Dr. Temte agreed. He noted that the official data and the time signal were based on a total of 23 patients from VAERS. It was about 52% within 5 minutes of vaccination for TDap, MCV4, or HPV. At 15 minutes, this is about 30% of patients. It turns out that 7 of 10 serious injuries occurred within 15 minutes, meaning that 3 of 10 occurred outside that period. This is a difficult issue and there are insufficient data.

Dr. Baker agreed that they should vote on the general recommendations as presented.

Dr. Kroger reiterated that the language shown on page 28, lines 9 through 18, included a discussion of the epidemiology of syncope and the statement, “Providers should take appropriate measures to prevent injuries of weakness, dizziness, or loss of consciousness occurs. Although syncopal episodes are uncommon vaccine providers should consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve. Adolescents and adults should be seated during vaccination, and the observation period, to decrease the risk of injury should they faint.”

Motion: General Recommendations

Dr. Chilton made a motion to approve the General Recommendations as presented. Dr. Sawyer seconded the motion. The motion carried with 14 affirmative votes, 0 abstentions, and 0 negative votes.

Dr. Pickering noted that Dr. Kroger would be working and Dr. Atkinson on these general recommendations. There will still be an opportunity to review them and collect further comments. This is a very complex document, so perhaps wording can be improved to make it clearer. The plan is to revise, renew, or retire recommendations every 3 to 5 years. The general recommendations included about 5 or 6 recommendations that were very old, but have all been incorporated into the general recommendations for a couple of reasons. One reason is to fulfill the retire, renew, or revise criteria. The second reason is to place everything that is general about immunizations into one location.

Respiratory Syncytial Virus (RSV)

Lance Chilton, MD, Chair Respiratory Syncytial Virus Immunoprophylaxis Work Group

Dr. Chilton reported on the new Respiratory Syncytial Virus Immunoprophylaxis (RSV) Work Group, which at the time of this ACIP meeting had been constituted but had not yet met. The Work Group consists of an excellent group of experts from numerous fields (e.g., infectious disease, virology, pulmonology, neonatology, et cetera). The CDC lead is Gayle Fischer.

With respect to the burden of RSV disease, a study conducted by CDC a number of years ago showed that there was a marked increase in the percentage of childhood hospitalizations attributed to RSV (5.4% in 1980 to 16.4% in 1996) [Shay et al., JAMA, 1999]. Perhaps that has something to do with a decrease in admissions for other conditions, but RSV seems to be connected to approximately 1 out of every 6 or 7 admissions for children to hospitals, approximately 58,000 hospitalizations for RSV disease in children less than 5 years of age [Hall et al., NEJM 2009], and approximately 200 to 500 deaths in childhood per year [Shay et al., JID 2001].

Treatment for RSV / bronchiolitis consists basically of supportive care. Over the years at the University of New Mexico, where Dr. Chilton is from, the treatment has consisted of increasingly larger doses of Albuterol and then no Albuterol. It consisted for a while of Ribavirin and now no Ribavirin. That leaves prevention as the only course.

In the 1960s, an RSV vaccine was prepared by Fulginiti and others in Arizona that had negative effects in that children became sicker after receiving that vaccine. Thus, there was no vaccine at that point. Only in the last few years has there been passive antibody protection through a succession of products. First there was RSV-IVIG, which was called RespiGam® and was made available probably about 10 years ago. Then came Palivizumab or Syngaxis® that was made available shortly after that and replaced RespiGam® completely. Most recently, there is

Motavizumab, which has been submitted by the company manufacturing it as a Biologics License Application (BLA) to the FDA. The anticipated approval of Motavizumab motivated the formation of the RSV Immunoprophylaxis Work Group.

Over the next few months, the RSV Work Group will consider RSV immunoprophylaxis and will follow in the footsteps of the American Academy of Pediatrics (AAP) Committee on Infectious Diseases, which has had recommendations for immunoprophylaxis in place for the last 12 years. The most recent recommendations were published this year and sparked some controversy. ACIP has resources and systems in place to review scientific evidence from medical, public health, economic disciplines. In particular, and economic analysis that was not available to the Committee on Infectious Diseases (COID) can be reviewed by ACIP, so perhaps the RSV Work Group can work in ways that COID cannot. The goal is to develop evidence-based recommendations for RSV immunoprophylaxis that perhaps can be published simultaneously with or shortly after the granting of licensure for Motavizumab.

The plan is for the RSV Work Group to begin conference calls on November 5, 2010 to determine how to go about making recommendations. This is not a particularly easy task, given that the recommendations depend upon economic data, which are much more difficult to evaluate than safety and efficacy data. The proposed RSV Work Group activities are to review the epidemiology of RSV infections, including seasonality and host and environmental risk factors for severe disease; review the effectiveness of prophylaxis; assess the costs and benefits of prophylaxis; identify areas in need of further research for informing recommendations; and draft recommendations for ACIP consideration / decision-making.

Vaccine Supply

Jeanne M. Santoli, MD, MPH
Immunization Services Division
National Center for Immunization and Respiratory Diseases

During this session, Dr. Santoli provided a vaccine supply update for Haemophilus influenzae type b (Hib) vaccine; Hepatitis B vaccine (pediatric and adult); Hepatitis A vaccine (pediatric and adult); Tetanus and Reduced Diphtheria Toxoids (Td) vaccine; Diphtheria, tetanus, and pertussis with inactivated poliovirus vaccine (DTaP-IPV); and Diphtheria, tetanus, and acellular pertussis vaccine (DTaP) vaccine.

There are currently three Hib vaccine products. Sanofi pasteur is currently supplying about 18 million doses of Hib-containing vaccine this year to the US market. That is a combination of the monovalent and combination products. This volume supports a return to the 4th dose and some catch-up. GSK's monovalent Hib vaccine (Hiberix®) is also now available. The estimated supply for the remainder of 2009 is about 4.2 million doses. The vaccine began shipping the week of October 5, 2009, with more than 400,000 doses having been shipped to date. The indication for this vaccine is booster dose only. On 10/18/09, the *MMWR* announced the licensure of this product and encouraged broad catch up, including mass recall where feasible. For Merck's monovalent Hib vaccine, some doses are currently being utilized from the stockpile for Native American children. A limited supply is anticipated to become available in the fourth quarter of 2009, with full availability expected in the first quarter of 2010.

Since March of 2009, both manufacturers of the pediatric Hepatitis B vaccine, as well as CDC's 64 immunization grantees, have been managing provider orders to support judicious vaccine ordering to avoid changing the current recommendations for the product. GSK also brought some additional vaccine to the US beginning in September 2009 in order to enhance the supply. Merck expects their supplies to continue to be limited during the remainder of 2009, but anticipates a return to full supply in the first quarter of 2010.

Merck is not currently distributing its adult or dialysis Hepatitis B vaccines. These products will not be available during 2009, but Merck expects to return to full supply sometime in 2010. The supply of GSK's adult Hepatitis B vaccine in vials is currently limited, but additional vaccine is anticipated in November 2009, with a full supply of products expected in the first quarter of 2010. Alternative products are available, including the syringe formulation from GSK of the monovalent vaccine and their combination Hepatitis A-Hepatitis B vaccine.

The current supply of GSK's pediatric Hepatitis A vaccine is limited. New supply is anticipated in November 2009 and throughout the fourth quarter of 2010, with full supply anticipated by the first quarter of 2010. Currently, Merck is making additional vaccine available to meet demand for this product. Some doses have also been released from CDC's pediatric vaccine stockpiles to help meet demand.

Merck is not currently distributing adult Hepatitis A vaccine. This product will not be available for the remainder of 2009. More information will be forthcoming regarding 2010 availability. GSK's supply of adult Hepatitis A vaccine in both vials and syringes is available to meet demand, as is their combination Hepatitis A-Hepatitis B vaccine product.

The supply of GSK's Tdap vaccine in the vial formulation is currently limited. Additional vial vaccine is anticipated in November 2010, with a full supply expected in the first quarter of 2010. GSK's Tdap syringe formulation and sanofi pasteur's Tdap product are both available as alternatives.

There is currently a limited supply of GSK's DTaP vaccine in the syringe formulation. Additional vaccine is anticipated in November 2009, with a full supply anticipated in the first quarter of 2010. GSK's DTaP vial formulation, sanofi pasteur's DTaP vaccine, and several combination vaccines that include DTaP are available as alternative products.

DTaP-IPV combination vaccine is currently limited. Additional vaccine is anticipated starting late October throughout November and December 2009, with full supply anticipated in the first quarter of 2010. Alternative products include component vaccines (DTaP and IPV). In conclusion, the Hib shortage is resolving, with supply from three manufacturers anticipated in the first quarter of 2010. Hepatitis B supply constraints continue to be managed without the need for interim recommendations, with a return to full supply anticipated for the first quarter of 2010. There are some intermittent outages in products and / or formulations that are on-going for Hepatitis B vaccine (pediatric and adult), Tdap vaccine, DTaP vaccine, and DTaP-IPV vaccine. Sufficient supply of these vaccines to maintain current vaccine recommendations is available using alternative products, but providers may need to change formulations or brands.

CDC's vaccine supply / shortage webpage is updated regularly and can be found at the following url: <http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm>).

Discussion

Dr. Lett requested an update from the manufacturer regarding the specific problems occurring at GSK.

Dr. Quinn (GSK) reported that several of these issues have been formulation-specific, so GSK has experienced more pressure on some of its vial releases. Pre-fills are available. Overall, for the last couple of years, they have kept up a very high inventory and supply to meet the demand of the markets for both Hepatitis A and B vaccines across the board there. These are expected to be short-term production delays, and are not a reflection of any long-term, on-going, or upstream issues. GSK is committed to making sure that distribution is fair and equitable in the public and private sectors, including the VFC. The company continues to address the issues and to ensure that they are limited as much as possible in terms of GSK's ability to keep up with the demands of the market.

Dr. Sumaya requested further clarification regarding the meaning of the words "shortage" and "full supply." He wondered whether demand was relatively static from year to year, or if there were some percentages of increases in implementation in which the supply and demand were growing.

Dr. Santoli responded that "full supply" in general means that supply is sufficient to meet what is known based on historical demand plus what is projected in terms of growth. Returning to full supply would mean a return to the level at which demand was being met. The demand for some of these products is not static. There is generally a fairly constant demand for pediatric Hepatitis B; however, the shortages with Hib vaccine impacted Hepatitis B vaccine in that the demand for certain formulations has increased. For Hepatitis A, that recommendation is still being implemented. Catch-up is still underway, so that does not necessarily have a stable demand. Tdap vaccine is being implemented, so changes are expected in demand for that product. DTaP should be relatively stable, but again, the interaction with the combination products and the Hib shortage has had an impact there. DTaP-IPV was also impacted by the Hib shortage. Thus, demand is not really stable for any of these vaccines.

Dr. Lett inquired as to whether there were plans to discuss seasonal influenza vaccine and whether there are any supply issues.

Dr. Santoli responded that the issues pertaining to seasonal influenza vaccine would be addressed during the H1N1 session.

Meningococcal Vaccines

Introduction

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

In addition to acknowledging the Work Group members, Dr. Meissner took the opportunity to acknowledge the tremendous contribution that Dr. Carol Baker made to this Work Group as previous chair. Dr. Baker set a high standard, which he assured everyone he would do his best to sustain. He also extended his gratitude to Dr. Cohn for many helpful conversations and her patience that enabled him to gain a full understanding of the issues.

Three conjugated meningococcal vaccines are under discussion for use in infants and toddlers in the US, and are likely to be licensed in 2010 / 2011:

- HibMenCY: 4 dose series (2,4,6,12 months)
- MenACWY-Crm: 4 dose series (2,4,6,12 months)
- MCV4: 2 dose series (9,12 months)

The HibMenCY vaccine is manufactured by GlaxoSmithKline (GSK). This vaccine contains polysaccharide from serogroups C and Y and *Haemophilus influenzae* type b conjugated to tetanus toxoid. GSK has submitted a Biologics License Application (BLA) for this meningococcal vaccine to the FDA. The FDA has accepted the file. This vaccine would be administered as a 4-dose series at 2, 4, and 6 months, with a booster dose at 12 to 15 months.

The tetravalent meningococcal ACWY vaccine, MenACWY-CRM₁₉₇, is manufactured by Novartis. This vaccine contains polysaccharide from four serogroups which are conjugated to CRM¹⁹⁷, a naturally occurring mutant diphtheria toxin. This vaccine would also be administered as a 4-dose series at 2, 4, and 6 months, with a booster dose at 12 to 15 months.

MCV4 is a tetravalent meningococcal vaccine containing capsulate polysaccharide from serogroups A, C, Y, and W-135 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 of age, and presently is licensed for children as young as 2 years of age. The new indication for this vaccine would extend use of the vaccine to toddlers as a 2-dose series starting at 9 months and a booster dose at age 12 to 15 months.

The Work Group spent a considerable amount of time assessing the most appropriate role of these meningococcal vaccines for infants and toddlers. Many members of the Work Group were in the practice of pediatrics in the years prior to the introduction of the first conjugate *Haemophilus influenzae* type b (Hib) vaccine in December 1987. During those years, approximately 12,000 cases of Hib meningitis occurred each year, so the severity of meningitis and its complications are well known to many of the Work Group members from this personal experience

In the monthly working group discussions, the severity of meningococcal disease was balanced against a series of factors:

- ❑ The recognition that the incidence of meningococcal disease is at historically low levels, while also recognizing that future incidence of disease cannot be accurately predicted;
- ❑ The fact that group B meningococcus accounts for about 60% of disease in the first year of life and the 3 vaccines under consideration do not include serogroup B;
- ❑ The recognition that infant or toddler vaccination is unlikely to provide serologic protection until 11 years of age meaning that additional booster doses may be necessary;
- ❑ The impact on herd immunity that may come from adolescent immunization and how that may influence the incidence of disease in infants and toddlers is not known. Furthermore, meningococcal colonization rates are low in first year of life, increase in teenagers and peak in people in their early 20s. This means infant or toddler immunization is unlikely to eliminate the need for adolescent immunization.

The goal of this session was to offer a context for considering these three vaccines for infants and children, including the background and context of infant meningococcal vaccination discussion; an update on immunogenicity and safety of HibMenCY (combined *Haemophilus influenzae* type b and meningococcal serogroups C and Y conjugate vaccine); an update on the epidemiology of meningococcal disease in infants and young children; and considerations for use of meningococcal conjugate vaccines in infants.

Following the presentations, the group was asked to begin a dialogue regarding whether infant meningococcal conjugate vaccines should be recommended for routine use, recognizing that there are difficult issues to address. First, this would be one of the very few instances when a vaccine that has been developed for infants would not be recommended by the ACIP for routine use. These vaccines also raise the complex question of whether every vaccine should be recommended for routine use if it is safe and effective, regardless of how low the burden of disease may be.

In terms of continuing issues, results of the NIS teen survey collected from adolescents between 13 and 17 years of age in the US show that vaccination with one or more doses of MCV4 increased from 32% in 2007 to nearly 42% in 2008. Surveillance data show that decreased disease due to serogroup C and Y among adolescents continues to fall. Once MCV4 was licensed for adolescents, it was anticipated that protection would last through late teenage years; however, for high risk groups, a recommendation has been made for a booster dose 5 years after the initial immunization because of waning immunity. With respect to non-high risk individuals, particularly the 600,000 freshmen who live in dormitories and who may have waning immunity, MCV4 was licensed in January 2005 so in a few months, a number of students will be 5 years out from their vaccination. This will be a small number of teenagers with waning immunity in the beginning, but the numbers will increase in time. Consideration must be given to whether a booster dose will be necessary. The last ACIP recommendations for prevention and control of meningococcal disease were published in May 2005, and an update is planned for 2010.

Immunogenicity and Safety of Hib-MenCY-TT Combination Vaccine

Jacqueline Miller, M.D.

**Senior Director, Global Clinical Research and Development
GlaxoSmithKline Biologicals (GSK)**

Dr. Miller presented on GSK's pivotal phase III immunogenicity and safety data for its combination pediatric Hib and *Neisseria meningitidis* serogroup C and Y conjugate vaccine. As was stated, in the US there is currently a universal recommendation for vaccination in adolescents 11 to 18 years of age. There are additional recommendations for those at increased risk from 2 to 55 years of age. Unfortunately, the age group with the highest rates of disease is being missed—infants under 2 years of age. As stated, serogroup B is highly prevalent in this age group. Unfortunately, serogroup B is not preventable by polysaccharide protein conjugate vaccines. In infants, serogroup C and Y represent approximately 70% of remaining disease.

Another consideration, as GSK began to think about how to develop meningococcal vaccines pertained to how these vaccines are used in the rest of the world. An age distribution is similar to that in the US in that infants bear the highest burden of disease, although serogroup Y has not been as commonly observed. Therefore, the majority of provinces in Canada, Australia, and many countries in the European Union (EU) vaccinate infants and toddlers against *Neisseria meningitidis* serogroup C disease.

The vaccine is a combination of three discreet polysaccharide protein conjugates. Each capsular polysaccharide is covalently bound to tetanus toxoid. There are approximately 18 micrograms of tetanus toxoid in the vaccine, and the vaccine is preservative free. It will be given according to a 4-dose regimen starting at 2 months of age, and given at 4, 6, and 12 to 15 months of age. The vaccine was designed to ease implementation by combining with an antigen that children are already receiving. Furthermore, GSK wanted to initiate vaccination against serogroup C and Y as early as possible, and wanted to provide an additional source of Hib vaccine for the US market.

In terms of the clinical development program, to date 9148 subjects have received at least one dose of Hib-MenCY in 13 completed and 3 on-going studies. In this presentation, Dr. Miller focused on safety and immunogenicity data generated in the pivotal Phase 3 study Hib-MenCY-TT-009/010. In addition, she presented key results from Phase 2, including post-dose 2 immunogenicity data generated in the Australian study 007, and the antibody persistence one year after the fourth dose in study 013. To date, over 9000 subjects have received at least one dose of Hib-MenCY vaccine in 13 completed and 3 on-going studies.

In the Pivotal Phase 3 study, 4180 subjects were randomized 3:1 to receive 1 of 3 manufacturing lots of Hib-MenCY or licensed Hib control. For the first three doses, ActHIB, or Hib polysaccharide conjugated to tetanus toxoid, was the control vaccine. To align with the labeled indication for ActHIB, the Hib control vaccine used at the fourth dose was PedvaxHIB, which is conjugated to the outer membrane proteins of *Neisseria meningitidis* serogroup B. All subjects were vaccinated at 2, 4, 6, and 12 to 15 months of age, with routinely recommended pediatric vaccines co-administered. A subset of 695 subjects in the US served as the population for the primary evaluation of immunogenicity. Blood draws were obtained one month

after dose 3, immediately prior to dose 4, and 1 month after dose 4. Routine pediatric vaccines were co-administered.

Three primary immunogenicity endpoints were evaluated. The first was the total immunoglobulin response to the capsular polysaccharide to Hib measured by enzyme linked immunosorbent (ELISA) assay. The standard cutoffs of 0.15 µg/mL and 1.0 µg/mL were evaluated. The 1.0 µg/mL was the primary endpoint. Geometric mean antibody concentrations were also computed. For the serogroup C and Y responses, a functional assay which measured serum bactericidal activity using human complement as the exogenous complement source was utilized. Previously, seroprotection to MenC has been demonstrated to be correlated with titers of 1:4 or greater. In the GSK program, the primary endpoint is a conservative threshold of 1:8, and again geometric mean antibody titers were computed.

With respect to the anti-PRP immune responses at the post-dose 3, pre-dose 4, and post-dose 4 timepoints, the primary endpoint for post-vaccination Hib responses was the percentage of subjects with antibody concentrations ≥ 1.0 µg/mL. The pivotal Phase 3 study had non-inferiority hypotheses for both the post-dose 3 and post-dose 4 timepoints to rule out a 10 percentage point difference between Hib-MenCY and the control group. This statistical criterion was met at both timepoints, with a significantly higher percentage of Hib-MenCY subjects as compared to PRP-TT subjects achieving this threshold at the post-dose 3 and pre-dose 4 timepoints. In addition, the anti-PRP GMCs were significantly higher at all timepoints studied.

In terms of the immune responses to the MenC component of Hib-MenCY, after the first three doses, 99% of Hib-MenCY recipients had hSBA-MenC titers $\geq 1:8$, and 96% of subjects retained this level of antibody at the time of the fourth dose administration. There was an 11-fold increase in GMTs after the fourth dose. Only 22% of subjects in the control group had developed hSBA-MenC antibody titers $\geq 1:8$ by the end of the study. A higher proportion of control subjects, 73%, developed hSBA-MenY titers $\geq 1:8$, which appeared almost exclusively post-dose 4. However, it should be noted that the hSBA-MenY titers are at least two orders of magnitude lower than the Hib-MenCY group, even at the post-dose 4 timepoint. Nonetheless, this observation warrants further investigation.

As a secondary endpoint, IgG specific for the serogroup Y polysaccharide was measured by ELISA. Although 99% of subjects vaccinated with Hib-MenCY developed IgG antibody directed against the polysaccharide capsule at the post-dose 4 timepoint, only 6% of the Hib group did. Additional data indicate that antibodies induced to the outer membrane proteins in PedvaxHIB, which are shared with the MenY strain used in the hSBA assay, led to a low level of hSBA activity.

Regarding safety data, within 4 days after vaccination, local reactions were solicited. In all cases, the rates in the Hib-MenCY-TT group were comparable to or lower than that in the monovalent Hib control. For general solicited symptoms including fever, the rates were comparable between the Hib-MenCY-TT and Hib control group as well. This pattern was also observed when unsolicited adverse events were reviewed. The rates of unsolicited adverse events were also comparable between the two groups.

In terms of key post-dose 2 and antibody persistence data, a study was conducted in an Australian Phase 2 study. Blood samples were obtained 2 months after the second dose. High proportions of subjects achieved the short-term correlative protection 0.15 µg/mL after the second dose in both groups. They were statistically significantly higher in Hib-MenCY-TT versus Hib. The geometric mean antibody concentrations were higher as well. With respect to the meningococcal antigen components, at least 83% of subjects had titers greater than 1:8 after the second dose.

For the US Phase 2 study, one-year persistence data are now available. In the US study, subjects did not receive a fourth dose of PedvaxHIB. Instead, they received their fourth dose of ActHIB. One year after receiving the fourth of either regimen, high proportions of subjects retained the short-term correlative protection greater than 96% and 75% of HibCY recipients retained the 1.0 µg/mL concentration. There was persistence of the meningococcal antibodies as well with 97% retaining MenC antibodies and 84% retaining MenY antibodies.

In summary, the highest burden of meningococcal disease is in children under 2 years of age. Hib-MenCY-TT is immunogenic against MenC and MenY components after the second dose. The anti-PRP responses are non-inferior to licensed Hib after dose 3 and dose 4. There were no immune interferences observed with Pediarix™, Prevnar®, MMRII®, or Varivax®. The persistence of antibodies one year after the fourth dose was demonstrated. The safety profile was comparable to monovalent Hib. Hib-MenCY-TT has the potential to add vaccination against a potentially devastating invasive bacterial disease, disease versus serogroup C and Y without adding shots or medical office visits.

Discussion

Dr. Keitel inquired as to whether there were data from any other studies to estimate responses after the first and second doses.

Dr. Miller responded that the data following the second doses were presented. For the meningococcal responses after the second dose, 94% of subjects developed hSBC titers greater than 1:8 to MenC and 83% to MenY. Data after the first dose are planned as part of a Phase 4 program.

Epidemiology of Meningococcal Disease in Infants and Young Children

Ms. Jessica MacNeil, MPH
Division of Bacterial Diseases
National Center for Immunization and Respiratory Diseases

Ms. MacNeil presented an overview of the epidemiology and burden of meningococcal disease in infants and young children. She explained that meningococcal disease affects persons of all ages; however, the proportion of cases caused by each serogroup varies with age. Meningococcal disease typically has a high case-fatality ratio and causes substantial morbidity among survivors. An adolescent vaccination program began in 2005; however, because coverage levels were very low during the first years of the program, it is still too early to assess the impact the adolescent vaccination program has had on disease incidence.

There are two sources of surveillance data that provide information on meningococcal disease incidence. The first is the Active Bacterial Core surveillance system (ABCs). ABCs is an active, laboratory, and population-based surveillance system that collects data on culture confirmed cases of meningococcal disease in 10 states. Cases in ABC sites can be projected to the US population to estimate incidence; however, because there are so few cases of meningococcal disease annually, there is some variability around these estimates of incidence. To account for this and to provide stability around the estimates, averages are presented from combined years of data. The National Notifiable Diseases Surveillance System (NNDSS) is a passive surveillance system that all states and territories report data to for all nationally notifiable diseases. Because this system collects data for the entire US, actual incidence rates can be calculated; however, serogroup information is very limited in NNDSS. Both of these systems provide valuable and complementary information. Ms. MacNeil used data from each throughout this presentation.

During the 1920s-1950s, incidence rates reached up to 13 cases per 100,000 persons every 8 to 10 years. Beginning in the early 1950s, the pattern of disease shifted to much smaller peaks of disease incidence every 8 to 10 years. Rates of disease have been declining for the last 10 to 15 years. The US is currently at a nadir in disease incidence. The reasons for this sustained low in disease incidence are not known, and it is unknown if the disease will cycle back up in the next few years or if this sustained low incidence may represent another shift in the pattern of meningococcal disease incidence in the US.

Over the last decade, rates of disease have declined in all serogroups, including serogroup B. Incidence has also declined in all age groups, not just among adolescents, who are currently the only age group recommended for routine vaccination in the US. To summarize the current trends of meningococcal disease, rates of disease are low and declines in incidence have been observed in all serogroups and among all age groups.

From 1999 to 2008, there were three peaks in disease incidence: one in infants, one in adolescents, and one among older adults. However, the first peak in meningococcal incidence among infants and young children is higher than rates of disease seen in later peaks during adolescence and in older adults. The proportion of meningococcal disease caused by serogroups A,C,Y,W135 (compared to serogroup B) is lowest in children less than 5 years of age and the proportion increases with increasing age. If the incidence of disease in children less than 5 years of age is broken down further, the greatest incidence in this youngest age group is among children less than 1 year of age. In addition, 50% to 60% of disease in this age group is caused by serogroup B, which remains true throughout the first 5 years of life.

With regard to the estimated annual number of cases caused by each of the three major serogroups for children less than 5 years of age, 50% of disease in this age group occurs in children 0 to 8 months. In the 0 to 8 month olds, serogroup Y is more common than serogroup C; whereas, serogroup C is more prevalent in children over one year of age. However, minus the disease that occurs during the first 6 months of life, which would not be preventable with the use of infant meningococcal vaccines, the maximum number of cases that could potentially be prevented with 100% coverage of a 100% effective vaccine is approximately 88 cases per year.

In terms of the estimated cases of meningococcal disease caused by serogroup C + Y among children 6 to 59 months by year, declines in the incidence have been observed from 2000 to 2008 and the annual number of cases in children 6 to 59 months has decreased 50% during this time. Comparing the number of cases in children 6 to 59 months to cases among adolescents, the absolute number of annual meningococcal cases is similar in both groups. However, the proportion of disease caused by serogroup C + Y is lower in infants than adolescents.

With respect to the 10-year average annual incidence of disease caused by serogroup C + Y in infants compared to adolescents, the absolute number of cases that could be prevented is lower in infants than in adolescents; however, because the adolescent cohort is so much larger in this scenario, the incidence rate in both of these groups is the same. In terms of the estimated number of annual preventable cases using data from just 2005 to 2008, a similar pattern is observed in that the number of cases prevented is less, which is a reflection of the decrease in incidence during the time frame being assessed.

To summarize the data presented on the burden of disease in infants and young children, the overall incidence of meningococcal disease is higher in infancy than in adolescence; however, the burden of disease in young children is higher among 0 to 8 month olds. Additionally, a high proportion of infant cases are caused by serogroup B which leads to a lower absolute number of C + Y cases in infants.

Measuring the severity of cases of meningococcal disease is challenging because surveillance systems are not set up to capture this type of information, particularly long-term sequelae that may not be recognized until long after the hospitalization for acute illness (e.g., sensorineural hearing loss, skin necrosis and scarring, amputation of digits and / or limbs, neurologic complications). Ms. MacNeil presented data that were combined from surveillance systems along with data collected from reports in the published literature to estimate the severity of meningococcal disease in infants and young children (e.g., length of hospitalization, clinical signs of severity, long-term sequelae, and mortality).

Of the ABCs meningococcal cases, 92% were hospitalized and many of those who were not had fatal outcomes. The median length of hospitalization was 6 to 7 days in all age groups analyzed, and the length of hospitalization did not vary by month of age for children less than one year, by serogroup, or by syndrome. Meningitis syndrome occurs in approximately half of meningococcal cases in children less than 5 years, regardless of the serogroup. Typically, survival in children with meningitis syndrome is better; however, the risk of sequelae, like sensory neural hearing loss and neurological complications, is higher.

Based on a study from a multi-center study of pediatric meningococcal disease in the US from 2001-2005, children less than or equal to 5 years of age were significantly less likely to require mechanical ventilation than older children. A higher proportion had hypertension, and purpura was reported in approximately 1/3 of children less than 5 years. However, the mortality rate was greater for children over 10 years of age than it was for children less than 10 years of age. In terms of the frequency of sequelae that were recognized at hospitalization in 146 surviving children, 2 children had amputations, 1 lost all 4 limbs, and 1 had toe losses. Skin necrosis occurred in 14 children with invasive infections, 9 of these children were 4 years of age or less. Unilateral and bilateral hearing loss occurred in 14 patients with meningitis, and all of these were 10 years of age or less and 8 were 2 years of age or less [Kaplan et al., *Pediatrics* 2006, 118(4):e979-84]. With respect to sequelae broken down by serogroup, focusing on children less than 5 years of age, necrosis is more commonly observed in serogroup C + Y cases, while

cases of hearing loss were fairly equally distributed between both serogroup B and serogroup C + Y cases [Updated data January 2001-present. [Personal communication, S. Kaplan].

Data from a study conducted in Quebec, Canada from 1990 to 1994 were included because it is one of the few studies available that provides information on sequelae specifically in serogroup C cases. Based on these data, major complications are less prevalent in younger age groups while minor complications and deaths are fairly similar among all of the age groups [Erickson and De Wals. CID 1998, 26:1159-64].

Long-term neurological sequelae are more difficult to measure and the data are limited to all-cause bacterial meningitis. One of the studies showed that more than 2/3 of patients exhibited neurologic or neuropsychological deficits after acute bacterial meningitis [Merkelback et al., Acta Neurol Scand 2000, 102: 118-123]. The second study showed that nearly 1 in 5 of children who had meningitis as infants have permanent severe or moderate severe disabilities and subtle deficits are also more prevalent [Bedford et al., BMJ 2001, 323: 533-7].

In terms of the number of annual deaths and the case fatality ratio by serogroup for each age group, infants and 1 to 4 year olds have a lower case fatality ratio compared to older ages. Additionally, serogroup Y in these age groups have a relatively low case fatality rate. ABC data estimates that approximately 21 deaths occur annually in children less than 5 years, 8 of which are caused by serogroup C or Y disease [ABCs cases from 1999-2008 and projected to the US population].

According to deaths reported to NNDSS from 2000 to 2008, as well as estimated deaths from serogroup C + Y, the total number of deaths has generally declined, with total number deaths ranging from 19 to 27 per year during this time period, and estimated deaths from serogroup C + Y disease ranging from 8 to 11 per year.

To summarize the morbidity and mortality data presented, up to 15% of cases in less than 5 year olds may have long-term sequelae; however, the most serious complications are less common in infants than in adolescents. Additionally, the case-fatality ratio is lower in infants and young children compared to older age groups. The epidemiology of meningococcal disease is highly dynamic and will need to be monitored frequently for changes in disease patterns in infants and young children. However, at this time, the amount of meningococcal disease that could potentially be prevented with infant vaccination is low. The reasons for this are multi-factorial: current nadir in disease incidence in the US, a low proportion of infant disease is caused by serogroups C + Y, and a large proportion of disease occurs in the first 6 to 8 months of life. Additionally, morbidity and mortality in infants is lower than in other age groups.

Discussion

Dr. Meissner wondered whether the estimate of 18 children who had either unilateral or bilateral hearing deficit or loss might have resolved later, such that the estimate may be high.

Dr. Baker responded that this was during hospitalization before discharge. Almost all of the children in this multi-center study had hearing tests because of the historic association. About 9% of children from studies in the 1980s had unilateral or bilateral hearing loss, so the vast majority in the Kaplan study patients had hearing tests before discharge. She was not aware of data showing whether this resolved. This is a fixed complication. The ataxia resolves, but not the hearing loss.

Dr. Cohn added that good measures have not been found for long-term hearing loss post-hospitalization or many other long-term sequelae that occur after hospitalization.

Dr. Turner (ACHA) noted that in 1997, ACHA recommended that college students consider getting the polysaccharide, with less than 1% of college students vaccinated at that point. In 1999, ACIP made the same recommendation. In the year 2000, 20% of college students were vaccinated. This past fall, it was 62%. While polysaccharide is not supposed to decrease the carrier state, if the administration can say that the stimulus package saved 1,000,000 jobs, he thought he could say that perhaps vaccinating college students in 1997 might have started this decline. It is going to take a few years to figure that out.

Dr. Hosbach (sanofi pasteur) added that the sales for the polysaccharide vaccine in 1999 were close to 1 million doses sold and then steadily increased up to 2005 during which about 2 million doses were administered to the college population. He did not know if it had an impact, but there was certainly a coincidence occurring.

Ms. MacNeil pointed out that incidence fell among all age groups and all serogroups, including serogroup B during that time.

Considerations for Use of Meningococcal Conjugate Vaccines in Infants

Amanda Cohn, MD
CDC / NCIRD / DBD

Dr. Cohn summarized the many issues the Work Group has been discussing over the past year, and the group's considerations for use of meningococcal conjugate vaccines in infants. While a BLA has been filed for HibMenCY, it is important to consider this vaccine in the context of the two additional stand-alone vaccines that have the potential to be licensed in the next one to two years. The goal during this session was to hear ACIP's feedback about the direction of the recommendation, and about any additional information the members may like to review before making a decision on this issue. Cost-effectiveness data being collected on provider vaccine acceptability will be presented at the February 2010 ACIP meeting. Cost-effectiveness has been a major issue during Work Group discussions but the results of the cost-effectiveness analysis are not available at this time. By putting the discussion of cost-effectiveness aside, the Work Group was able to focus on the question of whether these vaccines should be recommended, given the low burden of preventable disease.

Meningococcal disease can cause devastating illness in all ages. While there are groups at increased risk, most cases occur in otherwise healthy people. The initial presentation is similar to viral illness, and it can rapidly progress to meningitis or meningococemia. There are substantial long-term sequelae and mortality, and the Work Group is aware that primary prevention is important.

The data presented by GSK during an earlier session was encouraging, and the Work Group believes that this vaccine will be highly immunogenic and safe. At least 83% of infants after 2 doses and 99% of infants after 3 doses had protective activity. It is also immunogenic against Hib. Mild and local systemic reactions occurred at similar rates to a monovalent Hib vaccine. Although current data show persistence of antibody data one year after the 4th dose, the Work Group members believe that boosting will be necessary to maintain protection until the 11 to 12 year old booster.

The UK experience with MenC conjugate vaccines illustrates the high efficacy of multiple doses of conjugate vaccines, as well as waning immunity even in the setting of herd immunity. The UK schedule for infants during this study was a 3 dose schedule with no dose given after 1 year of life. Therefore, this is not directly applicable. However, there is clear evidence of waning immunity after 3 doses in 2 to 4 month olds and suggestion of waning immunity in children who are vaccinated at 5 months and older [Trotter et al. Effectiveness of meningococcal serogroup C conjugate vaccines 4 years after introduction, *Lancet*, 2004;364: 365-367].

Disease burden is currently lower than at any other time period. While disease incidence in infants 6 to 59 months is similar to incidence in adolescents, the proportion of serogroup C + Y disease in children 6 to 59 months is lower than the proportion of disease in adolescents. Therefore, the absolute number of cases and deaths that are potentially vaccine preventable in infants is lower.

In terms of how the timing of vaccination would coincide with disease incidence, assuming no protection is obtained by infants until after the second dose, in the ideal setting vaccination would be at the peak of serogroup C + Y disease incidence. The third dose would be given as disease incidence was decreasing. This is very different than vaccinating adolescents at the beginning of rise in incidence. While duration of protection for adolescent vaccination is still unknown, the goal is to provide protection during the rise and fall of the disease peak in this age group [ABCs, 1998-2007 average annual estimated rates to the U.S. population].

The US infant program has been very successful attaining high coverage with the recommended vaccines, but infants do not always get vaccinated in the week or even the month they turn the recommended age. When there is coverage with 2 doses of Hib and PCV7 and three doses of PCV7, by the end of the fourth month of life, there is about 78% coverage for Hib and 70% coverage for PCV7. However, 3 dose coverage with PCV7 falls to 60% at the end of the sixth month of life.

Defining "under-vaccinated" in the first 24 months of life as not receiving the vaccine by the end of the month during which it is recommended, NIS data show that only 46% of children received all of their Hib vaccines during the recommended month and only 26% of children received all vaccines during the recommended month [Lumen et al, *JAMA* 2005]. Taking into account that there will be delays in vaccination, many children will be vaccinated not during, but after the period of highest risk. This limits the overall impact that an infant meningococcal vaccine recommendation would have on disease burden. While this is the case for all vaccines, is

particularly important for this vaccine for which overall disease burden is low and the peak in incidence is early in life [ABCs, 1998-2007 average annual estimated rates to the U.S. population].

Data were combined on vaccine effectiveness, anticipated coverage, increase with increasing age, and burden of disease to determine an estimate of the number of cases that may be prevented with a 4 dose infant meningococcal vaccine series, a 2 dose series starting at 9 months, and a comparison to the 11 to 12 year old vaccine recommendation. With the 4 dose series, it was estimated that an infant vaccine would prevent only a quarter of cases that occur in 0 to 59 month olds. An estimated 84 cases and 4 to 6 deaths would be prevented each year. This compares to close to 50% of cases prevented in adolescents and about 100 cases and 11 to 19 preventable deaths [Active Bacterial Core Surveillance Data].

With the understanding that the number of meningococcal disease cases prevented would be low, the Work Group spent a considerable amount of time discussing the programmatic implications of the meningococcal recommendation for infants. While reframing this discussion around the HibMenCY vaccine, the two other vaccines, MCV4 and MenACWY-Crm, need to be considered because the differences between these vaccines are complex. The Work Group discussed the practical aspects of an infant vaccine recommendation and the need to obtain high coverage early in order to protect during the highest period of risk.

HibMenCY vaccine would protect against meningococcal disease in combination with Hib vaccine without adding shots; however, providers would not be able to use other combinations that include Hib vaccine. MCV4 would be a 2 dose series starting at 9 months, which would be half the number of doses, but misses the 6 to 12 month age group at risk. MenACWY-CRM would be a standalone 4 dose series but would add protection against serogroups A and W-135, which is not critical for disease prevention in the US, but may be important for infants who are travelling.

The following table is an attempt to convey the minimum number of shots that would be needed to provide DTaP, HepB, Hib, IPV, and meningococcal vaccine, presuming combination vaccines are used:

	2 months	4 months	6 months	9 months	12-15 months	4-6 years
HibMenCY	2	2	2	0	2	1-2
DTaP-HibB-IPV						
DTaP						
MCV4-D	2	1	2	1	2	1-2
DTaP-Hib-IPV						
HepB						
MenACWY	3	2	3	0	2	1-2
DTap-Hib-IPV						
HepB						

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DEPARTMENT OF HEALTH AND HUMAN SERVICES



HibMenCY has the potential to provide protection against meningococcal disease without adding additional shots; however, it is not straightforward. The vaccines the provider is using before adding meningococcal vaccines will greatly impact how many additional shots are added to the schedule. HibMenCY is not necessarily 4 shots less than MenACWY-CRM as a standalone, for example because there is no 4-month Hepatitis B vaccine and MenACWY-CRM could be used with DTaP-Hib containing combination vaccines for the 12- to 15-month visit.

If meningococcal vaccines are added to the infant schedule, there may be up to 10 vaccines indicated for a 12- to 15-month old child. For several vaccines, there is a time frame during they could be given, especially after 6 months of life. Thus, these vaccines could be spread into multiple visits to limit the total number of shots given, even when using all stand alone vaccines. However, there was concern among Work Group members about the practical aspects of delivering so many vaccines during a short time span and what impact that may have on overall on-time vaccination coverage.

While these programmatic issues are of concern, they could be overcome. However, the Work Group felt that they compounded the concerns of a vaccine recommendation for a disease with such low disease burden. Questions about whether a catch-up recommendation for older children would be needed, and the potential need for a booster shot before the 11- to 12-year old booster vaccine recommendation were also raised.

A cost-effective analysis is in progress and, as noted earlier, will be presented during the February 2010 ACIP meeting. A price point for this vaccine has not been set. There will also be data in February from a provider knowledge and attitude survey of pediatricians and family physicians. Attitudes toward using meningococcal vaccines in infants and practical aspects of adding this vaccine into their practice will be assessed.

While there are no specific data on parental acceptability for meningococcal vaccines, it is known from previous studies and focus groups that there is a spectrum of parental attitudes toward vaccination, which is also related to their perception of disease severity, versus disease occurrence, versus the perception of risk of adverse events. Some parents will move between groups depending upon their experience. For example, if they know a child with meningitis, they will be more likely to consider vaccination. Healthcare providers play the most important role in guiding parents about their vaccination choices. It is also known that meningitis is usually perceived as a very serious illness by parents [Courtesy of Michelle Basket and Alison Kennedy].

A few key questions cannot be answered prior to proposing recommendations: Will the disease incidence cycle back up again or remain low? Will higher adolescent MCV4 coverage provide indirect protection in other age groups? What is the duration of protection of meningococcal conjugate vaccines?

Currently, there is consensus among Work Group members, but there is a difficult balance. There is a strong desire to prevent morbidity and mortality and it is difficult to know that there is a safe and effective vaccine that would likely prevent disease and not use it. Conversely, there is strong recognition of opportunity costs of adding meningococcal vaccines, given the low disease burden that would be prevented by these vaccines. Adding this vaccine may impact on-time vaccination with other vaccines currently on the schedule. There are always rare adverse events associated with every vaccine, but in the setting of low disease occurrence, these events may add to the costs of a vaccination program. The long-term implications of

adding a vaccine with potentially limited impact on disease burden was of concern to the Work Group members.

At this time, the Work Group believes that the ACIP should consider not adding meningococcal conjugate vaccines to the routine infant schedule. Various Work Group members prioritized the reasons for this differently, but the dominant reason pertained to the low disease burden. Other reasons included a large portion of serogroup B disease, the case-fatality ratio being lower among infants, the difficult programmatic challenges, the need to attain high coverage early, the potential for rare adverse events, and the undetermined need for a booster.

The Work Group proposed that that infants at increased risk for meningococcal disease (e.g., asplenia, complement component deficiencies, travelling to highly endemic area) be recommended for vaccination. Importantly, the Work Group feels strongly that flexibility be maintained to recommend these vaccines in the future should the burden of disease increase or when serogroup B vaccines become available. Therefore, disease epidemiology and immunogenicity data will be reviewed on a regular basis and recommendations may be modified in the future.

As the Work Group came to this consensus, they grappled with the question of how there could be a recommendation for adolescents and not for infants. This difference was rationale by several points. Disease rates were 2 to 3 times higher when the adolescent vaccination recommendation was made. A greater proportion of adolescent disease is vaccine-preventable. Mortality and long-term sequelae are lower in infants with meningococcal disease, and there are multiple doses that would be needed in infants compared to a single dose in adolescents.

Dr. Cohn concluded by paraphrasing a Work Group member who made a comment that she thought reflected what many of the members were thinking, "In general, it's difficult for me to not recommend a likely effective vaccine for a serious problem I have worked on for a long time to prevent." That said from a public health perspective, these overall conclusions make sense.

Discussion

Dr. Sawyer noted that when working on the MMRV Work Group, which is another vaccine given at the crowded time between 12 and 15 months of age, there was a lot of discussion about how many doses are really acceptable to parents. There are some older data, largely based on surveys of parents, but the modern version of that is perhaps to examine current practice now that electronic systems are available (immunization registries and electronic medical records) in terms of how many doses most pediatricians and family physicians are giving at a time.

Dr. Pickering noted that there are four other Hib-containing vaccines that this could potentially be in competition with HibMenCY: DTaP-Hib-IPV, Hib-HepB (2, 4, and 12 to 15 months), DTaP-Hib (15 to 18 months), and Hib alone. It seems that the disruption of the schedule would only occur if substituted for Hib vaccine by itself. He inquired as to whether it would be possible to obtain data about these combinations and what is frequently or commonly used so that the members could see the addition of this vaccine, and how disruptive it potentially could be in terms of current vaccines that are utilized.

Dr. Cohn responded that they plan to ask this question of providers. The planned survey will differentiate between providers who use Hib-containing combination vaccines and do not use

Hib-containing combination vaccines, and how adding this vaccine to their schedule would impact their current practices.

Joanne Langley (Canada) wondered whether the committee considered the indirect protective effects of an infant meningococcal vaccination, and whether consideration had been given to a 1-dose option at 12 months. In all of the Canadian provinces, meningococcal C infant vaccine programs have been offered but have not been very effective. For cost reasons, many of the provinces give one dose at 12 months.

Dr. Baker asked Dr. Langley to clarify whether the epidemiology of Canada's infant disease was similar to what has been observed in the US in terms of serogroups.

Dr. Langley replied that it is very similar. Overall, 60% of disease is C and it has the highest case fatality rate.

Dr. Cohn indicated that there is no direct evidence for the indirect protective effects of meningococcal vaccines. Carriage studies suggest that protective effects from herd immunity would potentially be from vaccinating the adolescent age group and not the younger children and infants, who very rarely carry *Neisseria meningitidis* in their nasopharynx. Regarding the consideration of a 1-dose vaccine schedule, there would be no licensed vaccine for a single dose for 12 month olds in the US. The meningococcal conjugate vaccine is licensed for 2 year olds as a single dose, and the ACIP voted to not recommend that vaccine given the high burden of disease occurring prior to 12 months of age.

Dr. Langley clarified that Canada's vaccine is not licensed for a single dose at 12 months either.

Dr. Baker inquired as to whether she was referring to the MCV4 product.

Dr. Langley responded that Canada has 3 monovalent C products.

Dr. Baker asked whether Canada was offering the choice of any three of the monovalents. The Work Group decision in the US for the 2 year olds was based on the data for only one conjugate vaccine, the quadrivalent or the MCV4.

Regarding cost-effectiveness, Dr. Judson pointed out that as the incidence rate continued to decrease, with much of it being serogroup B, it really did not make for a very favorable equation. He wondered if there were better ways to target. For example, they would know who was asplenic at that age, and there would probably be very few of them. They would not know complement levels, and that is important.

Dr. Cohn replied that there would be far fewer asplenic infants under the age of 2 compared to the 2 to 10 year olds. Even children with complement deficiencies often present as toddlers and not as infants for some reason. They develop bacterial infections starting at age 2 to 3 typically.

Dr. Judson wondered whether screening for complement would be many times more expensive than the vaccine.

Dr. Baker responded that the usual situation is repeated infections or first meningococcal infection in children over 6 through adolescence.

Dr. Katz said that the missing link that might make this more acceptable would be a group B vaccine. He wondered whether their colleagues from Novartis or any of the other firms could offer an update on the prospects for a group B vaccine.

Niranjan Kanesa-thasan (Novartis) responded that meningococcal B vaccine is in Phase 3 studies currently in Europe, but the timeframe to licensure will not be until after 2010.

Peter Paradiso (Pfizer) reported that Pfizer is also working on a meningococcal group B vaccine for adolescents and infants. Those are in Phase 2 studies. The timeframe is further out for this product.

Jacqueline Miller (GSK) indicated that GSK also has a meningococcal serogroup B vaccine in development; however, it is in early stage development and the timing would be beyond what was being discussed.

Dr. Marcy inquired as to whether the meningococcal serogroup B vaccines were monovalent or combination.

Dr. Baker responded that they were all monovalent to her knowledge.

Dr. Cohn added that they would likely be licensed as monovalent vaccines, but this is based on the protein membrane.

Peter Paradiso (Pfizer) indicated that the Pfizer vaccine is a common protein antigen. The antigens preserve in all meningococcal, so while they were focused on the meningococcal B initially, they are also assessing reactivity against the other serogroups and hope to see some cross-protection.

Jacqueline Miller (GSK) added that meningococcal B development is much more complicated than the other serogroups. The other serogroups have a single polysaccharide capsule that is a single antigen, so it makes sense to talk about monovalent, bivalent, and so forth. For serogroup B, because they are looking at different antigens, it is likely that any vaccine is going to require more than one antigenic component. Monovalent versus bivalent depends on whether it is a single strain of serogroup B, all strains of serogroup B, or a subset of serogroup B.

Niranjan Kanesa-thasan (Novartis) indicated that Novartis has a recombinant meningococcal B vaccine that is being developed with multiple antigens. This was initially considered as a monovalent for addressing meningococcal B disease, but Novartis also has an early stage program that is assessing it in combination with the MenACWY-CRM vaccine.

Dr. Meissner pointed out that no one had expressed any concern about the proposal made in terms of a limited recommendation. He wanted to ensure that, in fact, it was an accurate reflection of what everyone thought.

In view of the thoughtful analysis of the epidemiology, vaccine development, and cost-effectiveness presentation anticipated in February 2010, Dr. Lett indicated that she was comfortable with the recommendation as proposed.

Joel Ward (UCLA Center for Vaccine Research / Consultant) thought it was admirable that the committee had given so much careful thought to this question, but urged them to remain open-minded. They really did not have a decision to make until there was a licensed product. They were making several assumptions that may or may not be true currently or in the next year. They were making the assumption that there is no protection until the infant series is completed; however, he would not be surprised if there was some marginal protection with the first or second dose. Herd immunity has not been assessed. Over a period of 5 to 10 years, the impact of herd immunity could be important. Within the last 20 years, meningococcal serotypes have changed probably 3 or 4 times. ACIP recommendations often impact future vaccines, which can cause further complications. When the vaccines are licensed, ACIP will also have to deal with a permissive recommendation. Some people may opt to take it even though it costs more and requires an additional dose.

Frank Malinoski (Independent Consultant) expressed surprise that they had not heard anything from the Work Group about maternal immunization, especially given the chair's past history. The epidemiology clearly suggests that there should be a discussion with the manufacturer now rather than later about that.

Dr. Baker responded that the burden of disease in the first 6 months of life, not just for meningococcal disease but some other diseases as well, was worthy of considering maternal immunization.

Day 1: Public Comments

Frankie Milley Meningitis Angels

Hi, my name is Frankie Milley, and I am the founder and National Director of an organization called Meningitis Angels. More importantly, I'm the mother of an only child, Ryan, who I watched go from perfect health to blood coming from every orifice of his body and death in less than 14 hours. Before I go any further, I want to thank this committee for the amazing work that they do every day to save lives. You are the best in the world at preventing vaccine preventable diseases. As you have moved forward to pass recommendations for adolescent immunization against meningococcal disease, and as states pass laws to require them, we've seen a fall in the incidence rate. It's now time to protect the smallest of our children. We know that the death rate can be 6% in disease incidence in infants. We know that maybe 11% to 19% of those end up with serious disabilities—lifelong disabilities that cost millions and millions of dollars in a lifetime.

I want to share with you two of our smallest angels today. They are very close to my heart because in Meningitis Angels, we're like a giant family. We become close in our passion, and our love for each other grows as each day passes. This is Ethan (shared a photograph). At 7 months old, Ethan contracted meningococcal disease. It left Ethan with severe disabilities. He undergoes constant reconstructive surgery of his small and frail little body. His legs were amputated so high up that his family has been told that he will probably never receive prosthetics. This is precious Bella (shared a photograph). Bella was 5 months old. Bella died from meningococcal disease. Before Bella died, she lived 40 days. Her legs and her arms were amputated and her face literally fell off in the pillow of her bed.

I'm asking you over the next few months as you proceed with this committee, and you look at this disease, and the burden, and the death, and the high cost of care for children who possibly live, not to mention the cost to a family who's lost a child—many with an angel end up in financial ruin. They end up in family breakups, and we've even had some that ended in suicide of siblings because they couldn't bear the thought of losing a sibling. This disease does not stop at a dorm door. It does not stop at adolescent age and doesn't just affect the person that contracts the disease. It affects all of us—everybody around those children.

I ask you to look at this disease, meningococcal disease, as a sinking ship with 100 infants and children on it. You have a life raft that you can put 30 to 40 on. Do you save them or do you let all 100 of them go down with the ship? Infants and children have no voice. I believe if they did, they would choose vaccine over deadly and debilitating disease. We, as advocates, a committee that looks at the passing of immunization rules and recommendations, and physicians, have to be that voice. We have to be that voice of reason, we have to be that voice of science, and sadly, sometimes we have to be that voice of economics, but what price can you put on the life of a child? What price can you put on the life of a child like Ethan, who will go through his life possibly with no legs? We have to be that voice and most of all we have to be that voice of protection of the least of us. Thank you.

October 22, 2009

Agency Updates

CDC / CCID / NCIRD

Dr. Melinda Wharton reported that as part of on-going organizational improvement activities at CDC, Dr. Frieden has created a new position of Deputy Director for Infectious Diseases. For those who work in infectious diseases at the agency, this seems like a great opportunity to have a focus for infectious disease leadership within the inner leadership team of the agency. Dr. Rima Khabbaz, known from her leadership of the National Center for Preparedness, Detection, and Control of Infectious Diseases (NCPDCID) and prior to that her work in the National Center for Infectious Disease (NCID), is currently acting as Deputy Director for Infectious Diseases.

In addition, Dr. Wharton reported that the National Immunization Survey (NIS) data for 2008 were published recently in the *MMWR*. Although this may have been referred to in the meeting, the data have not been presented to the committee. There continues to be high series, complete coverage at levels similar to those observed in previous years for the 4/3/1/3/3/1 series of 76.1%, which is similar to that observed in the previous year of 77.4%. Also tracked are the number of children who have received new vaccines, which continues to be very low with a point estimate of 0.6% in the 2008 NIS data. The individual antigen coverage continues to be much higher than the series completed, which is a much more sensitive measure with any dose missed. A decrease was observed in coverage with three or more doses of Hib vaccine in the 2008 data, which is thought to reflect in part the impact of the shortage because the cohorts included in the 2008 data were impacted by the Hib shortages. The Teen National Immunization Survey data have also recently been published, and increases in uptake are being observed in the new adolescent vaccines. Though the desired numbers are not being reached with any of these vaccines, increases are being observed that appear to be consistent with

being in the early stages of program implementation. Continued increases are anticipated over time as those programs are fully implemented.

Center for Medicare and Medicaid Services (CMS)

Dr. Linda Murphy indicated that CMS disseminated a state health official letter on September 29, 2009 outlining exactly what was expected of the states with respect to H1N1. Mentioned in the letter is that any state that reviews its state plan and finds that their non-VFC vaccine administration fee is not adequately covered, may submit a state plan amendment and that CMS would expedite the request. Dr. Murphy is the expeditor. A couple of states have submitted their revised state plan addressing only H1N1, so she was able to turn the request around in 24 hours. However, one state decided to submit a "grocery list" of amendments and used this as an opportunity to make such a request. This slowed down the process considerably, given that she is only responsible for immunizations and had to submit the remainder of the list to her other colleagues. She will not be able to approve the request until the items other than those related to immunizations are approved as well. She requested that those present take the message to their state Medicaid officials that in order to quickly receive approval for an amendment to H1N1 administration fee, they should not include other requests.

Department of Defense (DoD)

COL Ted Cieslak reported that seasonal influenza vaccination is well underway in the military in both Active Duty and dependent populations. Regarding H1N1 vaccine, the dependents within the system (e.g., spouses, children, retirees, non-mobilized National Guard and Reservists, civilian contractors, et cetera) attain their vaccines through the same channels anyone else would. The military received FluMist® at many military treatment facilities on October 5th and have begun to receive injectable forms of H1N1 vaccine. Thus, vaccination of dependents and civilians is well underway. For the Active Duty force, the military has a separate piggyback contract to purchase 2.7 million doses, which was originally designed to immunize the 1.35 million members on Active Duty in the five Armed Services with two doses each. Since learning that one dose is adequate, the Military finds itself in the enviable position of having far more vaccine than they believed they would have. Unfortunately, none of these doses have been received yet. Therefore, the military is in an unusual situation in which its civilian / dependent program is underway, but the Active Duty forces are not yet being immunized. It is anticipated that this will be resolved soon. There is an extensive system in place to monitor for adverse effects of the H1N1 vaccine, and the DoD is working closely with CDC's VSD to do that.

Department of Veteran's Affairs (DVA)

Dr. Linda Kinsinger indicated that the DVA has had its seasonal influenza campaign underway for a month, and is beginning to get H1N1 into its facilities. H1N1 is being obtained through the state route, which is a different way for DVA to obtain the vaccine, but that has been worked out. The DVA has an active influenza-like illness (ILI) surveillance program underway, from which weekly reports are received about the number of cases begin reported. The most recent report indicated that 1.4% of visits were for ILI symptoms.

Food and Drug Administration (FDA)

Dr. Wellington Sun reminded everyone of the recent FDA approvals for Cervarix® and Gardasil®. He reported that a great deal of the FDA's current work deals with H1N1. FDA is working closely with the vaccine industry and the Biomedical Advance Research and Development Authority (BARDA) to expand the supply of H1N1 vaccines, including possible new technologies and expanding age indications for vaccines for existing licensed manufacturers. For example, FDA recently approved one of GSK's vaccines down to age 3 years. In addition, a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting will be convened on November 18-19, 2009 to address 13-valent pneumococcal conjugate vaccine (PCV13); review H1N1 vaccine safety post-marketing surveillance, and consider a seasonal influenza vaccine using insect-cell technology from protein sciences (e.g., influenza vaccine, purified recombinant influenza hemagglutinin).

Health Resources and Services Administration (HRSA)

Dr. Geoffrey Evans indicated that the National Vaccine Injury Compensation Program (VICP) program turned 21 on October 1, 2009. A recent trend is that during the past year, non-autism claims accounted for the most filed in any fiscal year and is being driven now by seasonal influenza vaccine. In the past year, 41% of claims submitted in the past year were for seasonal trivalent influenza vaccine. The next most common vaccines for which injuries have been claimed include DTaP, MMR, MMRV, Td, HPV, and HBV. The trend has really changed and not surprisingly, as of 2007, has had as many claims for adults as children and is now predominantly adults (n=60% of claims). The trust fund stands at \$3 billion. The program brought in \$200 million over the past year. Regarding the autism proceeding, two of the three cases that were affirmed on appeal at the US Court of Claims level have now been appealed to the US Court of Appeals for the Federal Circuit. The third case is expected to be announced shortly as being appealed. The decisions on the level of appeal probably will not occur for another year. Additional funding has been received to add additional vaccines to the Institute of Medicine (IOM) contract. HAV, DTaP, MMR, and meningococcal vaccines have been added to this contract. A new working list of adverse events will be posted on the IOM website for public comment. This project is expected to have a final report sometime in mid-2011.

Indian Health Services (IHS)

Dr. James Cheek indicated that the IHS has a robust ILI surveillance system, using the electronic health record system. Currently, there is a very heterogeneous distribution of disease. Some areas have over 10% of inpatient and outpatient visits that are due to ILI, while others are barely affected. IHS is beginning to get vaccine out into the community, and has been working intensively in Arizona over the last few months, which was one of the earliest and most affected areas in the IHS community. Hospitalization and mortality rates have been documented that are two to three times the non-Indian population in that state. There is concern that this trend will continue. IHS has been in contact with New Zealand, Australia, and Canada which have observed a similar situation in their indigenous populations, with the rates of hospitalization and mortality approximately two to three times that of the non-indigenous populations.

National Institutes for Health (NIH)

Dr. George Curlin indicated that NIH's report would be covered during the H1N1 session, and the he had nothing further to add.

National Vaccine Advisory Committee (NVAC)

Dr. Bruce Gellin reported that NVAC had spent a great deal of time on H1N1, and had carved out vaccine safety and vaccine financing as its spheres of recommendations. He indicated that more would be presented about vaccine safety during the H1N1 session.

National Vaccine Program Office (NVPO)

Dr. Bruce Gellin indicated that NVPO has appointed a Deputy Directory, Dr. Mark Grabowsky. The National Vaccine Plan was updated a year ago. Since then, NVPO has requested that the IOM review the National Vaccine Plan and recommend priorities. IOM has convened a series of five meetings throughout the country on each of the five goals, and their report is anticipated to be available at the end of November 2009. That will offer an opportunity for the next phase of considering a vision for the National Vaccine Plan for the next decade.

Yellow Fever Vaccine

Introduction

Dr. Carol Baker, Chair Yellow Fever Vaccine Work Group

Dr. Baker lamented that this would be her last Work Group chairmanship, given her new role as ACIP Chair. She particularly recognized Dr. Staples and Gershman, the CDC leads on this Work Group, for their incredible assistance.

The charge of the Yellow Fever Vaccine Work Group was to review indications and safety data for yellow fever vaccine; and update and revise the 2002 ACIP recommendations for use of yellow fever vaccine among US travelers. Organizations represented on the Yellow Fever Vaccine Work Group include the following:

- American Academy of Family Physicians
- Centers for Disease Control and Prevention
- Department of Defense
- Department of State
- Food and Drug Administration
- Infectious Diseases Society of America
- International Society of Travel Medicine
- Public Health Agency, Canada
- Academia (Boston Medical Center; Harvard School of Public Health)

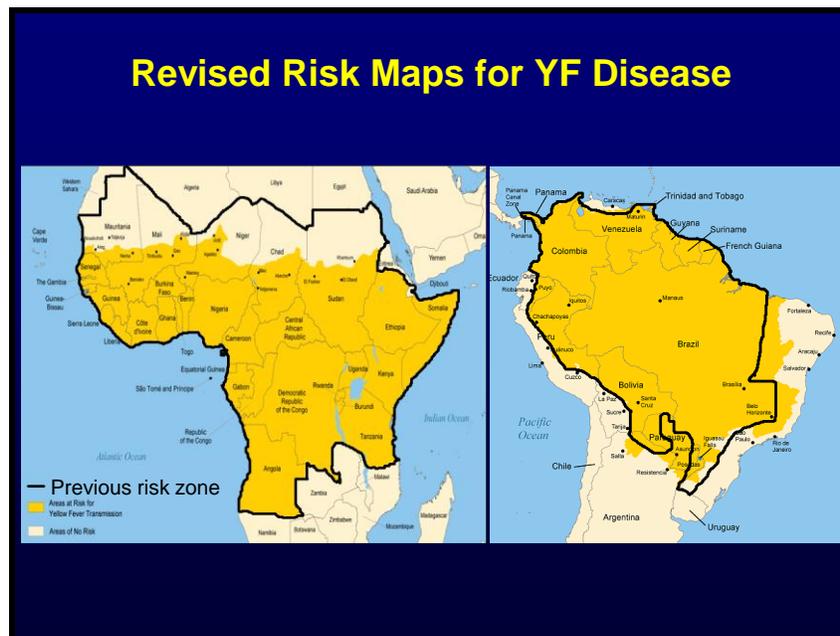
The agenda for the Yellow Fever Vaccine Work Group during this ACIP meeting was to: 1) review epidemiology of yellow fever (YF) and risk of travel-associated YF; 2) review efficacy, immunogenicity, and safety data for yellow fever vaccine; and 3) present, discuss, and vote on revised recommendations for the use of yellow fever vaccine among US travelers.

Revised Recommendations for the Use of Yellow Fever Vaccine in US Travelers

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

Dr. Staples explained that yellow fever is caused by the yellow fever virus (Flavivirus). The virus is transmitted to humans predominantly by *Aedes* mosquitoes. In urban settings, *Aedes aegypti* mosquitoes can spread the infection from human to human. The virus is endemic in 47 countries in equatorial Africa and South America. Infection in humans can cause a range of disease from mild febrile illness to jaundice and hemorrhage. The case fatality rate for severe disease is 20% to 50%. An estimated 200,000 cases and 30,000 deaths due to yellow fever occur each year. However, the majority of these cases are not recognized.

Over the last year, the World Health Organization (WHO) and CDC have been working together to update and harmonize the risk maps for yellow fever disease, which are shown as follows:



Areas at risk for the disease are shown in yellow and outlines from the previous risk zone are illustrated by the black line. The greatest changes occurred along the Northern border of Africa and the Eastern and Southern borders of South America.

Travelers' risk for yellow fever is determined by various factors such as immunization status, location and season of travel, and activities and duration of exposure. During 1970 through 2009, of the 9 cases of YF reported in unvaccinated travelers from the US and Europe, 8 died. The estimated risks of YF for an unvaccinated traveler spending 2 weeks in an endemic area are 50 per 100,000 population in West Africa and 5 per 100,000 population in South America [Monath and Cetron. *Clin Infect Dis* 2002;34:1369-1378]. Decisions regarding vaccination need to weigh these risks for disease against the risks for vaccine adverse events.

Yellow fever vaccine was developed in the 1930s and is a live-attenuated vaccine produced in eggs. It is administered as a single subcutaneous dose, with booster dose every 10 years. There is only one licensed manufacturer in the US, sanofi pasteur. They produce YF-VAX[®], which is derived from the 17D-204 vaccine substrain. Yellow fever vaccine is the only vaccine covered under the International Health Regulations (IHR), which includes the most recent IHR updated in 2005. The intent is to limit the introduction and spread of yellow fever virus into new areas. Proof of yellow fever vaccination is required in many countries for travelers arriving from endemic areas. Some countries require proof of vaccination for all travelers, including those from non-endemic countries such as the US. Per the IHR, travelers without proof of vaccination can be detained for 6 days, which is the upper range of the normal incubation period for the disease.

Regarding yellow fever vaccine efficacy and immunogenicity, no yellow fever vaccine efficacy studies have been conducted in humans. Yellow fever virus neutralizing antibodies are a presumed correlate of protection. In first time vaccine recipients, a low level of viremia usually occurs 3 to 7 days after yellow fever vaccine is administered and resolves in 1 to 3 days later as antibodies develop. Neutralizing antibodies develop in 90% of recipients within 10 days, and in 99% of recipients within 30 days.

With respect to yellow fever vaccine safety data, from 1937 through 2008, over 500 million doses were administered worldwide. From multiple studies of field use, overall the vaccine has been noted to have a good safety profile. Approximately 10% to 30% of vaccinees report mild systemic adverse events following vaccination. Serious adverse events (SAEs) have been reported to the US VAERS at a rate of 4.7 per 100,000 doses distributed. The three main types of SAEs following yellow fever vaccination include anaphylaxis, yellow fever vaccine-associated neurologic disease (YEL-AND), and yellow fever vaccine-associated viscerotropic disease (YEL-AVD). Anaphylaxis following yellow fever vaccine presents most commonly as urticaria with respiratory symptoms (e.g., dyspnea, throat tightness, wheezing). The overall rate of these reactions is 1.8 cases per 100,000 doses. The only known risk factor is allergy to a vaccine component (e.g., eggs, chicken proteins, gelatin). With appropriate medical interventions, these reactions are rarely fatal. YEL-AND is due to either direct viral invasion of the central nervous system (CNS) or an autoimmune-mediated process. Clinical presentations include meningoencephalitis, Guillain Barré Syndrome (GBS), acute disseminated encephalomyelitis (ADEM), and cranial nerve palsies. Onset is typically 11 days post-vaccination, with a range of 3 to 28 days. Almost all cases have occurred after the first dose, with an overall rate of 0.8 per 100,000 doses based on US VAERS data. These SAEs are rarely fatal. YEL-AVD occurs when yellow fever vaccine virus replicates out of control and disseminates into multiple tissues. Similar to the wild-type form of the disease, this often results in multisystem organ failure. CDC is aware of over 50 cases of YEL-AVD that have occurred since it was first recognized in 2001. The typical onset is 3 days post-vaccination, with a range from 1 to 8 days. All cases for which information is available have occurred following the first dose, with an overall rate of 0.4 per 100,000 doses and a case fatality ratio of 64% among US travelers.

Given that yellow fever vaccine is a live attenuated vaccine, there are multiple conditions that are known or suspected to increase the risk of SAEs. Possible risk factors for SAEs include selected age groups (infants, older adults); immunodeficiencies (thymus disorders, HIV-infection, primary immunodeficiency, malignant neoplasm, and transplantation); and immunosuppressive / immunomodulatory therapies (radiation therapy, chemotherapy, systemic corticosteroids, immunomodulatory drugs).

Infants and older adults have increased rates of yellow fever vaccine-associated SAEs. The rates in those < 6 months old of YEL-AND are 50 to 400 per 100,000 doses [Data derived from before YF vaccine universally contraindicated in infants < 6 months]. This observation led to the universal recommendation not to vaccinate children less than 6 months of age. In adults aged 60 and older, the rates of YEL-AND and YEL-AVD are elevated above that for all age groups, with more than a 2-fold increased risk for neurologic disease and a 3-fold increase for viscerotropic disease [As reported to VAERS 2000-2006. Ref: Lindsey et al. *Vaccine* 2008; 26: 6077-6082]. In the 2002 recommendations, the vaccine was contraindicated for infants < 6 months age. Infants 6 to 8 months and adults ≥ 65 years were listed as precautions. In the 2009 recommendations, there is no change for infants and the age for precaution in adults is lowered to ≥ 60 years based on recent VAERS data.

Of the initial 23 YEL-AVD cases, 4 (17%) occurred in persons who had thymectomies performed for thymomas [Eidex RB. *Lancet* 2004; 364: 936]. In 2003, "thymus disorder" was added to the yellow fever vaccine package insert as a contraindication. A review by the Work Group found no evidence of immune dysfunction or increased risk of yellow fever vaccine-associated SAEs followed incidental surgical removal or distant radiation therapy. At the time of the 2002 recommendations, this risk factor had not yet been identified and thymus disorders were not addressed. In the 2009 recommendations, the vaccine is contraindicated for persons with thymus disorders associated with abnormal immune cell function, such as thymomas. However, incidental surgical removal of the thymus or distant radiation therapy is not a contraindication or precaution.

No large prospective studies have been performed in HIV-infected persons receiving yellow fever vaccine. There have been several small studies and case reports of approximately 450 HIV-infected persons receiving yellow fever vaccine, with one YEL-AND death reported in a 54-year old male with undiagnosed HIV and a CD4 count of 108. No other serious adverse events have been reported in these studies, which included at least 11 persons with CD4 counts < 200. The studies have found variable levels of seroconversion with a low of 17% in HIV-infected children in Africa to 100% in case studies of less than 5 persons [Ref: Receveur et al. *Clin Infect Dis* 2000; 31:E7; Kengakul et al. *J Med Assoc Thai* 2002; 85:131; Wilson et al. *Ann Int Med* 1991; 114:582; Tattevin et al. *AIDS* 2004; 18:825; Pistone et al. *BEH thematique* 2007; 25: 238; Ho et al. *AIDS Pt Care STDS* 2008; 22:65; Veit et al. *Clin Infect Dis* 2009; 48:659; Goujon et al. 1995; 4th *Conf travel Med*; Sibailly et al. *PIDJ* 1997; 16: 1177]. In the 2002 recommendations, HIV was a contraindication or precaution to yellow fever vaccination depending upon the patient's clinical status. There was limited guidance to define who should receive the vaccine, and immune reconstitution was not addressed. The 2009 recommendations refer to the new DHHS guidelines for age-appropriate CD4 counts and clinical manifestations to define when HIV-infection is a contraindication or precaution in HIV-infected persons [<http://aidsinfo.nih.gov/Guidelines/>]. For HIV-infected person with immune reconstitution following highly active antiretroviral therapy (HAART), current CD4 counts and symptoms of HIV-infection, rather than CD4 nadir or past symptoms, should be used to categorize the persons risk for vaccination. If international travel requirements are the only reason to vaccinate

an HIV-infected person, rather than an increased risk for acquiring yellow fever, the person should be excused from immunization and issued a medical waiver to fulfill health regulations.

No data are available on the use of yellow fever vaccine in persons with other immunodeficiencies. Primary immunodeficiencies, malignant neoplasms, and transplantation are presumed to increase the risk of yellow fever vaccine-associated SAEs. In the 2002 recommendations, the vaccine was contraindicated in persons with malignancies. However, primary immunodeficiencies and transplantation were not addressed. In the 2009 recommendations, yellow fever vaccine is contraindicated for persons with primary immunodeficiencies, malignant neoplasms, and transplantation. Given that there is no specific information on the use of yellow fever vaccine in these immunodeficiencies, the 2009 recommendations will refer to the ACIP 2009 General Recommendations regarding the use of live viral vaccines in persons with specific immunodeficiencies.

There are minimal to no data pertaining to the use of yellow fever vaccine in persons receiving immune suppressive / modulatory therapies. In the past few years, there has been an increase in the number and use of immunomodulatory drugs such as TNF- α inhibitors (e.g., etanercept), IL-1 blocking agents (e.g., anakinra), and monoclonal antibodies (e.g., rituximab, alemtuzumab). Most immune suppressive / modulatory drugs are presumed to increase the risk of yellow fever vaccine SAEs. The package inserts of most immunomodulatory drugs state that the use of live viral vaccines is contraindicated. In the 2002 recommendations, the vaccine was contraindicated for persons receiving immunosuppressive treatments. Limited guidance was included regarding corticosteroid regimens considered to be immunosuppressive, and immunomodulatory drugs were not addressed. In the 2009 recommendations, yellow fever vaccination is contraindicated for persons whose immunologic response is either suppressed or modulated by current radiation or drugs, such as corticosteroids, alkylating drugs, antimetabolites, TNF- α inhibitors, IL-1 blocking agents, or monoclonal antibodies targeting immune cells. Due to the lack of specific information for yellow fever vaccine, the 2009 recommendations will refer to the ACIP 2009 General recommendations to clarify corticosteroid regimens considered contraindications for the receipt of live viral vaccines.

Other than age and immunodeficiencies, two special populations were reviewed by the Work Group: pregnant women and breastfeeding women. Regarding safety and immunogenicity, no prospective trials have been conducted in pregnant women. Limited data from studies in which women were either inadvertently vaccinated or vaccinated during an outbreak setting suggest that there is no increased rates of major malformation in infants [Cavalcanti et al. *Trop Med Int Health* 2007; 12:833-837] or in increased rates of spontaneous abortions [Suzano et al. *Vaccine* 2006; 24:1421-1426; ³Nasidi et al. *Trans Roy Soc Trop Med Hyg* 1993;87:337-339]. There are limited and conflicting immunogenicity data, which report seroconversion rates between 39% and 98% [Cavalcanti et al. *Trop Med Int Health* 2007; 12:833-837; and Suzano et al. *Vaccine* 2006; 24:1421-1426; ³Nasidi et al. *Trans Roy Soc Trop Med Hyg* 1993;87:337-339]. In the 2002 recommendations, pregnancy was a precaution for the use of the vaccine. These recommendations also stated that if travel was unavoidable and vaccine risks outweighed yellow fever disease risks, these women should be excused from immunization and issued a medical waiver to fulfill health regulations. Also stated was that pregnant women who must travel to areas with high yellow fever risk should be vaccinated. There is no change in the 2009 recommendations for pregnant women.

Since 2007, two YEL-AND cases have been recognized in breastfed infants whose mothers received yellow fever vaccine [MMWR in press; unpublished data obtained from B Flannery PAHO and M Sabourin PHAC]. Both infants were less than 1 month of age and were exclusively breastfed. Both infants developed encephalitis. Yellow fever vaccine virus was recovered from cerebrospinal fluid (CSF) in one infant, and YFV-IgM antibodies were identified in CSF in the other infant. No breast milk was available for testing to confirm the milk as a source, but the mechanism of breastfeeding appeared to play a role in the transmission. Given that it is unknown how many breastfeeding women have been vaccinated without adverse events, the overall risk of transmission of yellow fever vaccine virus through breastfeeding is unknown. In the 2002 recommendations, breastfeeding is a precaution. These recommendations also stated that yellow fever vaccine should be avoided in breastfeeding women; however, when travel of nursing mothers to high-risk yellow fever endemic areas cannot be avoided or postponed, these women should be vaccinated. There are no changes in the 2009 recommendations for breastfeeding women other than noting the two cases of infants developing encephalitis.

To recap, the major changes for the 2009 recommendations are to update the 2002 risk maps for yellow fever disease; include information about 2005 IHR; detail serious adverse events and vaccine safety incidence data from recent information; adjust the adult age precaution to ≥ 60 years; align the language with the General Recommendations for contraindications and precautions; add primary immunodeficiencies, transplantation, immunomodulatory drugs, and thymus disorders as contraindications; and describe new data for pregnancy and breastfeeding.

The proposed 2009 ACIP recommendations for use of yellow fever vaccine are as follows:

“YF vaccine is recommended for persons aged ≥ 9 months who are traveling to or living in areas at risk for yellow fever transmission in South America and Africa.”

“Since serious adverse events can occur following YF vaccine administration, providers should only vaccinate persons who: 1) require proof of vaccination for country entry, or 2) are at increased risk of exposure to YFV.”

“To minimize the risk of serious adverse events, medical providers should carefully consider the contraindications and precautions to vaccination prior to administration of YF vaccine.”

Contraindications for yellow fever vaccine include the following, with updated or new contraindications underlined:

- Hypersensitivity to vaccine components
- Infants < 6 months of age
- Immunodeficiencies
 - Thymus disorder
 - HIV-infection with severe immune suppression or symptoms
 - Primary immunodeficiencies
 - Malignant neoplasm
 - Transplantation
- Immunosuppressive and immunomodulatory therapies
 - Radiation therapy
 - Chemotherapy
 - High-dose systemic corticosteroids
 - Immunomodulatory drugs

Precautions for yellow fever vaccine include the following, with updated or new precautions underlined:

- Infants age 6 – 8 months
- Adults ≥ 60 years of age
- HIV-infection with moderate immune suppression and no symptoms
- Pregnancy
- Breastfeeding

Discussion

Dr. Baker reminded Dr. Staples that dashes should be replaced with the term “through.”

Dr. Keitel inquired as to whether Dr. Staples could comment on the age-specific case fatality ratios, and suggested that perhaps they should be included to help clinicians make a risk-benefit assessment for administration of vaccines to older individuals, particularly in South America. She also requested that Dr. Staples comment on the highly variable seroconversion rates in pregnant women.

Dr. Staples responded that with respect to the seroconversion rates in pregnant women, there are essentially only two studies in which seroconversion was assessed. The first study was conducted in Nigeria of pregnant women in their third trimester, which showed approximately 39% seroconversion. There could be some question in regard to vaccine uptake in that situation. The most recent study was published in 2006 and was in Brazilian women who received yellow fever vaccine during a vaccine campaign. That cohort includes approximately 200 women versus less than 100 in the first cohort. All of the women in the most recent cohort were in their first trimester and did not know they were pregnant at the time of vaccination. Whether the seroconversion is due to just the differences in the settings in which the vaccine were received, or whether it has to do with something related to the trimester the women was in and her ability to seroconvert is not clear. The studies are very different in terms of the timing and where they were conducted. Regarding the case fatality rate for the disease, in endemic areas this is very difficult because South America and Africa have to be treated differently. In South America, there is currently very good vaccine uptake, so most of the population is protected against the disease. The highest risk of acquiring the disease is in unvaccinated, middle-aged men who are forest workers are exposed to the vectors. In Africa, because of

either acquisition of the disease or through previous vaccine campaigns adults are often protected against the disease, children are the most susceptible to the disease. Therefore, it is difficult to determine a specific case fatality ratio in those two groups.

Dr. Keitel asked whether there were data from the pre-vaccine era.

Dr. Staples replied that because there had been worldwide use of the vaccine since 1930, there were very little pre-vaccine data. There are earlier studies, such as one in which Walter Reed subjected people purposely to infected mosquitoes. In those studies, most cases were uniformly fatal.

Dr. Schaffner (NFID) inquired as to whether “medical waiver” was described in the recommendations.

Dr. Staples indicated that it will be described in the updated recommendations, under the specific section for international health regulations. An example of “medical waiver” is included and a cross-reference is made to the Yellow Book, which is updated every two years and may have more pertinent information if there are changes over time.

Regarding persons who are older and who may have been immunized 25 years ago and are now contemplating a trip to an endemic area, Dr. Schaffner (NFID) wondered whether there was a serologic correlate of protection, and whether an internist could submit a specimen of blood to a laboratory to determine whether the individual was still immune and thus could avoid another exposure to yellow fever vaccine.

Dr. Staples replied that it is believed that the risks are lower for those who are receiving repeat vaccinations, particularly for the neurotropic and viserotropic diseases. Monkey studies have been conducted that show a level of protection, which is an LNI of greater than 0.7, but for practical purposes, CDC does perform a neutralization assay in which a level greater than or equal to 20 is considered to be seroprotective. CDC has received multiple samples from clinics for those who received vaccine during their military service who are now older, or who have developed a contraindication. This service is provided free of charge.

Dr. Iskander (ISO) commended the Work Group for a very thorough update and serious consideration of the safety issue. The updated recommendations clearly embody the principle of safety first. He suggested a potential friendly wording change regarding the phrase “consider the contraindications and precautions.” A precaution can be considered; however, a contraindication is “observed.”

Regarding the common scenario of travelers over 60 years of age to South America on cruise lines, Dr. Duchin (NACCHO) pointed out that the risk of anaphylaxis, YEL-AND, and YEL-AVD approximately equal the calculated incidence in a 2-week stay in an endemic area. He thought it would be useful to discuss the cruise scenario specifically in the recommendations in that these travelers clearly are not going to have a very extensive exposure, particularly given the amount of time and energy it takes to determine the need for yellow fever vaccine.

It seemed to Dr. Chilton that the discussion was similar to discussions earlier in the year regarding Japanese Encephalitis (JE) in which the risks and benefits seemed not to have been considered to the extent they are for more widely used vaccines. The risks of yellow fever vaccine seemed similar to the risk for contracting the disease; therefore, it was not clear to him that the cost of vaccinating 100,000 people to prevent 5 cases of disease outweighed the benefit.

Dr. Staples responded that 9 cases were reported; however, this is in light of the fact that yellow fever vaccine has been covered under IHR and there has been a very good uptake of this vaccine versus JE vaccine, which has not had good uptake. The recommendations are also somewhat hindered by IHR. Yellow fever is the only vaccine covered by IHR, and a traveler could be detained at the border for 6 days or potentially turned around at his or her own expense.

Dr. Baker added that yellow fever vaccine was very different from JE vaccine in that people have been turned away, and it is an incredibly expensive situation when that occurs.

Dr. Hahn (CSTE) expressed concern with the first sentence in the recommendation regarding the way it was written; people may read no further and assume that everybody should receive the vaccine. She suggested "recommended for certain persons" or "persons as described below." The second paragraph is limiting in terms of using the vaccine only if absolutely necessary.

Dr. Baker suggested, "Persons 9 through 60 years of age" and being more specific in an additional sentence. She thought the spirit of Dr. Hahn's suggestion could be captured with a writing modification.

Dr. Judson indicated that he was comfortable recommending another dose for someone over 60 years of age who previously received yellow fever vaccine uneventfully.

Dr. Cieslak inquired as to how risk was addressed in the 2009 recommendations, noting that the 2002 recommendations discuss areas listed in the "Bi-Weekly Summary of Countries with Areas Infected with Quarantinable Diseases," which he did not think was being produced any longer. He wondered whether this section was being revised to refer readers to the maps.

Dr. Staples responded that this section was basically rewritten to emphasize the current risk maps and refer the reader to the Yellow Book where the information is updated on the website on a routine basis with respect to which areas are considered to be at risk. There are also ongoing efforts with WHO and CDC to provide even more specific guidance, which will be included on the Yellow Book pages.

Dr. Cieslak concurred with the risk-benefit point made by Dr. Chilton, suggesting that the physician would be well-served to have more discussion pertaining duration of stay and activities that put one at risk for mosquito bites.

Dr. Sun requested that Dr. Staples comment on why immune reconstitution syndrome in HIV was included.

Dr. Staples replied that this was included in the Work Group's general discussion in terms of HIV and an attempt to provide more specific guidance with regard to questions that are posed to CDC by travel practitioners about what to do in specific situations.

Motion: Yellow Fever Vaccine

Dr. Sawyer made a motion to approve the yellow fever vaccine recommendations as presented, with the minor revisions suggested during the discussion to be incorporated. Dr. Temte seconded the motion. The motion carried with 12 affirmative votes, 1 abstention, and 0 negative votes.

Rotavirus Vaccines

**Dr. Umesh Parashar
CDC / NCIRD / DVD**

To refresh everyone's memory, Dr. Parashar indicated that there are currently two rotavirus vaccines that are recommended for routine use in US children. ACIP recommended a pentavalent vaccine in February 2006, and the monovalent vaccine in June 2008. The uptake of the monovalent vaccine is still rising steadily; however, there are limited data on the safety and effectiveness of that specific vaccine at this time. Three years of data have now been accumulated on post-licensure safety and effectiveness of the pentavalent vaccine in US children, which was the focus of this session.

Post-Licensure Monitoring of Intussusception

**Christopher Mast, PhD, MSc
Merck Research Laboratories
Epidemiology Department**

Dr. Mast reported on the post-licensure safety and effectiveness data of RotaTeq® (RV5) available to date. The study population used to evaluate the safety and effectiveness of RotaTeq® is from a large, insured population in the US with a birth cohort of approximately 100,000 children each year. The study subjects are infants enrolled within one week of birth who received RotaTeq® (RV5) and a concurrent group of children who did not receive RotaTeq® (RV5) but received other vaccines. Notably DTaP was used as a reference since it is given on the same schedule (2/4/6). Children were evaluated from 2006 to 2007 period after licensure. A large cohort was also evaluated for historical background rates from 2001 to 2005. Given that this is a large, linked automated medical claims database, the investigators were able to link children who were vaccinated with the medical outcomes of hospitalization and emergency department (ED) visits. This provided a good denominator base to assess safety and effectiveness.

The study design was observational prospective surveillance, assessing the routine use of the vaccine. The sample size specified in the protocol was to have at least 44,000 children who were vaccinated with three doses. The primary outcome of the study was intussusception.

Later, Kawasaki Disease (KD) was added as a defined outcome. Due to the way the database was set up, the investigators were able to evaluate general safety for any medical outcome. There was sequential monitoring (e.g., every quarter) for intussusception and KD, and relative incidence for general safety was also evaluated. The primary protocol follow-up period was 30 days post any dose. An external and independent Safety Monitoring Committee (SMC) was utilized, and there were also two adjudication committees—one to ensure that all of the cases of intussusception were chart-reviewed and confirmed, and the other to adjudicate all cases of KD.

For intussusception, a variety of ICD-9 codes were used to evaluate and determine whether there were any suspected cases of intussusception. Two ICD-9 codes were used to look for KD, and any ICD-9 code that occurred after vaccination that was associated with an ED visit or hospitalization. With regard to comparisons, the monitoring boundary was the primary outcome of the study used to evaluate whether the incidence rate was above what was expected. In addition, there was a concurrent DTaP control group, which consisted of the peers of the children who received RotaTeq® (RV5) but who did not themselves receive it because it was just being introduced. Thus, there was a natural concurrent control group. In addition was the historical DTaP control group. The monitoring boundary, concurrent DTaP controls, and historical DTaP controls were used to monitor intussusception and KD. For general safety, RotaTeq® (RV5) self-controls were used. This was possible because the risk period evaluated was the 30 days following vaccination and there were self-controls in the 31- to 60-day period after vaccination. Historical DTaP controls were also used from the 2004 to 2005 period before the vaccine was introduced.

Over 240,000 infants were evaluated as part of this study. The number of RotaTeq® (RV5) recipients that received at least one dose was 85,150. These were identified quarterly in 2006 and 2007, with follow-up in the database for outcomes through March 31, 2009. This represented 210,071 doses that were evaluated in the database. Of these 85,150 received one dose; 70,998 received two doses; and 53,923 received all three doses. Thus, the protocol sample size of 44,000 was exceeded. The number of concurrent DTaP controls vaccinated in the same calendar quarter was 62,167. A total of 100,000 infants were evaluated before the vaccine was introduced to look for background rates of intussusception during the 2001 to 2005. For the 2004 to 2005, a subset of 40,000 infants were used for historical background rates for general safety.

Regarding the findings of the monitoring boundary for intussusception, 6 chart-confirmed cases did not exceed the boundary 0 to 30 days after any dose, which was close to what would be expected based on background rate alone and well below the statistical monitoring boundary. The safety monitoring committee reviewed this data every quarter, and at the end of the study concluded that the number of cases observed was consistent with the background and nowhere near the monitoring boundary in terms of chart-confirmed cases. RotaTeq® (RV5) was also not associated with intussusception for any risk window or comparison:

RV5 Not Associated with Intussusception For Any Risk Window or Comparison

Chart Confirmed Cases

Controls	Follow-up Window (Days)	RV5	DTaP	Relative Risk		
		Cases / Person-Yrs	Cases / Person-Yrs	RR	95% CI	p-value ¹
Concurrent	0-30	6 / 17,433	5 / 12,339	0.8	0.2 – 3.5	0.507
Historical (2004-5)	0-30	6 / 17,433	3 / 7,807	0.9	0.2 – 5.5	0.562
Historical (2001-5)	0-30	6 / 17,433	5 / 20,938	1.4	0.4 – 6.0	0.378
Concurrent ²	1-7*	4 / 4,571	1 / 3,237	2.8	0.3 – 139.5	0.312

²Notes for 1-7 day window: This was exploratory analysis. Study not designed to detect differences in 1-7 day period
 - RotaTeq recipients: 1 case of IS occurred after Dose 1 for days 1 – 7; 3 cases occurred after Dose 2 for days 1 - 7
 - DTaP controls: 1 case of IS occurred after Dose 3 for days 1 - 7 ¹ one-sided α level of 0.025

An exploratory analysis was also done examining the 1- to 7-day period after any dose, which the study was not powered to examine. However, 4 cases were found in the RotaTeq® (RV5) group and 1 case was found in the DTaP group, with a relative risk of 2.8 and very wide confidence intervals of 0.3 to 139.5 given the small numbers, and not statistically significantly different. Of the 4 cases found in the RotaTeq® (RV5) group, only 1 was following Dose 1.

KD was added to the study after it was added to the label because it was observed in post-marketing reports and the investigators believed it was important to monitor this outcome. At the end of the study, 1 chart-confirmed case did not exceed boundary 0 to 30 days after any dose. That is not significantly different from the background rate and not near the monitoring boundary.

A very rigorous process was used to monitor any health outcome associated with RotaTeq® (RV5) vaccination. The SMC met every quarter to review each significantly elevated or decreased diagnosis to assess possible associations with RotaTeq® (RV5) based on pattern of elevation, clinical judgment, knowledge of the scientific literature, and biologic plausibility. They also assessed clinical significance of health events that might be associated with receipt of RotaTeq® (RV5). At the end of the study, in totality the SMC concluded that none of the specific diagnoses or patterns of diagnoses were a cause of concern or warranted additional follow-up for safety purposes.

Regarding the post-licensure effectiveness monitoring done during the same period, Merck had an interesting ability to compare children who received RotaTeq® (RV5) with those who did not. Using the same database, for the 2007 and 2008 rotavirus seasons, the investigators evaluated 33,000 children who were vaccinated with 3 doses of RotaTeq® (RV5) compared to children in the concurrent DTaP control group, either aged matched in 2006 or calendar and quarter matched in 2007 who did not receive RotaTeq® (RV5) but received other vaccinations. Based on an evaluation of ED visits and hospitalizations, there was 100% reduction of rotavirus-related medical care for ED or hospitalizations, with confidence intervals from 87 to 100. There was a 96% reduction in physician office visits, with confidence intervals from 76 to 100. This basically reflects what occurs when someone receives vaccine or not during the rotavirus season [Wang et al, Pediatrics, In press].

Dr. Mast also shared new data from 2009 from an evaluation of all medical insurance claims in the overall underlying database related to the ICD-9 code for rotavirus over an 8-year period from January 1, 2002 to June 30, 2009. By 2008, a dramatic reduction was observed in the peak rotavirus claims, which was previously report. What is new is that in 2009, the same sustained peak reduction was observed as in 2008. Compared to the average peak in the previous 6 years, this represents a 72% decrease in the seasonal average seasonal peak.

In conclusion, with respect to safety, extensive post-licensure study supports that RotaTeq® (RV5) is generally well-tolerated. No statistically significant association was detected between RotaTeq® (RV5) and intussusception or Kawasaki Disease for any follow-up period or comparison. There appear to be no specific general safety concerns. In terms of impact, RotaTeq® (RV5) is highly effective in routine use in US. Sustained reduction in rotavirus disease during more than 3 years of use in US. RotaTeq® (RV5) continues to provide significant public health benefit.

Continued Surveillance of Pentavalent Rotavirus (RotaTeq®) Vaccine Safety in the Vaccine Safety Datalink Population

**James Baggs, PhD
Immunization Safety Office
Centers for Disease Control and Prevention**

Dr. Baggs reminded everyone that the VSD is a collaboration between CDC and 8 managed care organizations (Group Health Cooperative, Harvard Pilgrim, HealthPartners, Kaiser Permanente Colorado, Marshfield Clinic, Northern California Kaiser Permanente, Northwest Kaiser Permanente, Southern California Kaiser Permanente). Data from over 9 million members is captured annually, which represents 3% of the US population.

Approximately a year previous to this meeting, results were reported from the VSD Rapid Cycle Analysis (RCA) of the RotaTeq® vaccine from May 2006 to May 2008. The study objectives were to monitor for increased risk of intussusception during a 30-day window after receipt of RotaTeq®; and monitor for increased risk of other pre-specified adverse events following receipt of RotaTeq®. The major findings were that 5 cases of intussusception were found within 30 days after RotaTeq® in the computerized data (2 cases after Dose 1, 2 cases after Dose 2, and 1 case after Dose 3). The risk ratios were all close to 1.00 and there was no signal associated with any of the doses. This did not exceed the expected number of cases, and no cases were identified within 7 days of vaccination. This was based on a total of 207,621 doses. Only 2 cases were validated after medical record review, neither of which occurred following Dose 1. The results provided no evidence that RotaTeq® receipt is associated with an increased risk for intussusception or other pre-specified adverse events.

Given the heightened interest in the intussusception outcome with this vaccine, a subsequent analysis was conducted in the VSD to continue surveillance for intussusception occurring at 1 to 30 and 1 to 7 days after RotaTeq® vaccination. In the previous study, 7 of the 8 VSD sites participated. All 8 of the VSD sites participated in the subsequent study. The exposed population was children who received any dose of RotaTeq® with or without other vaccines from age 4 through 34 weeks. The concurrent comparison group was any children who received any immunization, but not RotaTeq®, from age 4 to 34 weeks. The subsequent study included data from May 2006 through October 2009.

With respect to the results of continued surveillance intussusception in the 1- to 30-day window following RotaTeq®, there were 28 exposed cases out of 650,990 visits and 16 unexposed cases out of approximately 351,159 comparison visits. In terms of the results of continued surveillance of intussusception 1 to 7 days following RotaTeq®, there were 6 exposed cases out of 650,990 visits (2 after Dose 1 and 3 after Dose 3) and only 3 unexposed cases out of approximately 351,159 comparison visits. To qualify this, exact Poisson Regression was used, controlling for age strata when appropriate, to calculate the risk ratio for the 1- to 30-day window and the 1- to 7-day window following RotaTeq®. The risk ratios were all close to 1.00 for any of the comparisons: 1 to 30 days following RotaTeq® (RR 0.94; CI 0.49, 1.87); 1 to 7 days following RotaTeq® (RR 1.15; CI 0.24, 7.28); 1 to 30 days following RotaTeq®, Dose 1 only (RR 1.46; CI 0.39, 8.08); and 1 to 7 days following RotaTeq®, Dose 1 only (RR 0.73; CI 0.04, 43.16). When limited to Dose 1, the confidence intervals become quite wide due to the limited power.

In summary, the RCA results provide no evidence that receipt of RotaTeq® vaccine is associated with an increased risk for intussusception 1 to 30 days or 1 to 7 days following vaccination.

Update on 2009 Rotavirus Season

**Dr. Jennifer Cortes, EIS Officer
Centers for Disease Control and Prevention
National Center for Immunizations and Respiratory Diseases
Division of Viral Diseases**

Dr. Cortes explained that the National Respiratory and Enteric Viruses Surveillance System (NREVSS) is a passive lab surveillance system that provides real-time data in the form of weekly reporting by virus and test type, including number of specimens tested and number of positive tests. There are no clinical or demographic data with this system. The reporting year is from July to June, and a median of 67 laboratories have been reporting rotavirus annually since 2000.

For this analysis, the 2008-2009 reporting year was examined and compared with the 2007-2008 reporting year, and also with the median of the 2000-2006 pre-vaccine baseline years. The 2006-2007 transitional year was excluded. Timing, peak, and duration of rotavirus season were assessed. Rotavirus testing practices and test results were also assessed by examining the total number of tests performed and total number of rotavirus positive tests obtained. This was also stratified by region.

With respect to the proportion of tests positive for rotavirus by week of year [NREVSS, July 2000-June 2009], although the 2008-2009 season was slightly longer and had a higher proportion of positive tests than 2007-2008, both post-vaccine seasons were substantially later in onset, shorter in duration, and diminished in magnitude when compared to the baseline.

In terms of reduction in the number of positive rotavirus tests from the pre-vaccine baseline by region [NREVSS, July 2000-June 2009] in each year, there was a reduction of approximately 60%. Uniquely, the West is the only region that in the 2008-2009 season there was an increased reduction compared to the 2007-2008 season. Moreover, the reduction during 2007-2008 in the West was less than in the other regions.

In conclusions, the 2008-2009 rotavirus season continued to have later onset, later peak, and shorter duration compared to pre-vaccine baseline. There was a persistent decline in the number of rotavirus positive tests. There were regional variations, including the largest reduction in the West. Continued monitoring is needed to better characterize rotavirus vaccine impact and data pertaining age and vaccine status of rotavirus cases, circulating strain types, and field vaccine effectiveness. An *MMWR* will soon be published that will further detail the findings of this analysis.

Discussion

Dr. Pickering pointed out that one of the differences that may account for the 2007-2008 and 2008-2009 seasons was serotype differences, and inquired as to whether information was available on serotype differences between

Dr. Cortes responded that there are preliminary data from the New Vaccine Surveillance Network (NVSN).

Dr. Parashar added that they are just beginning to receive strain data for this season. During this season and the previous season, there appears to be an increase in the proportion of cases caused by G3 strains. Although data are still coming in, G3 appears to be the more dominant strain for this season, which did not occur in pre-vaccine years. He cautioned against rushing to the conclusion that this increase is related to vaccine. A study was conducted at Texas Children's Hospital with Dr. Baker last year during the rotavirus season in which the predominant strain was G3, in which they found that the vaccine had a very high effectiveness comparable to the clinical trial. This issue will continue to be monitored.

Regarding the analysis of the effectiveness of 3 doses, Dr. Marcy wondered whether there were any subsets of 2 doses and their effectiveness.

Dr. Mast responded that they are in the process of evaluating the less than 3-dose effectiveness; however, he did not have that data ready to share at this point.

Dr. Temte reported that Wisconsin has been able to monitor the uptake of rotavirus vaccine through its registry. Approximately two-thirds of infants are well-covered. During that time, they have witnessed an approximately 60% to 70% reduction in surveillance detections and have realized about an 82% reduction in hospitalizations for rotavirus-coded discharges. More interestingly, they have assessed visitation rates for all-cause diarrhea in clinics associated with his department, which has approximately 350,000 visits per year. Over the 3-year period between 2006 to 2008, they have experienced a 50% reduction in visits for children under a year of age for all-cause diarrhea; a 25% reduction in children from 1 to 4; absolutely no change between 5 and 64 years of age; and a 25% reduction in those over age 65. Whether these are all linked is unknown, but this is a very impressive and rapid change in clinical behavior.

Dr. Meissner pointed out that most Kawasaki Disease occurs after one year of age. He wondered whether the expected background rate of 1 to 5,000 was corrected for the expected background rate for children in the age group receiving the rotavirus vaccine.

Dr. Mast responded that there is little good data on the incidence of KD in younger children; however, the best background rate available was used when the study was begun, which was from a study conducted in a managed care organization that found a background rate of 20 per 100,000. In their own database, they were able to consistently monitor the rate of KD. They assessed children under six months of age, and even though the sample size was small, the background rate was about the same. Again, caution should be taken because the numbers are small and this is a very rare disease, but in the data examined it was also about 20 per 100,000.

Dr. Chilton wondered whether there were data on the dosing of this vaccine later than the recommendations (e.g., after 8 months). If not, and there are no data suggesting that there is an increased risk of intussusception with this vaccine, he wondered whether the last date could be relaxed so that the vaccine could be given to more children later in their first year of life.

Dr. Parashar responded that they are very interested in generating the data on both dose 1 given later than its recommended cutoff, which was initially 12 weeks and is now 15 weeks, and for the full series being given later than the recommended cutoff. The vaccine is being given on time, meaning that practitioners are adhering to the recommended schedule. Therefore, it is not possible to generate adequate data to be able to indicate whether the doses given outside the range are safe and effective. That being said, once enough data are accumulated on safety within the recommended ages, that factor can perhaps be used to open the age window. This discussion has been on-going, and it is a matter of having sufficient evidence to go that route. That data was used in part to recommend the 15-week cutoff from the original 12-week cutoff.

Dr. Katz (IDSA) inquired as to whether there were any data on effectiveness of vaccine when used in resource-poor nations.

Dr. Parashar responded that Dr. Neuzil had been spearheading clinical trials of the vaccine with both of the manufacturers in developing country settings.

Dr. Pickering indicated that Dr. Neuzil would be calling in at some point during the day.

Given that those data had been presented at some meetings, Dr. Parashar reported on the summary results from the clinical efficacy trials. Given the potential concerns with oral vaccines in developing countries, both vaccines were tested in resource-poor settings of Africa and Asia. In general, their efficacy has been lower than what has been observed in industrialized and middle income countries, which is not unexpected. Efficacy has ranged by setting from 50% to 75%. Clearly, in settings with high disease burdens and background rates, even a moderately efficacious vaccine in terms of absolutely disease prevented has a substantial impact. That was one of the reasons in considering these data that WHO issued a global recommendation for rotavirus vaccine use in April 2009. There are also some exciting data on impact from settings in Latin America. He requested that Dr. Richardson comment on the data from Mexico.

Dr. Richardson (NIACCHO) responded that perhaps in February 2010, they could present the details of these data. There is a remarkable decrease in mortality from gastrointestinal disease, both in children under 1 year of age and in children less than 5 years of age. The hospitalization rate has not decreased much, but the mortality rates from diarrheal diseases are substantially decreased.

Indicating that he was not familiar with the NREVSS surveillance system, Dr. Schaffner (NFID) wondered in the most recent year what the testing practices were, and whether it was possible that the denominator of tests had increased substantially, which might have created a surveillance artifact.

Dr. Cortes responded that this was taken into consideration. In terms of number of tests performed by region, when considered together, there is not much of a difference from the baseline or between the two years. However, by region there are some differences. When the percent change in the number of tests is compared with the percent change in positive tests, even though there were variations, it was not enough to account for all of the decrease in positive tests.

Dr. Schaffner (NFID) inquired as to whether Dr. Cortes had any data on vaccine uptake over time, the proportion of infants protected, and any speculation about what the difference in the two seasons was.

Dr. Cortes replied that there are preliminary data from this season from their sentinel immunization system that includes 8 sites. For last year, at the end of March 2008, uptake was approximately 60% and this year it has increased to approximately 70%. Again, these data are preliminary, but an increase is shown. However, it is still below levels of DTaP and Prevnar®, which exceed 80% in most sites.

Dr. Baker inquired as to whether that was uptake of 3 doses.

Dr. Cortes clarified that this was one dose. There has been a slight change in the way that this is assessed because of the ACIP recommendations changed. For 2007-2008, they examined 1 dose in children by 3 months of age, and this year are assessing 1 dose by 5 months of age. That has to be taken into consideration as well.

Dr. Whitley-Williams (NMA) asked whether there were any data on the cost savings as a result of the reduction in the number of rotavirus cases. She also wondered whether the coverage rates or uptake had been assessed by ethnicity, and if there appeared to be any disparities in the burden of disease.

Dr. Cortes responded that they are assessing cost savings in a large administrative database that appear to show some cost savings. With regard to ethnicity and difference, there are preliminary data from the Healthcare Cost and Utilization Project (HCUP) database that assess rates of disease. While there have been reductions in the rates of disease, it does appear that there is still a higher rate in African Americans in the lowest age groups of children who are eligible for vaccine. Nevertheless, all races have shown a substantial reduction.

In the effectiveness study in which vaccine effectiveness by three doses was assessed, Dr. Mast indicated that they examined the reduction in hospitalization and costs associated with hospitalization. Obviously, with 100% reduction there was 100% reduction in medical costs associated specifically with rotavirus in that study. So, there were significant cost reductions. That is consistent with the cost-effectiveness analyses that were conducted when the vaccine was first licensed. Regarding the question of evaluating the safety of RotaTeq® for those children who received it later, very few children receive the vaccine late and there was a very small number of children in Merck's own database who received it after the 32-week schedule. There were no cases of intussusception after the third dose in Merck's study, so they are not able to evaluate that.

As someone very involved in some of the work done when the first rotavirus vaccine was withdrawn from the market in identifying intussusception in Minnesota, Ms. Ehresmann stressed how wonderful these presentations were and how delighted she was to see this information and the positive impact of the vaccine.

Dr. Offit was on the Rotavirus Work Group when the original RotaTeq® recommendations were made. The thinking at the time regarding the first and third dose restriction ages was because they were fearful that if they went outside the Phase III trial, they would push more vaccine into the second half of the first year of life when intussusception occurs and there would be coincidental associations. Therefore, they decided to wait until there were more safety data. There are now three more years of data, which are reassuring. When this vaccine first rolled out, for many clinicians the first and third dose restrictions were burdensome. He wondered whether it remained the case that physicians were concerned about administering the vaccine a week beyond the dose 1 or a week beyond the dose 3 recommendation. If this is a problem, they should decide what the endpoint would be for being reassured that this vaccine does not cause intussusception. If they were waiting for off label use, they would be waiting a long time since there is very little off label use.

Dr. Parashar responded that this is a matter of determining that there are enough data to suggest that the vaccine does not cause intussusception. Given that this is such an uncommon event, despite the reassuring data they heard during this session, risk of low magnitude intussusception cannot be ruled out. If a confidence bound was put around the current estimate of risk, it is a relative risk of about 6 or 7 after the first dose. Lower risk remains a consideration and will continue to be examined. That was not to say that they should not engage in the discussion regarding risk and benefit, considering the possibility of a lower level risk. This discussion began when they were harmonizing the recommendation for pentavalent and monovalent vaccine and indeed revised the initial 12-week cutoff to the 15-week cutoff, so the recommendation was somewhat relaxed. Given that the vaccine is now in routine use, the incremental increase by relaxing more than 15 weeks is not going to be too much. With DTaP, at 15 weeks about 94% of the first doses are given. An increase of about 4% to 5% would be observed in coverage, but it will not be that marked as an initial catch-up campaign for example. However, the point is valid and will be assessed.

Dr. Offit inquired as to whether they had a point in mind at which they would feel comfortable that there were enough data to show that this vaccine does not cause intussusception.

Dr. Chilton indicated that a study was conducted in Philadelphia regarding the restriction on RV5 being given related to age at which DTaP was given. An increase in the availability of RV5 to children in that dataset related to the expansion of the age group from 12 weeks to 15 weeks. There may be data from elsewhere with respect to how much the current restrictions decrease the amount of rotavirus vaccine that could be given if there were an expansion of the age category. Anecdotally, in his experience, it is primarily premature infants who are released from the nursery later than 3 months of age who then are possibly eligible for the first dose but do not get the third dose in on time according to the current recommendations.

Dr. Kuter (Merck) responded that Dr. Chilton was correct that in the first year of use in Philadelphia the off label use for first dose was approximately 20%. However, those numbers have decreased substantially with increased education and use of the vaccine. The best estimate, not only from the data that Dr. Mast showed, but also from the VSD, is that off label use for first dose is approximately 10%. Regarding the third dose, the best estimate is 2% to 3%.

Regarding Dr. Katz's question about efficacy data in resource-poor countries, Dr. Friedland (GSK) reported that at GSK, in addition to field efficacy studies in South Africa and elsewhere, GSK continues to conduct vaccine effectiveness studies in Latin America, Asia, and other resource-poor countries. The data are very reassuring in all of these countries where the vaccine is being widely used.

13-Valent Pneumococcal Conjugate Vaccine (PCV13)

Introduction

Dr. Mike Marcy, Chair Pneumococcal Conjugate Vaccines Work Group

Dr. Marcy reported that since the last ACIP meeting in June 2009, the Pneumococcal Vaccine Work Group has been discussing the 13-valent pneumococcal conjugate vaccine (PCV13) via several conference calls in which policy options for the use of PCV13 when FDA approval of licensure occurs. As a reminder, following introduction of the PCV7 vaccine, the decrease in invasive pneumococcal disease due to PCV7 serotypes was dramatic, unmasking or revealing a large percentage of disease due to six other serotypes. The result was Wyeth's development of PCV13, the 13-valent vaccine, which extended the serotypes to types 1, 3, 5, 7F, 6A, and 19A.

Topics under review by the Pneumococcal Work Group were largely three-fold. The group discussed the immunogenicity and safety of the 13-valent vaccine in terms of primary immunization, transition from the 7-valent to the 13-valent when available, and catch-up options for children with incomplete immunization. Cost-effectiveness in terms of the burden of invasive pneumococcal disease, the public health impact of that disease and the vaccine's prevention thereof, and the economic impact of the use of the vaccine were also discussed. In addition, Dr. Nuorti developed some draft recommendations and an immunization schedule for the full ACIP's consideration. It was the Pneumococcal Work Group's hope that the information provided during this session would be adequate for ACIP to make a decision regarding use of this vaccine should it become available in December 2009.

During the course of the Work Group's discussions, the H1N1 issue arose and it became quite clear that the 0 to 4 year old age group for which the vaccine is directed, was prominent in the morbidity of disease due to the H1N1 virus as well as infection and hospitalizations. The group felt that this increased the importance of getting the 13-valent vaccine into the public domain as quickly as possible. A recent *MMWR* revealed that in 22 fatal cases, only one of whom was 2 months of age and could not have been altered too much by the use of the vaccine, there were 7 children between the ages of 2 months and 15 years of age. The important issue was that the bacterial co-infections that were associated with the H1N1 infection leading to fatality were in large part pneumococcal. The lung tissues that were cultured showed 10 patients with *S. pneumoniae*, 7 with *S. aureus* (MRSA), 6 with *S. pyogenes*, 2 with *S. mitis*, and 1 with *Haemophilus influenzae*, and 4 with multiple pathogens (*S. pyogenes* + MRSA; *S. pyogenes* + *S. pneumoniae*; *S. pyogenes* + *S. mitis*; and *S. aureus* + *H. influenzae*) [*MMWR*; October 2, 2009 / 58(38);1071-1074].

The pneumococcal issue is an important one, and one that the Work Group hopes will be resolved with the introduction of the PCV13 when it becomes available. It is hoped that there will be licensure by the end of the year. The potential role of PCV13 in reducing secondary bacterial infections complicating H1N1 influenza may be mitigated to some extent to some extent by release of that vaccine.

Update on PCV13 Licensure Status and Immunogenicity

Dr. Peter R. Paradiso
Vice President, Scientific Affairs
Wyeth / Pfizer

Dr. Paradiso reported on the transition from Wyeth to Pfizer, the transition from PCV7 to PCV13, the new serotype catch-up with PCV13, and the supply of PCV13. The Pfizer purchase of Wyeth was completed the week prior to this ACIP meeting. Dr. Paradiso quipped that the pneumococcal vaccine program and he have both now been a part of four different corporate entities over the last 20 years. He assured everyone that Wyeth's vaccine business and excitement about vaccinations is unchanged. Pfizer now has a new business unit that is focused on vaccines. The company is excited about the introduction of the 13-valent vaccine, as well as the portfolio of vaccines in general.

Regarding the transition from PCV7 to PCV13, the indications being sought for unvaccinated children are the same schedule as for PCV7. For children who have started on PCV7, PCV13 can be substituted at any point in the immunization schedule. This is not a major issue in the US, given that the vast majority of children have received the 7-valent vaccine, so the unvaccinated population over 12 months of age is very small. The PCV7 serotypes are common in the two vaccines in terms of the conjugation chemistry, the carrier, and the quantity of vaccine, and the 6 new serotypes in the 13-valent vaccine are similar in terms of the carrier, the conjugation chemistry, and the characteristics. The safety database of those two vaccines in comparison have show to be quite the same. Because of the commonality of the two vaccines, it is believed that the transition can be made at any time in the schedule, which will make for an easier transition. A single dose of PCV13 as the booster dose in the second year of life (12-15 months) will induce a response to the 6 new serotypes in over 90% of the children. One dose of PCV13 appears to be sufficient to immunize against the 6 new serotypes in

children >12 months of age. This is an important point in terms of the catch-up immunization program.

A number of situations will be observed when the 13-valent vaccine is introduced in that children will be at various stages of their Prevnar® immunization program schedule. They will have already received 1, 2, 3, or 4 doses of the 7-valent vaccine, and then can transition to the 13-valent vaccine. The following illustrates the various transitions that could occur, including the last one which is children who have been fully immunized with Prevnar® and are now in the older age group, who need to be protected against the 6 new serotypes in the vaccine:

Infant				
2 mo	4 mo	6mo	> 12 months	
7v	13v	13v	13v	--
7v	7v	13v	13v	--
7v	7v	7v	13v	--
7v	7v	7v	7v	13v

One of the important characteristics is that the data suggest that one dose of the 13-valent vaccine induces immunity to the 6 new serotypes in children over 12 months of age. When Prevnar® was introduced, the evaluation of how many doses to use in older children was to assess the immune response in older children and compare that to the response after 3 doses of the vaccine in infants. The following quote is from the label showing how the comparison was done, "GMCs attained using the various schedules among older infants and children were comparable to the immune responses . . . after 3 doses" [PCV7 package insert]. That was based on the efficacy data available at the time from Northern California in children who had received only 3 doses, and that is supported by effectiveness data that has been collected since then, as well as efficacy trials with prototype vaccines that do not use a booster dose. There is confidence that the comparison to the post-infant series is an appropriate one. When Prevnar® was licensed, several of serotypes in children 12 to 24 months did not achieve a good response with 1 dose, so it was necessary to administer 2 doses of 7-valent vaccine in that age group.

With regard to the determination of the number of doses required for children >12 months of age for the 6 new serotypes, like some of the original 7, one dose appears to be sufficient for inducing immunity. The CDC case-control study showed 93% and 96% effectiveness in children 12 to 23 months after 1 or 2 doses, respectively. Trials of PCV9 in South Africa and Gambia show efficacy after 3 doses with no booster. The effectiveness of PCV7 in Australia without a booster dose showed a 90% reduction in <2 year olds and an 82% reduction in 2-14 year olds.

In a transition study conducted in France, the schedule was 3 doses at 2, 3, and 4 months of age with a booster dose at 12 months of age. The French Study had three arms: 1) An arm in which children received all of their doses as PCV7; 2) An arm in which children received all of their doses as PCV13; and 3) A Mix-Match arm in which children received 3 doses of PCV7 for the primary series and a dose of PCV13 for the booster dose.

Regarding the IgG antibody response to the 6 new serotypes (e.g., anti-polysaccharide specific antibody) post dose 3 in infants versus post dose 1 in toddlers, there is a greater response to 1 dose in the 12-month old group when compared to the 3 doses in infants. This passed the criteria showing that a dose would give a response that was comparable after 3 doses in infants. That is, antibody responses following a toddler dose of PCV13 are non-inferior to that achieved after infant series with PCV13 [Kieninger et al, 2008; 48th Annual ICAAC / IDSA Annual Meeting, Washington DC – 006].

With respect to the opsonophagocytic activities (OPA) antibody response to the 6 new serotypes, with a 4-dose series in the 13-valent vaccine group versus 1 dose in toddlers, there was a generally as good functional antibody response in children after receiving 1 dose than after 4 doses for the 6 new serotypes [Kieninger et al, 2008; 48th Annual ICAAC/IDSA Annual Meeting, Washington DC – 006]. Like some of the original Prevnar® serotypes, these 6 serotypes induce a good response with 1 dose in the second year of life and beyond.

The second study was known as Study 3011, which assessed tolerability of PCV13 in children >15 months of age after having received the 7-valent vaccine. The primary objective was to assess the pneumococcal immune responses induced by 13vPnC when measured 1 month after the last scheduled dose in each age group. The safety objective was to evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence rates of local reactions, systemic events, and adverse events.

There were two groups: 1) Group 1 was >15 months to < 2 years of age (n = 125) at the time of enrollment; and 2) Group 2 was ≥ 2 to < 5 years of age (n = 182) at the time of enrollment. Both groups had to have received at least 3 doses of Prevnar® at the time of enrollment. Group 1 received 2 doses of 13vPnC administered at least 56 days apart, while Group 2 received 1 dose of 13vPnC. In terms of disposition of the subjects, 37 subjects in Group 1 had received 3 doses of 7-valent vaccine prior to receiving the 13-valent vaccine, and 86 had received all 4 doses of the 7-valent vaccine before receiving the 13-valent vaccine. Of the subjects in Group 2, prior to receiving a dose of the 13-valent vaccine, 9 subjects had received 3 doses and 171 had received all 4 doses of 7-valent vaccine.

The safety assessment examined prompted symptoms on days 1 through 7, including local injection site reactions (e.g. redness, swelling, tenderness); temperature nightly and when fever is suspected, reporting highest daily temperature; decreased appetite, irritability, increased sleep, decreased sleep and hives; and antipyretic use for treatment or prevention of symptoms. Data were collected via an electronic diary. With regard to unsolicited adverse event reporting, all AEs were assessed for dose 1; all AEs were assessed for dose 2 only for Group 1; and 6 months post vaccination SAEs, newly diagnosed chronic medical conditions, and hospitalizations were assessed.

The summary of local and systemic reactions for Study 3011 included the following:

- ❑ Significant tenderness:
 - 7 (7.7%) for Group 1 – dose 1
 - 5 (8.1%) for Group 1 – dose 2
 - 15 (10.6%) for Group 2
 - For comparison, in the primary series, significant tenderness ranged from 5.1-8.5% for PCV7 and from 4.9-7.5% for PCV13

- ❑ No severe redness or swelling was reported

- ❑ 1 subject (Group 2) reported a temperature greater than 40°C

- ❑ 4 subjects reported hives
 - 1 for Group 1 – dose 1
 - 2 for Group 1 – dose 2
 - 1 for Group 2
 - None were assessed as urticaria related to vaccine

With regard to adverse events in Study 3011, 60 (48.4%) subjects reported 113 AEs for Group 1–dose 1; 35 (31.3%) subjects reported 50 AEs for Group 1–dose 2; 48 (26.8%) subjects reported 78 AEs in Group 2; infections / infestations accounted for the majority of AEs and are consistent with common illnesses in each age group; and no vaccine-related SAEs were reported. The conclusions drawn were that PCV13 can be substituted for PCV7 at any point in the immunization schedule. One dose of PCV13 in >12 month olds induces a response that is non-inferior to 3 doses in the first year. Good OPA titers are achieved after one dose in toddlers. The safety profile of one or two doses of PCV13 after four doses of PCV7 is comparable to the safety profile observed in the four-dose series.

Pertaining to evaluating the potential public health impact of PCV13 catch-up in children aged 16 to 59 months, the direct effect will be a reduction in invasive disease, pneumonia, and otitis media. Indirect effects are anticipated to accelerate the impact on the reduction of invasive disease and pneumonia, based upon the herd impact observed with the 7-valent vaccine.

Dr. Paradiso reminded everyone that during the June 2009 ACIP meeting, data were presented from an economic study that examined the disease that could be prevented by the transition from PCV7 to PCV13. The number of cases over a 10-year period that can be prevented predominantly caused by the 6 new serotypes in the 13-valent vaccine include 110,358 cases of IPD; 913,836 of hospitalized pneumonia; 1.95 million cases of non-hospitalized pneumonia; and 20 million cases of acute otitis media (AOM). Additional cases avoided with new serotype catch-up program include 12,975 cases of IPD; 118,534 cases of hospitalized pneumonia; 302,287 cases of non-hospitalized pneumonia; and 2.9 million cases of AOM. The new serotype catch-up program includes vaccination of all children previously vaccinated with PCV7 in the first year after introduction of PCV13 with one dose of PCV13 [Rubin J, McGarry I, Strutton D, Klugman K, Pelton S, Gilmore K, Weinstein M. Public Health and Economic Impact of the 13-Valent Pneumococcal Conjugate Vaccine (PCV13). Presented to Advisory Committee on Immunization Practices, June 26, 2009].

In terms of the sensitivity analyses results for PCV13 with new serotype catch-up, if there is no acceleration in indirect effects, the new serotype catch-up program will cost \$39,200 per QALY gained. PCV13 with new serotype catch-up is cost-saving when acceleration of indirect effects is at least 6 months.

The status of the regulatory review process for the 13-valent vaccine is that Wyeth / Pfizer received a positive opinion from European regulators on September 24, 2009. Licensure is expected by the end of the year in Europe. Licensure has been achieved in Chile and Mexico. The FDA review is on-going. This vaccine will be discussed in the FDA VRBPAC meeting scheduled for November 18, 2009. Manufacturing site visits have been completed.

Discussions began with CDC in the spring regarding the potential for rapid introduction of the 13-valent vaccine, particularly with regard to catch-up dosing. That early conversation allowed Wyeth / Pfizer to move up the schedule of filling and finishing the 13-valent vaccine. PCV13 inventory is being built to supply the transition from PCV7 in infants and new serotype catch-up in toddlers and older children. At this point, approximately 14 million doses of the 13-valent vaccine have been filled. This has gone smoothly, and by the end of 2009 it is expected that there will be an inventory of 20 million doses of vaccine in preparation for the introduction of this vaccine globally. The mechanics of the transition from 7-valent to 13-valent is currently in the planning stages in order to manage the inventory of the 7-valent currently in doctors' offices and the market place between now and the introduction of the 13-valent vaccine. Currently, there is approximately a 30-day inventory of the 7-valent vaccine in doctors' offices. The goal is to begin to reduce that inventory by approximately half, such that it will be brought down quickly as the introduction of 13-valent nears. There are many "moving parts" in this transition and the introduction of a new vaccine (e.g., timing of the recommendations, timing of the VFC vote, beginning of use in the public market, reimbursement by private insurers to allow the transition in the public and private sectors). Plans are underway to work with providers to assure a smooth transition from the 7-valent to the 13-valent vaccine, with a goal to switch as rapidly and efficiently as possible.

In conclusion, PCV13 provides coverage for the 6 additional serotypes. The transition from PCV7 to PCV13 can occur at any point in the immunization schedule. There is a significant disease burden in children 1-5 years of age. A single dose in children over 12 months of age induces immunity to the 6 additional serotypes in PCV13. There is significant potential for an indirect effect against the six additional serotypes. The indirect effect of PCV13 could be accelerated with a catch-up program.

Cost-Effectiveness of PCV13: Routine and Catch-Up Program

Mark L. Messonnier, MS, PhD
CDC / NCIRD / ISD

Dr. Messonnier reported on a cost-effectiveness study of a routine and catch-up PCV13 program that was conducted with Drs. Fangjun Zhou and Pekka Nuorti titled, "Cost-Effectiveness of Using 13-valent Pneumococcal Conjugate Vaccine in Infants and Young Children to Prevent Pneumococcal Disease in the United States."

The study question assessed was: What is the cost-effectiveness of using 13-valent pneumococcal conjugate vaccine (PCV13) in infants and young children to prevent pneumococcal disease caused by PCV13 serotypes in the United States? Routine use as a replacement for PCV7; and routine use plus catch-up immunization for 6 new serotypes among children 12 to 59 months was assessed. Intervention strategies examined included routine use of PCV13 in a single birth cohort; and routine use *plus* PCV13 catch-up immunization among children 12 to 59 months old in 4 catch-up birth cohorts, with one PCV13 dose for children who have been fully vaccinated with PCV7 and an assumed 50% catch-up coverage rate.

The intervention time frame is 1 year for each vaccinated cohort (e.g., 1 year for cohort in routine use, and 1 year for 4 cohorts in catch-up). The analytic horizon was 10 years, with 5 years of full protection from the vaccine and 5 years of waning immunity. Events occurring within the 10 years but with long-term consequences are included as a health outcome as a result of the infection and are counted over the expected lifetime (e.g., deafness, disability). Cost and epidemiologic data are for the 2007, and discounting was done at the recommended rate of 3%. A societal perspective was used, although net costs are presented without including productivity gains that are included in the societal perspective.

A cost-effectiveness analysis (CEA) and a cohort model were used, with a single birth cohort for routine vaccination and 12 to 59 month olds for catch-up vaccination. Incremental cost-effectiveness ratios (ICER) were used as summary measures. The cost-effectiveness model presents net cost divided by the change in outcomes:

$$\frac{(\text{vaccine cost} + \text{administration cost}) - (\text{cost of illness averted by vaccination})}{\text{number of outcomes of interest}}$$

In terms of the outcomes of interest, for invasive pneumococcal disease (IPD) cases were counted of meningitis, bacteremic pneumonia, bacteremia without focus, and all other IPD. Other outcomes of interest include hospitalizations, deaths, life-years (LY), and quality-adjusted life-years (QALY). For the outcome of non-invasive pneumococcal disease, cases were counted of hospitalized and non-hospitalized pneumonia; and otitis media was broken down into simple and complex. Also included were deaths, life-years (LY), and quality-adjusted life-years (QALY).

The epidemiological model of invasive disease was as follows:

$$\begin{aligned} &\text{Number of health outcomes attributable to new 6 serotypes in cohort} \\ &= \\ &\quad \text{Cohort population by age} \\ &\quad \times \\ &\quad \text{Age-specific overall IPD rate} \\ &\quad \times \\ &\quad \text{Age-specific proportion of overall IPD rate new 6-attributable} \\ &\quad \times \\ &\quad \text{Age-specific proportion of new 6 cases by syndrome} \\ &\quad \times \\ &\quad \text{Age-specific hospitalization rate by syndrome} \\ &\quad \times \\ &\quad \text{Age-specific fatality rate} \\ &\quad \times \\ &\quad \text{Age-specific vaccine coverage and efficacy assumptions for PCV13} \end{aligned}$$

The epidemiological model for non-invasive disease was as follows:

$$\begin{aligned} &\text{Number of health outcomes attributable to new 6 serotypes in cohort} \\ &= \\ &\quad \text{Cohort population by age} \\ &\quad \times \\ &\quad \text{Age-specific non-invasive outcome rate} \\ &\quad \times \\ &\quad \text{Age-specific vaccine coverage and efficacy assumptions for PCV13} \end{aligned}$$

With respect to the vaccine characteristics included in the model, direct effects were modeled, but indirect effects were not. The 1-year intervention was included for either 1 or 5 total cohorts. The vaccine efficacy figures are adjusted in the calculations in the model for vaccine serotype. The coverage figures used for the catch-up dose was 50% for the 4 catch-up cohorts and the NIS data were used for 3-dose (91%) and 4-dose (75%) coverage currently for PCV7. The duration of protection was 5 years, and then waning for 5 years.

For vaccination program costs, the vaccine price was split into the public and private prices. An assumption was made that is observed with PCV7 that approximately 50% of the doses are purchased for use in the VFC program. Base prices used in the base case model are 125% of the current PCV7 price, so for the public price that would be 125% of \$71.04 which was used as a lower bound and for the private price \$83.88. The upper bound is 150% of the current PCV7. The following are the program costs calculated:

Program Costs			
	Base¹	Lower²	Upper³
Vaccine			
Public	\$88.80	\$71.04	\$106.56
Private	\$104.85	\$83.88	\$125.82
Percent public purchase ⁴	50%		
Administration ⁵	\$18.96		\$31.60
Wastage ⁴	5%	0%	10%

¹PCV13 price = 125% of CDC contract and private sector price for PCV7; ²PCV13 price = 100% of CDC contract and private sector price for PCV7; ³PCV13 price = 150% of CDC contract and private sector price for PCV7; ⁴Assumed; ⁵Zhou, et al., 2002, 2004

Where possible, medical and non-medical costs were included for age groups when these events occur in the model, and are for those things that are counted over a lifetime if someone is affected and suffers these sequelae during the 10-year analytic horizon:

		Medical			Non Medical		
		Base ¹	Lower ²	Upper	Base	Lower	Upper
	Age						
Bacteremia and non-meningitis IPD	0-4 yrs	\$3,106	\$2,485	\$3,728	\$444	\$355	\$533
Meningitis	0-4 yrs	\$16,267	\$13,013	\$19,520	\$2,326	\$1,862	\$2,792
All IPD ³	5-14 yrs	\$7,775	\$6,220	\$9,330	--	--	--
Meningitis sequelae	Age						
Deafness	0-4 yrs	\$92,351	\$73,881	\$110,821	--	--	--
Disability	0-4 yrs	\$476,513	\$381,210	\$571,816	\$261,644	\$209,316	\$313,973
Hospitalized pneumonia	0-4 yrs	\$7,236	\$5,789	\$8,683	\$332	\$265	\$398
	5-9 yrs	\$6,079	\$4,863	\$7,295	--	--	--
		Base ⁴	Lower	Upper	Base	Lower	Upper
Outpatient pneumonia	0-9 yrs	\$192	\$153	\$230	\$332	\$265	\$398
Simple otitis media	0-4 yrs	\$98	\$79	\$118	\$180	\$144	\$216
Complex otitis media	0-4 yrs	\$823	\$658	\$988	\$653	\$523	\$784

¹ Ray, et al, PIDJ, 2006; ² Lower and upper bound values assumed to be 80% and 120% of base value, respectively; ³ All IPD applied due to lack of cost data for 5+, ⁴ Meltzer, et al, EIDJ, 1999

Sensitivity analyses were performed on the cost-effectiveness ratios and net costs, with simulation values to give estimated confidence limits on some selected outcome measures. Ranking variables that have the greatest effect on the outcome measures were also assessed.

Health outcomes anticipated to be prevented for invasive disease include:

	Outcomes prevented	
	PCV13 routine v PCV7 routine	Catch up cohorts v no catch up
INVASIVE DISEASE		
Cases		
Total cases IPD	2,849	2,494
Total cases meningitis	256	224
Total cases bacteremic pneumonia	1,254	1,097
Total cases bacteremia w/o focus	1,054	923
Total cases all other	285	249
Hospitalized disease		
Meningitis hosp	256	224
Bacteremic pneumonia hosp	897	824
Bacteremia w/o focus hosp	406	392
All other hosp	110	106
Non-hospitalized disease		
Meningitis non-hosp	0	0
Bacteremic pneumonia non-hosp	357	274
Bacteremia w/o focus non-hosp	648	531
All other, non-hosp	175	143
Fatalities and life-years		
Fatalities	52	72
Life-years lost	3,975	5,319
Discounted life-years lost (3%)	1,427	1,939

Health outcomes anticipated to be prevented for non-invasive disease include:

	Outcomes prevented	
	PCV13 routine v PCV7 routine	Catch up cohorts v no catch up
NON-INVASIVE DISEASE		
Pneumonia		
Hospitalized	14,828	11,835
Not Hospitalized	32,481	34,482
Otitis Media		
Simple	540,449	454,899
Complex	107,319	73,340
Fatalities and Life-Years		
Fatalities	31	24
Life-years lost	2,334	1,790
Discounted life-years lost (3%)	846	672

Health outcomes anticipated for total and QALY include:

	Outcomes prevented	
	PCV13 routine v PCV7 routine	Catch up cohorts v no catch up
TOTAL LIFE-YEARS AND QUALITY-ADJUSTED LIFE YEARS		
Life-years Lost	6,309	7,109
Discounted Life-years Lost (3%)	2,272	2,610
Quality-adjusted Life-years Lost	59,964	47,309
Discounted Quality-adjusted Life-years Lost (3%)	52,277	40,719

In terms of cost outcomes, the net savings with productivity changes represents the net savings from society's perspective, while the catch-up in the 4 cohorts is a net cost:

	Incremental Cost (\$)	
	PCV13 routine v PCV7 routine	Catch up cohorts v no catch up
Cost Outcomes (Base)¹		
Program Costs	302,893,989	1,000,592,760
Medical + Non-Medical Costs	(433,406,298)	(343,988,664)
Productivity Costs	(89,903,324)	(96,959,252)
Net Without Productivity Changes	(130,512,309)	656,604,096
Net With Productivity Changes	(220,915,633)	559,644,844

¹Price of PCV13 set at 125% of current PCV7 price

The summary measures are cost utility ratios in this case. PCV13 routine use versus PCV7 routine use is cost-saving regardless of which denominator is used in the cost-effectiveness ratio because the net cost is negative, which means a savings. In the catch-up cohorts, the cost per QALY saved was approximately \$16,000:

Health Outcome	CE Ratio (\$/health outcome)	
	PCV13 routine v PCV7 routine	Catch up cohorts v no catch up
Years of life saved	cost-saving	92,368
Discounted years of life saved	cost-saving	251,544
Quality-adjusted life-years saved	cost-saving	13,879
Discounted quality-adjusted life-years saved	cost-saving	16,125

Price of PCV13 set at 125% of current PCV7 price

In the sensitivity analysis, when doing the simulations and given the variables in the model and the probability distributions that are associated with each of those variables and doing the Monte Carlo simulations, Dr. Messonnier repeated the net with productivity changes and then showed the 95% confidence limit; that is, 95% of the simulated values of the net savings for PCV13 versus PCV7. Thus, 95% of those values fall within a savings of \$401,000,000 and a cost of \$15,000,000. Similarly for the catch-up cohorts versus no catch-up, 95% of those net cost estimates range between \$393,000,000 and \$781,000,000. For the summary measure, the cost utility ratio, with discounted quality of life years as the denominator, the \$16,125, 95% of value estimates in the simulation fall within \$9,300 and \$40,200 per QALY gained.

In conclusion, routine use of PCV13 among infants to replace PCV7 is likely cost-saving. Catch-up immunization with one dose of PCV13 among children 12 to 59 months old who have been fully vaccinated with PCV7 may not be cost-saving when indirect effects are not considered but still appears to be comparable in cost-effectiveness to other accepted interventions.

In terms of limitations, indirect effects are not included, and the magnitude is unknown. PCV13 estimates are inferred from PCV7 data. Uptake of the catch-up vaccination is difficult to predict so 50% was used. The possible increase in disease caused by non-PCV13 types is not modeled.

In comparison to other studies, the manufacturer study reported on to the ACIP in June 2009, "Public Health and Economic Impact of the 13-Valent Pneumococcal Conjugate Vaccine (PCV13)" used a Markov model which followed for routine use 10 cohorts over 10 years. It did include indirect effects in the unvaccinated. It also found that PCV13 versus PCV7 in routine use is cost-saving, and that if indirect effects were accelerated by 6 months or more, catch-up would also be cost-saving. The conclusions are largely consistent between the two studies.

PCV13: Draft Recommendations and Immunization Schedules

Pekka Nuorti, MD, DSc
Centers for Disease Control and Prevention

Dr. Nuorti reminded everyone that the licensure decision for PCV13 was expected by December 2009. The Work Group felt that the timing of licensure and introduction may allow use of the vaccine during the current influenza season, depending upon how long the season lasts.

As background, Dr. Nuorti also reminded the committee of the disease burden and serotype coverage data that were presented during the June meeting. With regard to the overall incidence of IPD by age-group in children < 5 years in the US in 1998 and 2007, the baseline rates of disease are much lower currently than they were before PCV7 introduction. Particularly the rate differences in children < 2 years of age before PCV7 were on the order of over 100 and close to an incidence of 200 per 100,000. There was an overall decrease from 100 to 22 per 100,000. Regarding the incidence of IPD by age and vaccine serotype group in children < 5 years in 2007, overall the PCV13 type disease rate is about 14 per 100,000. The rates decline by age, which is to be expected, particularly after the second birthday. Also observed is that PCV6 types are proportionally similar in each of these age groups (e.g., causing a similar proportion of disease) in each one year age strata. The proportion of IPD cases by vaccine serotype in 2007 in children under age 5 were as follows: PCV13 types: 64.4%; PCV7 types: 1.9%; 19A: 41.9%; 19A, and 7F and 3 = 98% of PCV6 types (260/266). 1,5, and 7F are not commonly carried among children [CDC, Active Bacterial Core surveillance, unpublished]. When developing the draft recommendation, the Work Group felt that it should be fairly straightforward and simple for the most part because most of the recommendation is similar to what is currently recommended for PCV7. There are some details that are different, as well as some data gaps. Draft recommendations for use of PCV13 were prepared for the following groups:

- Unvaccinated infants and children
 - Children incompletely vaccinated with PCV7
 - Infants who have received 1 or 2 doses of PCV7
 - Children who have received 3-dose infant series
 - PCV13 catch-up immunization for children completely vaccinated with PCV7 to provide protection against the 6 new serotypes. (This completely new compared to what is recommended for PCV7)
 - PPSV23 after PCV13 for children ≥ 2 years who have underlying medical conditions
1. For unvaccinated infants and children, the recommendation is fairly simple and straightforward in that the proposed recommendation and the immunization schedules are the same as currently recommended for PCV7. PCV13 is recommended for all children 2 through 59 months of age [MMWR 2008;57: 343-4]. For unimmunized children ≤ 59 months, the proposed recommendation and schedules for PCV13 vaccination are the same as currently recommended for PCV7 [MMWR 2008;57: 343-4; and MMWR 2000;49 (RR-9)]. For routine immunization of infants, PCV13 is recommended as a 4-dose series (2, 4, 6, and 12 through 15 months) as illustrated in Table 1:

Table 1. Recommended routine immunization schedule for use of 13-valent pneumococcal conjugate vaccine (PCV13) among infants and children who have not received previous doses of PCV7 or PCV13 by age at time of first vaccination

Age at first dose (mos)	Primary series*	Booster dose
2-6	3 doses	1 dose at 12-15 months
7-11	2 doses	1 dose at 12-15 months
12-23	2 doses	--
24-59		--
Healthy children	1 dose	--
Children with certain chronic diseases or immunocompromising conditions**	2 doses	--

* Minimum interval between doses is 8 weeks except for children vaccinated at age <1 year, minimum interval between doses is 4 weeks.

** For complete list of conditions, see Table 3.

“--” indicates “through”

- For children incompletely vaccinated with PCV7, the Work Group considerations addressed a number of issues. When PCV13 becomes available, many children will be incompletely vaccinated with ≥ 1 doses of PCV7. The proposed recommendation for transition from PCV7 to PCV13 is based on the common serotypes and same vaccine formulation; data from clinical trials among healthy infants and children in which immune responses and the safety profile for PCV13 were comparable to PCV7 [Peter Paradiso, Pfizer, presentation during this session; Draft PCV13 Manufacturer’s Package Insert]; and programmatic and logistic considerations – interchangeability of vaccine doses

For transition from PCV7 to PCV13, the proposed recommendation is that infants and children who began immunization with PCV7 may complete the series by switching to PCV13 at any point in schedule. Children who have completed the infant series with PCV7 should be administered a single PCV13 dose during the second year of life. The following table reflects the proposed recommendations for transition:

Age at examination (mos)	Vaccination history: total number of PCV7 and/or PCV13 doses received previously	Recommended PCV13 Regimen*
2–6	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	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)

*- indicates “through”

- PCV13 catch-up immunization for children completely vaccinated with PCV7 is defined as one dose of PCV13 for children 12 through 59 months who have been completely vaccinated with PCV7. The goals are to provide direct protection against the 6 new serotypes, and to potentially enhance indirect effects. The rationale for indirect effects is that children aged ≥ 12 months may be important for transmission of *S. pneumoniae*, and there is a potential for reduced nasopharyngeal carriage for certain of the new serotypes for PCV13.

The Work Group considerations included information about the safety and immunogenicity of one dose of PCV13 in older children, as well as the cost-effectiveness analysis [presentation during this session by Dr Messonnier, CDC]. In terms of PCV13 catch-up immunization, an additional (5th) dose of PCV appears to be safe, based on preliminary data, and one dose of PCV13 is immunogenic in older children. The programmatic feasibility of implementation during first year after licensure is likely to be acceptable to providers. There is a possibility of preventing bacterial complications from H1N1 influenza.

In terms of PCV13 catch-up immunization safety and immunogenicity in healthy children age ≥ 12 months who had received 3 PCV7 doses, a single PCV13 booster dose induced antibody levels to the 6 new serotypes that were similar to those after primary infant series with PCV13 [Peter Paradiso, Pfizer, presentation during this session; draft PCV13 Manufacturer’s Package Insert] [Wyeth study 008]. The safety profile of 1 or 2 doses of PCV13 after 4 PCV7 doses appears comparable to 4 dose PCV13 series based on preliminary data [Wyeth Study 3011]. For children with underlying medical conditions, no safety or immunogenicity studies have been completed at this point. For children who have been completely vaccinated with PCV7, one dose of PCV13 is recommended for all children aged 12 through 59 months who have received 4 PCV7 doses or other age-appropriate, complete PCV7 schedules.

The following table illustrates the proposed PCV13 catch-up immunization recommendation in a schematic format:

Table 2. Recommended schedules for administering doses of PCV13 among children aged 12-59 months not completely vaccinated with PCV7 for age, and catch-up immunization

Age at examination (mos)	Vaccination history: total number of PCV7 and/or PCV13 doses received previously	Recommended PCV13 Regimen	
12–23	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 dose, ≥ 8 weeks after the most recent dose	
24–59			
	Healthy children	Any incomplete schedule	1 dose, ≥ 8 weeks after the most recent dose
		4 doses of PCV7 or other age-appropriate complete PCV7 schedule	1 dose, ≥ 8 weeks after the most recent dose
	Children at high risk ^(see Table 3)	Any incomplete schedule of <3 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 dose, ≥ 8 weeks after the most recent dose	

*For healthy children who have received at least 1 dose of PCV13 at age 12 months or older, no further PCV13 doses are needed.

There is a subtle detail in the table for 1-year olds for those children who have received the 3-dose primary series of PCV7, the PCV13 dose during the second year of life will be their fourth and final dose, completing the series. Whereas, for children who have received 4 doses of PVC7 the PCV13 will be their fifth dose and the first opportunity to provide that dose will be at 8 or more weeks after the last PCV7 dose. The Work Group felt that because up to a quarter of children do not receive their fourth dose of PCV7, the catch-up recommendation might also help to improve coverage for the fourth dose of vaccine. For healthy children who have received one or more PCV13 doses at age 12 months or older, no further PCV13 doses are needed.

There are a number of unknowns with respect to PCV13 catch-up immunization. For example, it is difficult to predict what the uptake will be, particularly in older children. Also not clear is whether one PCV13 dose will be sufficient for children ≥ 12 months who have underlying medical conditions. Currently, no data are available on reduction in carriage after a single PCV13 dose in older children, although there are some data for PCV7 available. The issue is that some of the new 6 serotypes (e.g., 1 and 5), as was discussed in the June 2009 meeting, behave differently in their epidemiology from the PCV7 types and are infrequently carried. Thus, predicting the magnitude of any potential indirect effects is difficult.

4. With regard to PPSV23 in high risk children who have received PCV13, there are limited safety data for PPSV23 after PCV7, and no data are available for PCV13. Although there is a good booster response for the common serotypes following PPSV23, the clinical effectiveness of this strategy is unknown. The rationale for giving PPSV23 to children who have underlying medical conditions has been the opportunity to provide additional serotype coverage with the additional serotypes in PPSV23; however, this opportunity may become more limited since the serotypes in PPSV23 but not in PCV13 caused 13% of IPD cases in children 24 through 59 months with medical conditions [CDC, Active Bacterial Core surveillance 2006-2007, unpublished].

The proposed recommendation and schedule for PPSV23 after PCV13 for children ≥ 2 years with medical conditions are the same as currently recommended for PPSV23 after PCV7. For children who are immunocompromised or who have chronic illness, one dose of PPSV23 is recommended ≥ 2 years of age and ≥ 8 weeks after the last indicated dose of PCV13. Revaccination is only recommended for immunocompromised children at 5 years after the first dose of PPSV23.

The anticipated indication for PCV13 is through 5 years of age (before 6th birthday). Therefore, the Work Group proposed that vaccine should be administered through age 71 months for children who have underlying medical conditions. There are currently no safety or immunogenicity data available for children with chronic illnesses; however, they will likely have reduced antibody response and remain at increased risk of disease. Although the doses of PCV13 should preferably be completed before PPSV23, PCV13 should also be administered to children aged 24 through 71 months with chronic illness who were previously vaccinated with PPSV23. It should be noted that no safety or immunogenicity data are available for this vaccine sequence.

To summarize the content of the recommendations, for unvaccinated infants and children, PCV13 is recommended for all children ages 2 through 59 months. The recommendation and schedules for routine PCV13 vaccination of unimmunized children aged ≤ 59 months is the same as currently recommended for PCV7, and PCV13 replaces PCV7 for all doses. Children who have begun their vaccination series with PCV7 may complete the series by switching to PCV13 at any point in the schedule. Children who have completed the primary infant series with PCV7 should receive a single PCV13 dose during the second year of life. One dose of PCV13 is recommended for children 12 through 59 months who have received 4 doses of PCV7 or other age-appropriate, complete PCV7 schedule.

The Work Group concluded that the transition from PCV7 to PCV13 has the potential to substantially reduce remaining IPD, and that it appears to be cost-effective. PCV13 catch-up immunization for children completely vaccinated with PCV7 is expected to provide direct protection against 6 new serotypes, may enhance indirect effects in unvaccinated groups, and appears to be cost-effective. Rapid PCV13 introduction after licensure, including catch-up immunization, might have the additional benefit of reducing pneumococcal infections complicating H1N1 influenza.

The full ACIP membership was asked to consider the following issues:

- ❑ The approach and proposed recommendations for PCV13
- ❑ The challenges for implementing the proposed recommendations in terms of the following:
 - Logistics of switching from PCV7 to PCV13
 - Incomplete PCV7 schedules
 - PCV13 catch-up immunization
- ❑ Additional issues that may require discussion before the vote when PCV13 is licensed

Discussion

As someone who oversees a universal state childhood immunization, Dr. Lett expressed concern regarding the issue pertaining to cost-effectiveness, indirect effects, and whether this is really the right investment. Her state spends approximately \$21 million per year on pneumococcal conjugate vaccine. They estimated that a 5% increase in cost with 100% uptake would cost the state \$12 million for catch-up. While she did not believe their catch-up cost would actually be that much, it is certainly a lot of money. While a proportion of that will be from the VFC, the remainder will be paid for with state funds. With that in mind, she requested that they explore further what is known about indirect effects and whether the year or two of catch-up was really worth the investment.

Dr. Nuorti responded that based on the two economic analyses that were conducted using two different methods and somewhat different assumptions, the overall conclusions were still largely consistent with each other. The CDC model took a more conservative approach by not including indirect effects at all, and still showing cost-effectiveness. It is true that the exact indirect effects are not known and predicting the exact indirect effects and how soon they will materialize is difficult, but based on the experience with PCV7, it can be assumed that there will be indirect effects. This was discussed in many meetings of the Work Group, and the proposal was based on this and the other considerations he reported earlier.

Dr. Messonnier added that when they conduct an analysis from a societal perspective, they typically do not go into very detailed sub-perspectives. The state perspective is different from the perspective of society as a whole. They could examine the state budget perspective and at least offer guidance on how to assess that.

Dr. Sawyer indicated that the recommendation for PCV13 in older children 16 to 71 months of age struck him as new, so he wondered whether that was already a recommendation for PCV7 for children at high risk. In addition, he requested further insight into the discussion that led to the age cutoff of 71 months.

Dr. Nuorti replied that this was a last-minute addition. PCV7 is licensed up to 9 years of age, although the recommendation only goes up to 5 years of age. There is a permissive recommendation for PCV7 for older children with HIV or other immunocompromising conditions. The upper age limit proposed for PCV13 is based on the fact that the anticipated indication for PCV13 will be through 71 months. Therefore, the Work Group felt that even though PCV13 was only being recommended routinely for healthy children up through age 5 years, the

recommendation should go to the upper age limit of the indication for children who have high risk conditions.

Dr. Sawyer inquired as to whether there would continue to be a permissive recommendation for immunosuppressed patients above that.

Dr. Nuorti replied that they anticipated that this would be the case for PCV13 as well.

Dr. Paradiso added that the study with children up to age 5 includes two more arms that are ongoing to assess 5- to 9-year olds, which was similar to the 7-valent vaccine, and 10- to 18-year olds with the same kind of comparison of immune response to the primary responses. When the results of those studies are available, probably sometime in 2010, the plan is to amend the application to cover all healthy children up to 18.

From the Pfizer perspective and implementation in clinics, Dr. Temte asked whether there would be any buy-back or exchange programs for the 7-valent vaccine, or whether clinicians would be expected to use their supplies.

Dr. Paradiso indicated that at this point, the goal is to manage the inventory so that they do not have to do an exchange because of the logistics of doing so. If that does not work out, they will consider a buy-back or exchange as a possibility. They would like 13-valent administered to children as soon as possible without creating a problem for the provider in an exchange or having a vaccine that is unused.

Regarding the indirect effects alluded to from Dr. Paradiso's and Dr. Messonnier's presentations, Dr. Temte wondered whether this was just in children or the potential effects in adults.

Dr. Nuorti responded that it is anticipated that most of the disease burden prevented by the indirect effects will be in working age and older adults, because after age 5 the rates of disease in children become quite low.

Dr. Cieslak indicated that his reaction to the recommendation for vaccinating children over the age of 2 as a catch-up was to examine the incidence of invasive disease in those children, and think about what recommendations have been typically made. It seemed to him that the incidence of infection that could be prevented by PCV7 in the 3- to 5-year old age group approached that in the general population for whom a recommendation has not been made for universal vaccination with the polysaccharide vaccine. Given that the polysaccharide vaccine protects against a few more serotypes, though perhaps somewhat less effective, it still struck him that all along they could have made a recommendation for universal use of the polysaccharide vaccine in children over the age of two because roughly the same amount of invasive disease could be prevented. Thus, he wondered why they were concerned about this relatively low incidence in this age group, particularly given that the polysaccharide vaccine seemed to be much cheaper.

Dr. Nuorti responded that the polysaccharide vaccine had not been recommended for any groups that did not have risk factors, except for those aged 65 and older, given the limitations of the vaccine, particularly in children, and the disease burden. A number of meta-analyses have examined the various strategies for use of the polysaccharide vaccine. Universal use of that vaccine in children has never come up. In addition, there are immunologic issues with the use of the polysaccharide vaccine, particularly in children. There have been a number of recent studies suggesting immunologic hypo-responsiveness following polysaccharide vaccine to subsequent polysaccharide antigen or subsequent conjugate vaccine dose. Given the recent information about polysaccharide and its ability to prevent disease in children, the Work Group did not raise this as an option to consider. He agreed that the rates of disease decline very quickly after 2, but the catch-up proposal was based on a number of other considerations and discussions by the Work Group. While rates of disease and cost-effectiveness were part of those discussions, also considered was that in addition to providing direct protection to the six additional serotypes that cause about two-thirds of the remaining disease, there is a potential to enhance the indirect effects, particularly among working age adults and the elderly.

Dr. Whitney added that the drive of the cost-effectiveness is not the invasive disease. It is really the musosal disease, the pneumonia, and the otitis media because there is so much more of that than invasive disease.

Dr. Baker noted that her center has seen a raging return of mastoiditis and its complications due to serotype 19A, also complicated by osteomyelitis, sigmoid sinus thrombosis, and occasionally cavernous sinus thrombosis. Those children are not bacteremic, so it is not clear whether surveillance even picks them up. These are children over 5 years of age who have no underlying risk factor.

Regarding cost-effectiveness of different strategies and given the high immunogenicity of the conjugated vaccines, Dr. Judson asked whether anyone had recently assessed the incremental cost-effectiveness of the fourth dose, particularly given that 25% are not receiving the fourth dose. With that in mind, he wondered whether it was possible to go to a 2-dose priming and 1-dose booster.

Dr. Nuorti replied that a number of European countries have chosen the 2+1 schedule and have conducted cost-effectiveness analyses to evaluate that approach. Some provinces in Canada also use a 2+1 schedule. In terms of the immunogenicity data, there may be some issues.

Dr. Paradiso added that the 2-dose primary series was not used for the efficacy trial and was not the indication the US because two of the serotypes in particular, 6B and 23F, after two doses in infancy do not give as good an immune response as is observed following the third dose. The reason for the 3-dose primary series was to achieve the maximum results in all of the serotypes. Following the booster dose, however, most all of the titers increase to approximately the same amount. In the countries using the 2+1 schedule, there has been a reduction in pneumococcal disease. There are not as much data under those schedules as are available in the US. Therefore, from a direct and indirect perspective all of the data for a lower dose schedule are not available. That schedule is also not part of the indication or licensure in the US.

Ms. Ehresmann noted that the catch-up data in Dr. Messonnier's presentation did not match the data in the members' handouts. With that in mind, she wondered what had changed in the analysis. The relative relationship between the numbers was similar, but they were different.

Dr. Messonnier responded that as he recalled someone found an error in which he had mistakenly subtracted the wrong columns from one another.

Dr. Meissner requested that someone comment on the number of increased cases of otitis media that were anticipated to be prevented with the 13-valent vaccine in contrast to the 7-valent vaccine.

Dr. Nuorti responded that the estimates used in the cost-effectiveness analysis for overall otitis media were relatively low, given that *S. pneumoniae* causes approximately 25% of otitis media. The number used in the CDC analysis was a 6% efficacy estimate for otitis media reduction, and that was adjusted for the PCV13 serotypes, so it is about two-thirds of that. Some studies have used insurance databases that have shown a larger reduction in otitis media visits, but in those studies it is difficult to distinguish the vaccine effect from other effects that may relate to changes in diagnostic practices and coding. While some of the available data suggest larger reductions in otitis media than what was seen in the clinical trials, CDC opted to utilize the estimates provided by the clinical trials. They had to assume that the serotype distribution for non-invasive disease was the same as for invasive disease, so the actual number would be in the order of 3% to 4%.

Dr. Bocchini (AAP) inquired about the plans for the VFC contract and how soon PCV13 could be placed into the VFC program.

Dr. Wharton responded that inclusion in the VFC requires a licensed product, a VFC vote, and a federal contract. On-going planning is underway with regard to how to do this expeditiously.

Dr. Langley (NACI) reported that the 2+1 schedules were first explored in the Province of Quebec, and resulted from the data emerging about the shortages in the US in which children were not receiving the full schedule, but there was still some protection. Quebec conducted analyses to assess the incremental benefit of the extra dose, and introduced the 2+1 schedule and have conducted very careful surveillance to assure that the direct and indirect protective benefits are still in place, which they are. Given these findings, British Columbia has also begun this schedule. The Province of Quebec has now moved from Prevnar® to Synflorix™, a 10-valent vaccine not available in the US.

Dr. Turner (ACHA) noted that five years ago in discussions pertaining to meningococcal disease, Dr. Meltzer presented data on the cost-effectiveness of PCV7, indicating that it was not cost-effective at \$80,000 per life year saved excluding cost of productivity lost. While Dr. Turner understood that that was not a QALY, he wondered what had changed between 2004 and 2009 to make it cost-effective to administer PCV7.

Dr. Messonnier responded that they had compared PCV13 with PCV7, and that moving from PCV7 routine use to PCV13 routine use would be cost-saving. That is not a function of the costs of treatment or programs, but a function of the epidemiology.

Dr. Nuorti indicated that before PCV7 was introduced, the projected cost was about \$200,000 per life year saved. Updated analysis afterward included the indirect effects, which reduced that number to approximately \$10,000 per life year saved in the latest analyses. One of the major changes was the accumulation of the indirect effects as a result of PCV7 use.

Dr. Messonnier agreed that \$80,000 per life year save was certainly not cost-saving. In this case, the greatest gain is in the non-invasive disease in terms of QALY because so many numbers of events are associated with even a small change in quality of life. That brings that number into much more favorable territory. In 2004, the picture looked much different than it does in 2009.

Regarding Dr. Wharton's comment about the necessity of waiting for licensure of PCV13 before ACIP could vote and before a VFC contract could be established, Dr. Chilton wondered whether if that would mean the vaccine could not be purchased for the VFC until February 2010 if it were approved in December 2009.

Dr. Wharton responded that there were provisions in place to conduct ACIP meetings via teleconference or other mechanisms between meetings, which would be done in case of an urgent need to do so.

Dr. Englund clarified that polysaccharide vaccine, particularly in 2- to 3-year old children, did not do very well in her experience even though they do give it. As a practicing pediatrician, she thought the catch-up schedule and cost-effectiveness of \$16,000 would be appealing.

Dr. Cieslak was thinking about the fact that 20 years ago there was a higher rate of disease and a less expensive vaccine, while currently there was much lower disease and a much more expensive vaccine. If the cost-benefit was really being driven by non-invasive disease categories that the polysaccharide vaccine was never thought to prevent, it was then clear to him. Nevertheless, he thought it would be beneficial to see a breakdown of where the savings are.

Influenza Vaccines

Introduction and Work Group Discussions

Anthony Fiore, MD, MPH
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Dr. Fiore pointed out that there were no votes scheduled during this session, which was intended to be an informational session. He also acknowledged that while this was always a hardworking Work Group, with the pandemic upon them the last six months they have been pushed to the limit. With that in mind, he wanted to publicly thank the members for all of their work between the ACIP meetings, often on very short notice.

The recommendations for seasonal influenza were published July 31 2009 in the *MMWR*. As a reminder of all of the milestones over the years, seasonal influenza recommendations have included the following:

Pre-2000

- Persons aged 65 or older
- Persons with chronic medical conditions that make them more likely to have complications of influenza
- Pregnant women in the second or third trimester

- Contacts (household and out of home caregivers) of the above groups
- Healthcare workers

2000

- Adults 50 and older

2004

- Children aged 6—23 months
- Contacts (household and out of home caregivers) of children aged 0--23 months
- Women who will be pregnant during influenza season

2006

- Children aged 6—59 months
- Contacts (household and out of home caregivers) of children aged 0—59 months

2008

- All children aged 6 months—18 years, if feasible

2009

- All children aged 6 months—18 years

Based on vaccine coverage from the NIS for children 6 to 23 months old, which is the provider-verified gold standard coverage survey, over time rapid progress is not being made in coverage this age group. As of 2007-2008, coverage of one or more doses in this age group is 40.7% and full coverage is 23.4% [CDC. MMWR 2009;58;1063].

The registry data offers a quicker update on influenza vaccine coverage, and includes the 2007-2008 and 2008-2009 seasons and two age groups: 6 to 23 months and 2 to 4 years. This mirrors the NIS coverage, adds an extra year to it, and shows that even during this past influenza seasons the percentage of children in these age groups is still lagging behind the target coverage goals. [CDC. Influenza Vaccination Coverage Among Children Aged 6 Months–18 Years — Eight Immunization Information System Sentinel Sites, United States, 2008–09 Influenza Season MMWR 2009;58:1063-6].

Based on the Behavioral Risk Factor Surveillance System (BRFSS), coverage in adults in three age groups (≥ 65, 50 to 64 years, and 18 to 49 years with high risk conditions), has hovered at current coverage levels for the past couple of years. It has been difficult to achieve the coverage levels that were attained prior to the 2004-2005 shortage season [CDC. Influenza Vaccination Coverage Among Children and Adults — United States, 2008–09 Influenza Season. MMWR 2009;58:1091-5].

According to preliminary data from 1989-2008 from the NIS on pregnant women and healthcare workers, there was an uptake in the most recent year in pregnant women. However, healthcare workers hovered at approximately 44%, a very slow increase in coverage in that group [Source: CDC, NHIS. <http://www.cdc.gov/flu/professionals/vaccination/pdf/vaccinetrend.pdf>].

The recommendations for Influenza A (H1N1) 2009 monovalent vaccines were published in the *MMWR* in August 2009. These recommendations were discussed and voted upon during the July 29, 2009 ACIP special meeting. The goals of this vaccination program were to vaccinate as many persons as quickly as possible; during initial limited availability to target those at higher

risk for influenza-related complications / infection; and encourage local flexibility and decision-making for expansion of target to larger population groups.

A number of planning assumptions informed these recommendations. It was assumed that the severity of illness and groups at higher risk for infection or complications would be similar to what had already been observed during April through July 2009. The safety profile and antigen content of unadjuvanted novel H1N1 vaccines would be similar to that of seasonal influenza vaccines. Adequate supplies of licensed unadjuvanted vaccine would be produced for all by approximately February 2010. Enough vaccines for all would not be available before the next pandemic wave, hence the need for targeting of certain higher risk populations with initial vaccines. Pandemic vaccine and seasonal vaccine availability would overlap and both would be recommended for many population groups. Two doses would be needed for protection. The initial demand for vaccination would be approximately the same as for seasonal vaccine, but would increase quickly if community transmission increased. Vaccine distribution would be timely. Implementation would be challenging.

The primary target group identified at that time included pregnant women, contacts of infants <6 months of age, healthcare personnel (HCP) / emergency medical service (EMS) workers, persons 6 months to 24 years of age, and adults high risk for complications < 65 years of age (e.g., chronic pulmonary, cardiovascular, renal, hepatic, cognitive, neurologic / neuromuscular, hematological or metabolic disorders, or immunosuppression). The total number in the primary target group was thought to be approximately 159 million persons.

Given that there was concern that initial availability would be limited, a smaller priority group was established. This group included pregnant women, contacts of infants < 6 months old, HCP / EMS in direct contact with infected patients, children 6 months to 4 years of age, and older children at higher risk due to chronic medical conditions. This group was estimated to total 42 million. The scenario during which this would be implemented was to address very high demand or very limited vaccine availability. Many areas are currently working off of this scenario.

As vaccine increases, the plan is to add to the primary target population healthy adults 25 through 64 years of age, which totals approximately 103 million. As demand is met for those groups, vaccine will be offered to those 65 and older, which totals an additional 38 million.

Update: Influenza Epidemiology

**Lyn Finelli, DrPH
CDC / NCIRD / ID**

Dr. Finelli reported on influenza-like illness surveillance (ILI), hospitalization surveillance, death surveillance, and epidemiology.

Regarding what has been occurring over the few weeks prior to this meeting, disease has spread more or less from the Southeast, up to the Northeast, and out to the West based on ILI reported to the US outpatient Influenza-Like Illness Surveillance Network (ILINet) from September 12, 2009 to October 10, 2009. ILINet includes approximately 3500 to 4000 providers. By the week ending October 3, 2009 there was widespread disease throughout most of the country. By the week ending October 10, 2009 there was fairly dense, widespread activity in the US.

Based on ILINet data, the overall ILI proportion of people seeking over total medical visits was 6.1% as of October 3, 2009. This is the highest proportion that has been observed in five influenza seasons. What is unusual is that this is the end of the summer / beginning of the fall, and this level of activity during this time of year has not been seen since the last pandemic. The last time rates of ILI this high were observed was during the 2003-2004 influenza season. The overall ILI proportion was 1.7% in April, 3.0% in May, 2.1% in June, 1.1% in July (a decrease to summer season levels), 1.6% in August, 3.7% in September (upon school starting back), and 5.6% for the first two weeks in October.

By the week of October 10, 2009 there was a great deal of disease over the increased activity threshold almost everywhere that ILINet has providers. It is important to note that the disease distribution differed by age group. In the 0 to 4 years of age group, there was moderate disease with about half of the ILINet providers over threshold in this age group. The amount of disease in the 5 to 24 years of age group was much denser, and was sustained into the 25- to 64-year old age group. The week of October 10, 2009 was the first week during which a dense number of providers were over threshold in this age group. During this week, hardly any providers were over threshold in the over 65-year old age group.

Based on data provided by Jim Turner of the American College Health Association (ACHA) regarding ILI calls or visits in colleges and universities, during the week of October 16, 2009 there were 7,099 new ILI cases reported. Over 47,000 cases of ILI among 3.4 million students have been reported in this system so far this season. Severity is fairly mild in this age group. Among these, there have been 78 hospitalizations and no deaths. These data are carefully examined and are reported every week during the CDC director's briefing.

There are now Behavioral Risk Factor Surveillance system (BRFSS) survey data for influenza, which is a new data collection system this year. These data have never been routinely collected previously. NCIRD is collaborating with scientists administering the larger BRFSS survey, which is primarily focused on chronic disease. Every week, people are called and asked about ILI in the last week. This system was initiated in September 2009 and will allow NCIRD to acquire an estimate of the proportion of the population affected with ILI on a weekly or bi-weekly basis. In September, this was a fairly good indicator of influenza activity. Moving into the winter months, there will be other causes of ILI, but it is still believed that the BRFSS data will correlate well with ILINet. Based on the BRFSS data from October 1 to October 11, 2009, 7.2% of adults who were called said that they had ILI. The overall percentage of children reporting ILI in this study was 20%.

By October 10, 2009 (Week 40), the map for weekly influenza activity estimates reported by states and territories was nearly entirely brown, reflecting widespread disease in 41 states and regional or local disease in the remainder of the US. A map reflecting this much widespread activity is never seen until the peak of influenza season in unusually high seasons. At the same time last year, there was little to no activity. This is a very unusual year for influenza activity so early.

There are several meetings each week at CDC in which severity measures are discussed, some of which Dr. Finelli shared during this session. There is a weekly aggregate reporting system through which 28 state health departments on average report laboratory-confirmed influenza hospitalization to CDC. The remainder of states report syndromic pneumonia and influenza hospitalization to CDC. These data are cumulative since September 1, 2009 and the age groups

are not equal. Overall, 44.1% of hospitalizations reported were in the 0 to 18 age group; 48.3% in the 19-64 age group; and 7.2% in the 65+ age group. This is very unusual compared with seasonal influenza.

The total number of hospitalized cases from the 28 states is divided over the total US population, given that sometimes these states vary from week to week. Thus, the denominator for cumulative data is variable. Based on these figures, the rates of hospitalization are highest in the very young and lowest in people over 65 years of age: 4.4% Age 0-4; 2.18% Age 5-18; 1.74% Age 19-24; 1.13% Age 25-49; 1.37% Age 50-64; and 0.92% Age 65+ for a overall 1.63% in all ages.

The Emerging Infections Program (EIP) laboratory-confirmed influenza hospitalization surveillance includes 10 routine sites, to which 6 new sites were added this year that are using the EIP protocol. For the purpose of this presentation, due to time constraints, Dr. Finelli combined the data for all sites (e.g., new and routine), although this is not typically done. The last seasonal influenza season was predominantly the pandemic virus 2009 H1N1, although there were some H3N2 viruses and B viruses. Comparing hospitalization rates from the EIP 2008-2009 season with the network rates from the 2009-2010 season (which began in this system on September 1, 2009) cumulative rates for the current season (6 weeks at the time of this presentation) for the 5 to 17, 18 to 49, and 50 to 64 age groups exceeded those for the entire 2008-2009 season. Comparing the spring wave with the fall wave, the rates for 6 weeks of fall approach the rates for the 4-month spring period. There was a rather small and focal outbreak in the spring, but since the fall, there has been a very large and widespread outbreak and cumulative hospitalization rates are quite high for the fall compared to the spring.

The cumulative hospitalization rate for all of the years' data have been collected by the EIP in the 0 to 4 age group 2003-2004 which was a severe season. For these data, usual influenza activity within a certain confidence limit was quantitated with severe influenza activity in terms of hospitalizations. For the 2009-2010 influenza season, in just 6 weeks cumulative hospitalizations in this age group were approximately 1.3 per 100,000 population (rates from 0 to 10), and the trajectory is much steeper than in a typical influenza season. The 5-17 age group looks much worse (rates from 0 to 2) and is already approaching much steeper trajectory than the worse season on record (2003-2004). There is also a fairly steep trajectory in the 18 to 64 age group as well, which is primarily due to hospitalization rates being higher for people underlying conditions and those in their 20s and early 30s, some with and some without underlying conditions. The worst influenza season on record for the over 65 population is 2007-2008. Thus far in the current season, there have been fairly low hospitalization rates in this age group, which has not been largely affected either by acquisition of influenza or hospitalization.

Turning to mortality and the 122 cities data, as of the week ending October 10, 2009, excess deaths have exceeded what would typically be expected. Rather than being in the elderly, who is customary, these deaths have been in younger people. During this season, which to date is almost exclusively H1N1, 43 pediatric deaths were reported over the 4-month influenza season and 44 reported in last six weeks.

With respect to the death data that parallel the hospitalization data, the number of cumulative deaths in each age group as of Influenza Week 40 ending October 16, 2009 were: 9 in the 0 to 4 age group, 40 in the 5 to 18 age group, 20 in the 19 to 24 age group, 95 in the 25 to 49 age group, 94 in the 50 to 64 age group, and 34 in the 65+ age group. Again, the age groups are not equal. Notably, 16.8% of deaths versus 44% of hospitalizations were in the 0 to 18 age

group; 71.6% of deaths were in the 19 to 64 age group, and there were very few deaths (11.6%) in the 65+ age group. The rates of laboratory-confirmed mortality from the 27 states reporting on a weekly basis, using the total US population denominator, are distinctly different from those observed in the hospitalization data, with death rates lowest in the very young and highest in the older populations with the exception of the 65+ age group: 0.04 in the 0 to 4 age group, 0.07 in the 5 to 18 age group, 0.08 in the 19 to 24 age group, 0.09 in the 25 to 49 age group, 0.17 in the 50 to 64 age group, and 0.09 in the 65+ age group.

Based on cumulative excess mortality calculated from the 122 Cities Surveillance, separated among the expected number of excess deaths for various viruses, in all ages the lowest excess deaths are observed for B viruses and H1s, with moderate deaths in H3s. Also included in these data were data from the 1968 pandemic. While no appreciable excess deaths were observed over all age groups, in the 15 years or less age group, there was an appreciable number deaths in excess of what is expected during this time of year and for influenza virus in general. The trajectory in this age group looks very much like that of the 1968 and some of the more severe H3 seasons. The story is largely the same for the 15 to 25 age group, with an appreciable number of excess deaths and a trajectory of that observed in the 1968 pandemic. There was not an appreciable increase in excess deaths in the 25 to 64 age group, and for the 65+ age group the number of deaths was barely discernable.

Again, this reflects that the populations most heavily affected are children of school age and young people. The risk groups have not changed since the spring wave. Children and adolescents continue to remain at the highest risk for acquisition. Hospitalizations are highest in young children and decline with age. Deaths increase with age, but only up to the 50 to 64 age group, and then decline slightly in ≥ 65 age group. The majority of those who die and adults who are hospitalized have underlying conditions, including pregnancy.

Of the 465 pediatric hospitalizations in the EIP data, 62% had one or more underlying conditions (thus, these do not calculate to 100%). Cases of ACIP recognized medical conditions in this pediatric group included the following: Asthma 166 (35.7%); Cystic Fibrosis 1 (0.2%), Other Chronic Lung Disease 23 (5.0%), Bronchopulmonary Dysplasia 5 (1.1%), Chronic Cardiovascular Disease 20 (4.3%), Chronic Metabolic Disease 14 (3.0%), Diabetes 6 (1.3%), Renal Disease 12 (2.6%), Neuromuscular Disease 24 (5.2%), Cerebral Palsy 13 (2.8%), Hemoglobinopathy 31 (6.7%), Immunosuppressive Condition 21 (4.5%), Seizure Disorder, including febrile seizures 27 (5.8%), Upper Airway Abnormality 4 (0.9%), Prematurity 27 (5.8%), Developmental Delay 33 (7.1%), and Pregnancy 6 (1.3%).

Of the 685 adult hospitalizations in the EIP data, 76% had one or more underlying condition (thus, these do not calculate to 100%). Cases of ACIP recognized medical conditions in this adult group included the following: Asthma 211 (30.8%), Cystic Fibrosis 2 (0.3%), Other Chronic Lung Disease 98 (14.3%), COPD 69 (10.1%), Chronic Cardiovascular Disease 118 (17.2%), Chronic Metabolic Disease 160 (23.4%), Diabetes 136 (19.9%), Renal Disease 57 (8.3%), Neuromuscular Disease 18 (2.6%), Cancer including lymphoma and leukemia 24 (3.5%), Immunosuppressive Condition 92 (13.4%), Seizure Disorder 21 (3.1%), Cognitive Dysfunction 15 (2.2%), and Pregnancy 76 (11.1%).

Underlying conditions were collected in a death case series on the first 300 deaths over the spring and summer. Unlike the EIP and hospitalization case series published recently in the *New England Journal of Medicine*, these patients had very limited clinical and underlying condition information collected. Among 299 of these patients, 38% of people who died from

H1N1 in the younger groups and 37% in the older group had asthma. Among children, notably 52% had neurologic disease, with 38% of these overall having a neurodevelopmental disease, 35% a neuromuscular disorder, and 27% a seizure disorder. This is also consistent with a recently published *MMWR* that assessed the first 33 cases of children who died with H1N1 who had an extraordinary proportion of neuromuscular disorder. Approximately 66% of children who die with H1N1 have an underlying disorder, compared to less than 50% on average from seasonal influenza. In the case series, 4% of children under 18 years of age were pregnant, 2% had renal disease, and 7% were obese. In the adults, 26% had cardiovascular disease, 12% had neurologic disease, 24% had diabetes, 15% had renal disease, 15% had cancer, and 50% were obese.

Dr. Finelli then shared data from Denise Jamieson and Peggy Honein from the Birth Defects and Reproductive Health Groups pertaining to pregnant women with H1N1 from April 15 to August 21, 2009. Of over 700 pregnant women with confirmed or probable 2009 H1N1 influenza over the spring and summer season, approximately 100 were admitted to intensive care units (ICU). There have been 28 deaths among pregnant women out of 484 total H1N1 deaths (6%) as of the end of August 2009. Pregnant women comprise approximately 1% of the general population. There are some anecdotal clinical observations regarding pregnant women with H1N1. These data are being collected systematically and should soon be ready for presentation. It is noted that these women experience rapid deterioration, and are extremely clinically fragile, have generally prolonged ICU admissions. There is growing evidence that this risk extends a few weeks postpartum. There has been a death in a woman who was 6 weeks post partum. Some of these women experienced delays in treatment due to false negative rapid tests. This is currently being examined.

Regarding additional clinical information on H1N1 deaths among pregnant women, data were published on 6 pregnant women in a *Lancet* paper published in late summer. All of these patients developed primary viral pneumonia with subsequent adult respiratory distress syndrome (ARDS) requiring mechanical ventilation. Of these pregnant women, 1 was in the first trimester, 5 were in the third trimester, 5 had cesarean deliveries (27-36 weeks gestation, 3 in ICU or ED), and 1 had a fetal loss at 11 weeks. Length of time from symptom onset to receipt of antiviral medication was 6 to 15 days, with a median 9 days. The length of time from presentation for medical care until receipt of antiviral treatment was 2 to 14 days, with a median 4 days.

In terms of race / ethnicity data, at the beginning of the outbreak a disproportionate number of Hispanics were observed among those affected largely due to travel to and from Mexico and residence in neighborhoods where people were engaged in a lot of travel. As the outbreak progressed, there was a declining proportion of Hispanics among reported cases overall. At the end of case report data collection in June 2009, the proportion of Hispanics approximated that in the general population. There are also some race / ethnicity data from the BRFSS. For the entire month of September 2009 accumulated, 5.48% Whites, 5.40% Blacks, 3.83% Hispanics, 6.41% other non-Hispanic, and 13.2% multi-racial / non-Hispanic reported ILI. Each racial / ethnic group had approximately the same proportion of healthcare seeking behavior among Whites, Blacks, and Hispanics.

Based on these data, it appears that acquisition of H1N1 or ILI was evenly distributed among racial groups, and that there was largely equal healthcare seeking behavior among these groups. However, based on data from the Pediatric Mortality System concerning children who died from influenza, there is a racial disparity. Hispanics had an overall higher proportion in the

spring season [17 (35%)], which declined somewhat at the end of September [6 (21%)]. This proportion is fairly consistent with season influenza deaths, although 25% is greater than the proportion of Hispanics in the population. Among Whites, it is a different story. There were greater numbers of deaths overall in the spring season [19 (40%)], with the overall proportion declining in the fall season [7 (25%)], compared with about 40% of the seasonal influenza population being White. In the spring season, Blacks accounted for 13% of all deaths (n=6), and that is about equal to the proportion in the population. However, since September 1 there has been an increase in the overall proportion of deaths among Blacks [9 (32%)]. Season influenza among Blacks is about 18% (n=13) overall, which is also slightly greater than the overall population of Blacks. There are only two Alaska Native / American Indian deaths to assess from H1N1 or seasonal in this system, and there are just two seasonal influenza deaths among Asians.

In conclusion, H1N1 is now widespread over most of the US. ILI Net rates are currently higher in October than they have been at the peak of the last 5 influenza seasons. Based on BRFSS data, 7% of the adult population and over 20% of the pediatric population reported ILI in the first 11 days of October. Hospitalizations are highest in the youngest children and decline with age, while excess hospitalizations are highest in the 5- to 17-year old age group. Deaths are lowest in the youngest children and increase with age, but only up to the 50- to 64-year old age group. Deaths decline slightly in the ≥65 age group. The majority of those hospitalized and dying from influenza have underlying conditions (76% pediatric and adult combined). Asthma is common among those hospitalized. Neuromuscular disorder is common among children dying from H1N1 influenza. Pregnant women are disproportionately affected by severe outcome. Racial / ethnic disparities in severe outcomes exist and warrant investigation.

Update on Influenza Virology

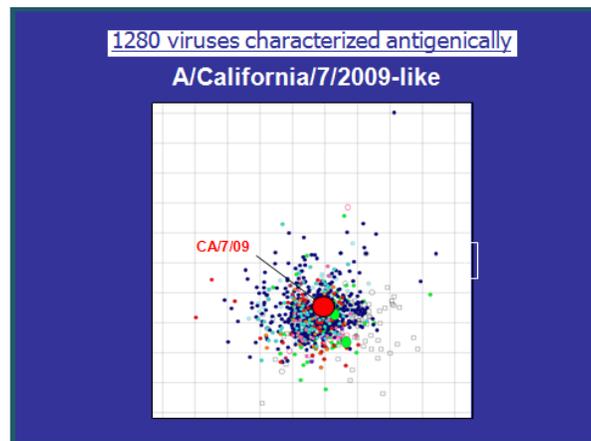
Nancy J. Cox, PhD
Director, Influenza Division
ACIP Meeting

Dr. Cox presented an update on influenza virology, pointing out that there was limited new information. Based upon the antigenic and drug susceptibility analyses of 2009 H1N1 viruses that have been conducted at CDC and globally, almost all 2009 H1N1 viruses characterized were antigenically and genetically similar to the A/California/07/2009 vaccine virus. Only a few viruses, and two analyzed by CDC's WHO Collaborating Center, have greater than 8-fold reductions in titers to the A/California/07/2009 vaccine virus, the antigenic difference considered to be significant. Where changes have occurred in the molecule is known, and the position of those changes makes sense in terms of the reductions in the HI titers.

Since May 1, 2009 CDC has characterized in detail 1280 virus isolates, of which 873 are from the US and 407 are from other countries. Among the viruses characterized, very minor genetic variation has been detected over time, although evolution is continuing. Complete genomes sequences have been completed for 76 of these viruses, with a focus on interesting cases (e.g., from fatalities, from individuals who were severely affected, those who have recovered with no complications). There is no evidence to date of reassortment between the 2009 H1N1 viruses and seasonal influenza or H5N1 viruses in the countries in which those viruses continue to circulate to infect humans. All 2009 H1N1 viruses are resistant to adamantanes. All 2009 H1N1 viruses are sensitive to zanamivir and the vast majority are sensitive to oseltamivir. A total of 38 oseltamivir-resistant viruses detected worldwide have been reported to WHO. When

a case is detected, there is an investigation. Most patients with resistant viruses had been taking oseltamivir for treatment or post-exposure prophylaxis at the time the oseltamivir-resistant virus was identified, suggesting that there is not a substantial amount of circulating oseltamivir-resistant viruses. All oseltamivir resistant strains are sensitive to zanamivir.

In the following illustration, the hemagglutination inhibition tables are shown, and the antigenic distances have been calculated and mapped onto this graph. This shows one US virus, which has an 8-fold or greater reduction in titer to the California reference virus, show by the large red dot. The remainder of the dots represents viruses that have been isolated from throughout the world that have been color-coded by region. In contrast to the seasonal picture observed for H3N2 viruses or seasonal H1N1 viruses, the 2009 H1N2 viruses are very nicely clustering tightly around the vaccine virus:



The following table illustrates more detailed information pertaining to neuraminidase resistance in seasonal and pandemic influenza viruses that have been collected over the last year:

Frequency of NI Resistance in Seasonal and Pandemic Influenza Viruses (Oct 01, 2008 – Sept 30, 2009)			
	Virus samples tested (n)	Resistant (%)	
		Zanamivir	Oseltamivir
US isolates:	4251	0 (0)	1156 (27.2%)
A/H1N1	1151	0 (0)	1146 (99.6%)
A/H3N2	266	0 (0)	0 (0)
Influenza B	655	0 (0)	0 (0)
A/H1N1pdm (Virus isolates)	1023	0 (0)	5 (0.5%)
A/H1N1pdm (Clin. specimens*)	1156	0 (0)	5 (0.4%)
Foreign isolates:	1207	0 (0)	206 (17.1%)
A/H1N1	305	0 (0)	205 (67.2%)
A/H3N2	260	0 (0)	0 (0)
Influenza B	217	0 (0)	0 (0)
A/H1N1pdm (Virus isolates)	425	0 (0)	1 (0.2%)
Global isolates:	5458	0 (0)	1362 (25.0%)
A/H1N1	1456	0 (0)	1351 (92.8%)
A/H3N2	526	0 (0)	0 (0)
Influenza B	872	0 (0)	0 (0)
A/H1N1pdm (Virus isolates)	1448	0 (0)	6 (0.4%)
A/H1N1pdm (Clin. specimens*)	1156	0 (0)	5 (0.4%)

Seasonal influenza H1N1 viruses remain predominantly resistant to oseltamivir, which is true for US viruses as well as viruses collected from abroad. In contrast, the seasonal H1N1 viruses isolated from the US are predominantly sensitive to oseltamivir, but there have been a handful of resistant viruses.

Serological studies using archived or banked sera demonstrated that only 4% of US residents born after 1980 had preexisting neutralizing antibody titers of 1:40 or greater against the pandemic H1N1 virus; whereas, approximately 34% of individuals born prior to 1950 and approximately 57% of individuals born before 1940 had titers of 1:80 or greater. This shows the age-dependent presence of cross-reactive antibody that seems to correlate very well with what is being observed epidemiologically. Vaccination with recent seasonal unadjuvated or adjuvanted influenza vaccines stimulated little or no cross-reactive antibody to the pandemic H1N1 virus in any age group. Seroepidemiologic studies to better understand secondary attack rates and risk factors for pandemic H1N1 infection in contacts of confirmed cases in household, healthcare, and community settings are currently under-way using both the HI and micro-neutralization assays.

The September 19-22, 2009 WHO Vaccine Strain Consultation convened in Melbourne, Australia focused on selecting vaccine strains for the Southern Hemisphere. The situation is very clear-cut. Seasonal Influenza A (H1N1) viruses predominated in many Asian and North American countries in early 2009, but have been isolated rarely since July. The majority of H1N1 viruses are closely related antigenically to A/Brisbane/59/2007, which was the recommended vaccine strain for the Southern Hemisphere. B/Victoria and B/Yamagata lineage viruses, which are very different from each other antigenically, co-circulated globally. However, the vast majority of viruses were of the B/Victoria lineage. Most B/Victoria lineage viruses are antigenically closely related to the B/Brisbane/60/2009 vaccine virus.

For H3N2 viruses, the situation is somewhat more complex. H3N2 viruses predominated in Europe last winter and caused outbreaks in several countries, including Southern China, more recently Northern China, and South Africa during the Southern Hemisphere influenza season. Many H3N2 viruses were antigenically and genetically similar to A/Brisbane/10/07, the previously recommended vaccine virus. However, an antigenically and genetically distinct variant represented by the A/Perth/16/09 virus has emerged and spread in recent months. An increasing proportion of H3N2 viruses analyzed globally are A/Perth/16/09-like in their genetic and antigenic characteristics. The majority of the small number of H3N2 viruses analyzed from the US are A/Brisbane/10/07-like or vaccine virus-like.

Because recommendations were being made for the Southern Hemisphere and an increasing proportion of viruses was being observed that were Perth-like, the H3N2 component was updated for the Southern Hemisphere vaccine, which will be used during the period March through May 2010. It was recommended that vaccines for use in the 2010 influenza season, the Southern Hemisphere winter, contain the following: an A/California/7/2009 (H1N1)-like virus, an A/Perth/16/2009 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus. Seasonal H1N1 was dropped from the recommendation.

Discussion

Dr. Keitel requested further information about the decision to drop seasonal H1N1, and the two lineages of B and whether any consideration had been given to increasing the valency of seasonal vaccines to account for these.

Dr. Cox responded that during the WHO consultation, the possibility of increasing the valency was not considered because it was known that it would be necessary to make as much pandemic H1N1 vaccine as possible and because the vast majority of influenza B viruses circulating were of Victoria lineage.

Dr. Keitel inquired as to whether antibody responses against H1N1 seasonal viruses had been examined among people who had been given the novel H1 vaccine.

Dr. Cox replied that this had not been done yet. CDC will be receiving serum from individuals who have been vaccinated with the 2009 H1N1 vaccine, so these studies can be done later. They will have a lower priority, but if there began to be a resurgence in seasonal H1N1 activity, that study would move to a higher priority.

Noting that Australia had experienced a greater seasonal epidemic this season, Dr. Judson inquired as to whether the epidemic there had followed a typical pattern from onset, to peak, to return to baseline.

Dr. Cox responded that the Australian activity had declined to more or less baseline. They were one of the first countries to roll out a 2009 H1N1 vaccination. While she did not know exactly how much vaccine had been delivered, their plan was to deliver as much vaccine as they could during a period when they would not expect to have much activity. There has been no indication that the activity has increased again. With respect to the pattern in Australia, it began earlier than usual but did follow more or less a typical pattern.

Dr. Marcy recalled that during the last ACIP meeting, it was reported that there was high oseltamivir resistance in H1N1 in Norway where it is hardly ever used, and in Japan where oseltamivir is used frequently, there is very little resistance. He wondered whether there was any change in the factors that were predisposing to a rise in oseltamivir-resistant strains, and whether Dr. Cox could explain this phenomenon and whether it had any pertinence to what was occurring currently. Use is being restricted due to concerns with this.

Dr. Cox responded that no one had been able to adequately explain oseltamivir resistance, and the ecological and virological factors that led to the emergence of the resistant seasonal H1N1 viruses may never be understood. What has been observed is that the majority of the seasonal H1N1 viruses that continued to circulate until recently, whether isolated in the US or abroad, retained resistance. If seasonal H1N1 viruses continue, this will be problematic for the foreseeable future. For the 2009 H1N1 viruses, an investigation is on-going to assess whether the individual from whom the resistant virus has been isolated was exposed to oseltamivir.

Dr. Sawyer inquired about the relative risk of pregnancy compared to other high risk conditions in women of similar age.

Dr. Finelli responded that she did not have the denominator of all people with underlying conditions to examine the risk of H1N1 hospitalization among women with underlying conditions or all pregnant women. It is not believed that pregnant women are at particularly high risk for acquisition of H1N1 or seasonal influenza, other than a slightly increased risk, but they seem to be at a much higher risk for severe outcome once they have influenza.

Based on the BRFSS telephone survey, Dr. Sawyer asked whether Dr. Finelli could estimate what percentage of the population has had H1N1.

Dr. Finelli replied that what is unknown is what proportion of the individuals surveyed actually had seasonal influenza, H1N1, or another respiratory virus. Over the next few weeks, a variety of sources of laboratory data will be reviewed to assess the attributable portion of influenza viruses among circulating viruses to try to specifically answer that question.

It seemed to Dr. Baker that among pregnant women, lung compromise would occur in the second and third trimesters. With that in mind, she wondered whether trimester information was available on the women who died.

Dr. Finelli responded that the 6 women who died were in the last trimester.

Dr. Jamieson added that greater than 90% of the 28 women who died were in the second and third trimesters.

Dr. Cieslak was impressed by the percentage of pediatric patients who had underlying conditions. He asked what the risk of hospitalization was among otherwise healthy children and whether it warranted a recommendation of vaccinating all children.

Dr. Finelli replied that there was a warranted recommendation for all children because they have such high hospitalization rates in general, especially the 0 to 4 age group compared to middle-aged adults.

Dr. Cieslak wondered whether otherwise healthy 5 to 17 year olds had a higher rate of hospitalization.

Dr. Finelli responded that she was not sure whether she could answer that question on a population basis, but in the normal influenza season there is a lower overall proportion of children with underlying conditions than with H1N1. About 50% of those children do not have underlying conditions in the regular influenza season.

Regarding the BRFSS data, Dr. Cieslak pointed out that at some point in season they would want to tally up the damage and he wondered whether there were any baseline data.

Dr. Finelli indicated that there were no baseline data. A very small BRFSS survey was conducted in 2006-2007 and a small survey was conducted in 10 states in May. Beyond that, there is no national baseline. However, CDC is trying to determine how to add up the damage.

Reflecting on the IHS report earlier indicating 2 to 3 times the rates of hospitalizations and deaths in the Native American populations in Arizona, Ms. Ehresmann noticed when Dr. Finelli presented the race / ethnicity data there were only a couple of people in the Native American categories.

Dr. Finelli responded that overall, the influenza-associated mortality system has not shown an extraordinary number of children with Native American race / ethnicity. Native American race / ethnicity is 3% to 4% of the total US population. Given that CDC has detected only a couple of deaths, they cannot make any conjecture.

At close to 8 weeks of influenza activity in the US, Dr. Meissner wondered whether Dr. Cox had any projection about what might be experienced in the next few weeks to months, and whether any experiences that have occurred in other countries could be used to anticipate what might occur in the US in January and February 2010 in terms of the seasonal strains.

Dr. Cox responded that it was very difficult to use what occurred in the Southern Hemisphere to predict what will occur during the US winter season. The US had a spring wave. The Southern Hemisphere had influenza H1N1 during their regular winter season. The US has had a very early season. In some communities, the influenza activity has begun to decrease, although in a number of areas there is a patchwork of activities. That is, some areas of the country really have not been hit as hard yet. It is known that influenza activity is not synchronous. H1N1 activity might be expected to decline significantly earlier than influenza tends to do in other years. However, that leaves plenty of time during the regular influenza season for seasonal influenza viruses to circulate if there are successful viruses and there is a susceptible population.

Noting that this was no longer a novel H1N1, Dr. Judson wondered when they would move on to designating this like the other epidemic strains.

Dr. Cox replied that the vaccine virus has been designated as A/California/7/09 for the reference virus and the vaccine strain. WHO made recommendations that included this as a vaccine component for the Southern Hemisphere, although they did not indicate whether it should be a trivalent vaccine or a bivalent plus a monovalent vaccine. It is very clear that the A/California/7/09 virus will be used for seasonal influenza vaccine in the Southern Hemisphere. There is not a clear definition of when a virus ceases to become a pandemic virus and becomes a seasonal virus. There is just a gradual change depending on the attack rates and how it blends into circulation of the other influenza viruses that are maintained in the population. The anticipation would be that as CDC meets at WHO and in Washington in February to consider recommendations for the next Northern Hemisphere vaccine for the world and the US, consideration will be given to what is being called the 2009 H1N1 virus as more or less a seasonal vaccine component.

Dr. Keitel requested information on what is occurring in tropical countries based on surveillance.

Dr. Bresee (CDC) replied that tropical countries have had predominantly pandemic H1, with substantially the same epidemiology of pandemic H1 as has been observed elsewhere (e.g., more frequently in the elderly).

Dr. Cox added that the viruses are antigenically similar to those isolated in temperate climates.

Dr. Bresee (CDC) noted that some tropical or semi-tropical countries have had continued H3N2 circulation, such as Laos and Southern China, with little or no H1 seasonal.

Dr. Cox emphasized that seasonal influenza viruses have continued to circulate in Southern China's normal season, the US's summer, and in Northern China as their season ramps up. They were still experiencing about 50/50 seasonal and 2009 H1N1 circulation

Dr. Baker requested that Dr. Finelli comment on the role of school children in the pattern of the decrease of H1 in the spring with school letting out and the increase in the fall with school reconvening.

Dr. Finelli responded that it was more than coincidence that little activity was observed at a time when few children were congregating in large settings like schools. There were fairly predictable outbreaks in schools about one to two weeks after school resumed.

Dr. Englund inquired about the burden of disease in children less than six months of age, for whom there are no vaccine and no antivirals.

Dr. Finelli replied that because she did not have those data with her she could not report the exact figures, but a very large proportion of the children hospitalized under the age of 4 are less than six months old. This is an extremely vulnerable population. She indicated that she would provide these data to Dr. Englund.

Dr. Baker suggested that perhaps immunizing the mother would offer a few months of protection in the infant.

Regarding the 38 oseltamivir-resistant isolates, Dr. Kimberlin (AAP) wondered whether their use of oseltamivir was prophylactic or treatment. He also wondered whether peramavir resistance had been tested.

Dr. Cox responded that peramavir resistant has been tested for and these viruses are not resistant to it. While she did not have a breakdown of how many were treated versus prophylaxed with oseltamivir, but they fell into both categories and there was not an overwhelming proportion in either category.

Dr. Keyserling (SHEA) asked Dr. Finelli to comment on whether what was occurring in this pandemic was solely driven by that fact that there was a very large non-immune population or if there were other factors involved.

Dr. Finelli thought that what was occurring was substantiated most elegantly by the ACHA data. In a population of 3.4 million in which there have been 47,000 infections, which is a lot, the college setting has had only 78 hospitalizations. That suggests that in a susceptible population there is a lot of disease, but the clinical spectrum is not severe. Also known is that there are unprecedented ILI rates at this time, and there is an extraordinary amount of transmission among young children, school-aged children, and young adults. Because there is such widespread disease, even if there is a condition with a mild spectrum of disease, a lot of deaths and hospitalizations can be expected.

Dr. Tan (AMA) reported on a "Dear Colleague" letter developed by the American Academy of Family Physicians (AAFP), the American College of Obstetricians and Gynecologists (ACOG), the American Medical Association (AMA), and CDC. This letter will be disseminated to all healthcare professionals across the country to draw attention to the need to vaccinate pregnant women against both H1N1 and seasonal influenza. The letter discusses the increased risk of

morbidity, why pregnant women should receive both seasonal and H1N1 vaccine, the safety of the 2009 H1N1 vaccine, and informs providers about how to acquire the vaccine. Accompanying the letter is a patient flyer fact sheet called "Pregnant Women and the Flu" that was developed by ACOG with AMA for physicians to provide to their patients to help assure them about the vaccine, and about the necessity to be vaccinated. Copies of the letter were distributed to the ACIP members and were placed in the back of the room for others who were interested in it.

Dr. Baker suggested disseminating such a letter each year for seasonal influenza.

Dr. Stephan Foster noted that in 1958 with the appearance of the H2N2 virus, H1N1 disappeared. In 1968 the H2N2 disappeared. With that in mind, he wondered why other viruses were continuing to circulate when there is such an extensive spread with the current virus.

Dr. Cox responded that in the Asian and Hong Kong pandemics, the emergent virus completely displaced the previously circulating influenza A virus though influenza B viruses continued to circulate, not just in that pandemic year but in subsequent years as well. In 1977, there was quite a different situation with the emergence of the H1N1 Russian Flu. Primarily those under the age of 20 or so were susceptible. People over that age had been exposed to similar viruses that had circulated during the 1950s and very similar viruses that circulated between 1950 and 1952. This meant that the population over the age of 20 had some immunity to the newly re-emergent H1N1 virus, but that compartment of the population remained susceptible to H3N2 and the virus could retain a foothold in that population. It is not clear what will occur with the current situation. Ideally, if the 2009 H1N1 virus would completely displace both influenza A viruses it would simplify vaccines, strain selection, et cetera. Given that a large compartment of the population who is older who had cross reactive antibody that seems in some sense to protect them, although it is a leaky antibody ceiling, from infection by the 2009 H1N1 virus, there certainly could be circulation of seasonal viruses in that population.

Dr. Turner (ACHA) agreed with Dr. Finelli that the congregate living and learning circumstances with a population that is 100% vulnerable to the infection is a set-up for spread of the disease. However, this age group is very social and they do not tend to socialize with 2 or 3 people. Rather, they socialize with many people packed into tight quarters that are not ventilated. They conducted a survey with approximately 700 students and even though they had been told not to share solo cups, which is code for beer cups, only 54% of students agreed with that statement and almost half of students did not believe sharing of cups to be a problem. Another challenge that concerns Dr. Turner is that when vaccine does become available, only about a third of college students are concerned about acquiring H1N1 because in reality when their friends get it, it is not severe. He did not believe they understood the transmission issue of giving the virus to someone who is highly vulnerable. He talked to CDC about messaging that could be given to young people to give some traction to notion that it is their social responsibility to obtain the vaccine in order not to spread the virus to others who may be vulnerable.

Dr. Duchin (NACCHO) expressed interest in focusing on the mortality rates, particularly with respect to those in the 25 to 49 and 50 to 64 year old groups, which are equal to or higher than the younger groups in terms of the number of deaths and the rates. In the context of the guidelines for H1N1 vaccine, which prioritizes by age and risk condition, people over 24 with an underlying risk condition would not necessarily be considered for vaccine during a shortage period. Therefore, he wondered whether any more information could be provided to help

prioritize the limited supplies of vaccines, particularly with respect to the presence of underlying risk conditions and the impact that they may have on the mortality rates reported earlier in the day.

Dr. Fiore responded that CDC is in the early stages of receiving hospitalization and death data through the new reporting system, and only limited information about underlying conditions was available from these data.

Dr. Finelli added that she does have information for the number of people with underlying conditions in the death case series for the different age strata conducted in the early summer 2009, but did not have it with her. She recalled that among those who died from influenza, 67% of the children under 18 had an underlying condition and approximately 80% of adults had an underlying condition. Overall, 78% of people in that case series had an underlying condition. Regarding underlying conditions in general, if they thought about overall underlying conditions or proportions of people with underlying conditions and proportion of risk groups in the context of pregnancy, it is known that 6% of people who die from influenza are pregnant women and pregnant women comprise only 1% of the US population. Also known is that 50% of children who died in this case series had neuromuscular conditions, which is 0.08% of the US population. About 38% of people of those who died had asthma, a common conditions among children overall. However, she did not believe anything was likely to exceed the increased risk noted among children with neuromuscular diseases.

Ms. Stinchfield (NAPNAP) noted that Children's Hospital in Minnesota where she is, there are thousands of children who meet the criteria for underlying conditions. However, they have only 1000 doses of vaccine. She requested further details on the metabolic disorders. She thanked the group for their terrific work, calling them heroes.

Dr. Finelli responded that other than diabetes she could not. She indicated that she could later provide further information.

With an infection that is by and large mild in most people, Dr. Katz (IDSA) wondered whether there was any evidence that there are people who become infected, but have no symptomatic disease but nevertheless develop immunity.

Dr. Fiore replied that this is known to occur with influenza viruses, in that people seroconvert over the course of a season without having a well-defined ILI.

Dr. Cox added that CDC is conducting some seroepidemiologic studies in some of the areas where the most complete outbreak investigations were conducted. The serologic data are not complete yet, but it appears that there was a lot more infection than there was reported ILI illness. It appears that a lot of the acute respiratory infections without fever actually may have been caused by the 2009 H1N1 virus. There will be asymptomatic cases, perhaps quite a few of those.

Robert Malone (Private Consultant) requested that CDC comment on the observation of Grayson concerning IgG-2 deficiency as a risk factor, and to comment on a related question regarding the role of bacterial suprainfection as contributing to morbidity and mortality in this case.

Dr. Finelli responded that she did not know the answer to the question regarding IgG₂ deficiency, although she did not believe they had any data on that. Regarding suprainfection, CDC is assessing in detail the pediatric deaths for which they have completed information. Of the 86 pediatric deaths that have occurred, they have completed medical records for 45 children. Of those, 12 had bacterial co-infection. Of those 12, 5 had MRSA, 2 had methicillin-sensitive *S. aureus*, and 1 had *S. aureus* sensitivity unknown. There are no other large groups of bacterial co-infections, although there are a lot of scattered organisms. About 20% to 25% of children who die have co-infection, which is consistent with seasonal flu, as is the distribution of organisms causing those infections.

Regarding the race / ethnicity data, Amy Groom (CDC Assigned to Indian Health Service) pointed out that the completeness of the data in the existing surveillance systems is fairly incomplete, especially with regard to the American Indian / Alaskan Native population that makes up less than 1% of the US population. Anecdotally within IHS, they know of more than one pediatric death and several adult deaths that are not getting picked up in the current surveillance systems. She wondered if someone could comment on what steps could be taken to help improve the race data in the existing system so that disparities could be effectively monitored.

Dr. Finelli responded that race / ethnicity data are routinely collected from all states willing to provide it. There are a few states that do not provide this data because they do not collect it themselves. With the American Indian population it is more complicated because there are some tribal nations which report their deaths to the state and others that do not. She thought they could work closely with the Tribal Nations Working Group (TNWG), which is an affiliate of CSTE to ensure that all of those deaths are counted and that better track is kept of them. This was discussed on a CSTE call the previous day.

Carlisle Creed (Creed Consulting) commented that in terms of disseminating information in the target population of age 12 to 30 years, she recommended using social networking and cell phones. Creed Consulting has had great success with that. The place to reach / vaccinate a lot of children who are on reduced lunch and Medicare / Medicaid is when they go for physicals to join athletic teams. These youth will have nice privatized hospital access.

Dr. Schaffner (NFID) requested that the information on bacterial co-infection be expanded for adults.

Dr. Finelli responded that there are data from the EIP that describe bacterial co-infection in children and adults. CDC is in the process of analyzing those data currently. They finally achieved a large enough number of bacterial co-infections in that system to make the data analyzable. An *MMWR* was recently published that addressed bacterial co-infections among 22 people of 77 on whom specimens were sent. For these 22 individuals, there was completed clinical and pathologic data. This study found that 28% had histopathological IHC or molecular evidence of bacterial co-infection, the majority of which were *Streptococcus pneumoniae* [n=10]. As she recalled, 9 of the 10 were adults and 1 was a 2-month old. There has been a fortunate phenomenon in the last couple of years in that, with vaccination, there has not been as much *Streptococcus pneumoniae* in children, although there continues to be *Streptococcus pneumoniae* in adults.

Dr. Neuzil reminded everyone that, as Dr. Fiore had noted at the beginning, the goal was to vaccinate as many people as quickly as possible. Unfortunately, the assumption about the next pandemic wave occurring before there was enough vaccine was correct. Therefore, everyone is struggling with many issues. One thing to point out is that these data are coming out in real time. The Work Group saw the death data during this session for the first time. The data do have some limitations. For example, the ethnicity data are not controlled for chronic diseases. There are also many other assessments that are difficult to do in real time, and for which the numbers are small. Therefore, she encouraged everyone to remember the limitation as these data were presented. Clearly, the missing piece was understanding vaccine supply and delivery before the group could deliberate whether the current recommendations make sense.

Given the delayed supply of H1N1, Dr. Baker inquired as to whether Dr. Neuzil believed the priority groups were still appropriate.

Dr. Neuzil responded that she would like to comment on that, but preferred to wait until the next two presentations were delivered.

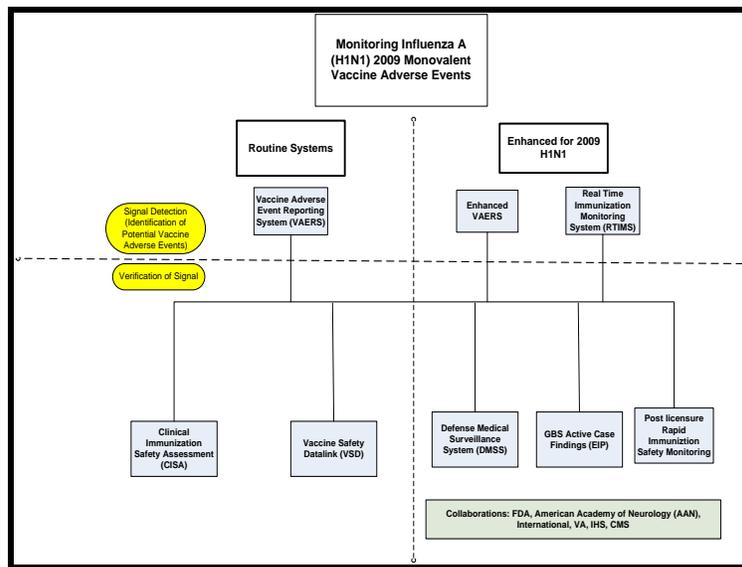
Influenza Vaccine Safety

Claudia Vellozzi, MD, MPH
Immunization Safety Office
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Dr. Vellozzi explained that vaccine safety monitoring is shared responsibility among many groups. Within HHS, CDC, FDA, and NVPO have the lead responsibility for implementing and coordinating this monitoring during the H1N1 response.

The objectives for 2009 H1N1 vaccine safety monitoring are to Identify clinically significant adverse events following receipt of 2009 H1N1 vaccine in a timely manner; rapidly evaluate serious adverse events following receipt of 2009 H1N1 vaccine and determine public health importance; evaluate whether there is a risk of Guillain-Barré syndrome (GBS) associated with the 2009 H1N1 vaccine; and communicate vaccine safety information in a clear and transparent manner to healthcare providers, public health officials, and the public.

Vaccine safety monitoring was not created for H1N1 vaccine. For the most part, CDC is building upon existing systems and increasing collaborations. The following diagram offers an overview of all of the systems that are in place:



In the above diagram, everything to the left of the broken line is systems that have been in place for several years. To the right of the broken line are new collaborations or new systems. Above the broken line are the systems that will help with signal detection to identify potential events quickly, while below the broken line are the systems that will help to strengthen and verify any signals identified. Collaborators are shown in the box in the lower right quadrant. Many countries are concerned about the safety of the vaccine; thus, CDC, FDA, and others are collaborating with international colleagues to share information that will help everyone.

Pertaining to the various systems, the Vaccine Adverse Event Reporting System (VAERS) is a voluntary reporting system jointly managed by CDC and FDA. CDC and FDA are engaging in daily meetings at this point to examine the VAERS reports on a daily basis. This system provides signal detection and is national in scope, flexible, scalable, and encourages reports from healthcare providers and accepts reports from vaccinees and others. For signal detection, basically VAERS uses the Medical Dictionary for Regulatory Activities (MedDRA) coding system for identification and frequency of symptoms, signs, and syndromes. The focus is on serious and other pre-specified adverse events that may have been identified through clinical trials, the literature, or case reports. Detailed clinical case reviews are conducted for every serious and pre-specified event with CDC and FDA on a daily basis. In addition to this clinical detail, various data mining tools are being used to sort through the data to find any new adverse events that may not have received clinical review, and to determine whether further review is needed of those found.

System enhancements to VAERS have primarily included communication efforts to promote timely reporting among healthcare providers. CDC is working diligently with states and partner organizations to increase staffing to process VAERS reports more rapidly, and to facilitate reporting of manufacturer and lot number by providing influenza vaccination cards to persons receiving 2009 H1N1 vaccine. VAERS limitations are typical to voluntary surveillance systems: Causality usually cannot be assessed, the quality of data is variable, there is no unvaccinated comparison group, denominator data are lacking, there is under-reporting (voluntary, passive reporting), and there is variation of reporting. Stimulated reporting can occur during times of heightened awareness (e.g., media attention, serious event occurs, *MMWR* release, other).

The Vaccine Safety Data Link (VSD) is a CDC collaboration with eight managed care organizations (MCOs) representing approximately 9 million US individuals (3% of the US population). This system can provide prospective weekly surveillance of pre-specified adverse events, known as rapid cycle analysis (RCA). Chart validation of outcomes can be performed. This requires vaccination information within the MCO's electronic vaccine registry (e.g., outcome linked with exposure). The VSD monitoring plan includes RCA, which is real-time surveillance of H1N1 vaccine adverse events. This is rapid assessment of pre-specified adverse events, including: GBS, seizures, meningoencephalitis, Bell's Palsy, demyelinating disease, anaphylaxis, other allergic diagnoses, and others. Up to 18 adverse events will be monitored on a weekly basis. An appropriate comparison group is used either through self-controlled case series (SCCS) analysis or comparisons with historical season influenza vaccines for rare outcomes. The VSD also has some limitations. There can be up to a 2-week delay for available outcome data. Adverse events with longer risk windows can add to the delay of analysis. Power may not be sufficient for rare outcomes with limited vaccine use. Vaccination information within the MCO is necessary.

Another collaborative effort is the Defense Medical Surveillance System (DMSS) Monitoring Plan, which is an ISO Vaccine Analytic Unit (VAU) collaboration with DoD, CDC, and FDA. This database is comprised of approximately 1.5 million Active Duty US military personnel per year. Use of this system includes electronic medical record reviews, and estimates of background incidence rates for this specific population. Also being done are signal detection and testing using rapid cycle analysis similar to the VSD analysis. Case-control or self-control case series analysis are conducted to assess specific vaccine association using similar methods as VSD. DMSS / VAU limitations are similar to the VSD limitations. There is an electronic medical record system; however, it is new and has not been tested for accuracy. Moreover, this database does not represent the general US population. However, it does offer data on early vaccinees.

The Clinical Immunization Safety Assessment (CISA) network supports H1N1 vaccine monitoring. This is a group of subject matter experts (SMEs) for 6 academic centers who review clinically significant adverse events and assist CDC with complex VAERS reports. They are readily available for consultation. This system has an infrastructure to collect and store biological samples for use in future hypothesis-driven studies, and they have the capacity to investigate a host of risk factors associated with adverse events.

The Real Time Immunization Monitoring System (RTIMS) is an automated web-based active surveillance system targeting certain sub-populations of vaccinees (e.g., school-aged children, healthcare workers, and pregnant women) who are enrolled at the time of vaccination and are followed up periodically post-vaccination up to 42 days. This is a collaboration between CDC and Johns Hopkins School of Public Health.

Dr. Vellozzi then explained that Guillain-Barré Syndrome (GBS) is an immune-mediated acute demyelinating polyneuropathy affecting the peripheral nervous system. The estimated annual incidence rate is 1 case per 100,000 population. In 1976, a type of influenza vaccine was causally associated with GBS. There was an excess risk of 1/100,000 persons vaccinated. Subsequent studies of influenza vaccines have found small or no increased risk of GBS [Institute of Medicine, 2004]. If there is a risk of GBS from seasonal influenza vaccines, it would be no more than approximately 1 case per million people vaccinated. In follow-up to that, GBS active case-finding surveillance is being conducted in collaboration with CDC's EIP. While this is an active GBS case-finding effort, it can be shifted to assess other adverse events as necessary. The Neurology Network is the source of the case-finding. Through this surveillance

vaccination status can be ascertained, and risk factors for GBS can be identified including antecedant infection. The catchment area includes approximately 50 million US population in 10 states. An important collaboration that will support this case-finding as well is the American Academy of Neurology (AAN) collaboration. The primary goals of the collaboration are to increase VAERS awareness to enhance GBS reporting, and to support active case finding in EIP. One webinar has already been completed for neurologists throughout the country, and another is planned to target the EIP areas. The Provisional Brighton Collaboration GBS case definition is being used for the active case findings [http://www.brightoncollaboration.org/internet/en/index/definition___guidelines.html].

The Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system is a new system that is a collaboration being led by the National Vaccine Program Office (NVPO) in collaboration with FDA and CDC to increase the capacity to monitor vaccine safety in near real time. This system links exposure data (e.g., vaccine registry data) to outcome data available in large healthcare plans in several states, and uses sequential analytical methods similar to the VSD system.

CDC support of state and local public health during H1N1 vaccine safety monitoring efforts includes collaboration between CDC's ISO and Vaccine Safety Coordinators in 62 locations throughout the US. There are frequent telephone calls with these coordinators. There is on-going training and communication for 2009 H1N1 vaccine safety issues. Technical and epidemiologic assistance are provided for vaccine safety investigations as needed. There is also regular communication with ASTHO, NACCHO, CSTE and other partners. Dr. Vellozzi expressed gratitude to the states for their dedication to participating in and enhancing reporting to VAERS and collaborating with CDC on vaccine safety monitoring efforts.

An important component of the vaccine safety monitoring effort is to provide high quality risk data to inform policy decisions. Under the auspices of NVAC, the H1N1 Vaccine Safety Risk Assessment Working Group has been developed. The purpose of this group is to provide a transparent, independent review of vaccine safety data as it accumulates; and to assist the federal government in rapidly assessing possible associations between vaccination and adverse events. This working group will include 10 members from federal advisory committees, the Institute of Medicine, and the public. Members must meet conflict of interest requirements. This working group will also receive support from ex-officio members from NVPO, CDC, FDA, NIH, DoD, VA, and other medical experts as needed. This working group will report to NVAC. CDC, FDA, DoD, and VA contribute scientific expertise and the data, while NVPO coordinates activities.

In summary, for 2009 H1N1 vaccine monitoring, the established vaccine safety infrastructure will be utilized, and enhancements will be implemented. New collaborations have been developed. CDC will provide support to states and territories during 2009 H1N1 vaccination program. The new HHS H1N1 Vaccine Safety Risk Assessment Working Group will provide an independent, systematic review of safety data. Vaccine risk communication is an important component of the vaccine safety monitoring effort.

Influenza Vaccine Supply

**Bruce G. Gellin, MD, MPH, Director
National Vaccine Program Office
Department of Health and Human Services**

Dr. Gellin reported that to date, the NVPO has contracted for 251 million doses of H1N1 bulk vaccine, and that 117 million doses have been contracted to fill into vials, syringes, and sprayers for immunization programs. Additional doses may be filled for delivery by the end of the year as needed. Vaccine development began in late May 2009 when the five US licensed influenza vaccine manufacturers received the virus reference strains from CDC and began making virus seed stocks. Commercial manufacturing began in late June and early July 2009. The US Government began to receive shipments of subsequently in early October 2009. The first immunizations began the first week in October. Shipments are expected every week into late December 2009 and beyond if necessary.

The amount of H1N1 vaccine currently available was less than earlier projections from last summer and revised in September. They were all reminded the previous day about other vaccine supply disruptions, illustrating that this was not limited to influenza vaccine. Influenza merely happened to be “under the microscope.” Obviously, there was concern about the impact that such disruptions would have on immunization programs and the health of the public. In an era when vaccines have, indeed, changed the epidemiology of vaccine-preventable diseases to the degree that some questioned their need, such disruptions highlighted the value of vaccines and their ability to prevent serious infectious disease and their complications, particularly in light of what was reported during this session about the epidemiology of this disease.

Dr. Gellin explained that there were several reasons for the delay of H1N1 vaccine, which was what he was asked to address during this session. Given that the available US supply is an aggregate of the production of the five suppliers with whom NVPO has contracted, Dr. Gellin stressed that he was presenting an understanding of the factors that contributed to the current supply situation, and that he could only offer a broad picture versus the specifics of individual manufacturers. However, he said it was worth noting that in contrast to the influenza vaccine supply situation a few years ago when there was just a single supplier, there are now five manufacturers of influenza vaccine who contribute to the supply each year. With respect to the medium- and long-term, a more diverse set of manufacturing technologies and next generation influenza vaccines are envisioned. In view of the current situation, the level of preparedness is a function of the overall capacity that is available and the great number of expanded resources that offers insurance against the “bumps in the road” that would otherwise derail immunization program plans. It is also encouraging that the recent era of pandemic preparedness, coupled with the significant funds provided by Congress and the private investments by manufacturers, will bring about additional production capacity in next generation vaccines that will add to preparedness for influenza pandemics and seasonal influenza.

The development and manufacturing of vaccines have many variables, beginning with growing virus seed strains, to formulation, to filling vials and syringes. From the beginning, the working guide was to obtain as much vaccine as possible as soon as possible. It is important to remember that vaccines are biologicals that depend on biology rather than chemistry. Projections of influenza availability are predicated on past experience with influenza viruses; the various production systems manufacturers use; manufacturers' production schedules, which are

regularly adjusted and readjusted depending upon production years; the availability of dedicated production lines; and how well and quickly issues arise and are resolved.

The issue the US is facing is the same issue being faced around the world. While it is often said that the “infectious diseases know no borders,” the biological basis of influenza vaccine manufacturing is transnational as well. As the first doses of H1N1 vaccine were available in the US in the first week of October and just prior to that in Australia, it was only earlier in the week that immunization began in the United Kingdom and France.

The projections ACIP was given in July were based upon the initial production yields, which were modest, and the assessment of manufacturing capacity that would be available, including the production and fill and finish lines. Those projections were made in the absence of the availability of a potency assay that would then later more precisely measure the amount of hemagglutinin being produced, and was a measure of the efficiency of the H1N1 virus in these various systems, particularly the production of the hemagglutinin—the key immunogen.

Early September, when the potency assay was available, was the first indication of the poor production yields. That was also a time during which there were many questions about how the virus was doing in these manufacturing systems. While there was some variability among the manufacturers in their production efficiency, it is worth noting that for some producers this was three- or fold-fold less than was expected. This meant that all vaccine bulk produced over the summer was going to be significantly less than initially projected. Given that the summer production was expected to make a major contribution to the initial bolus of vaccine in October, this problem greatly contributed to the total amount of vaccine currently available. When this issue was first detected, many manufacturers addressed it by using new virus strains that were provided to them or adapting the virus strains in their systems to improve production yields—something that they routinely do during seasonal flu vaccine manufacturing. The result of all of these efforts is that bulk vaccine production yields are now equal to or in some cases in excess of the original expectations, but the fruits of those changes in the initial manufacturing steps will not be realized for several weeks or beyond.

In addition to the change in the projections based on the potency assay results, the other key factor that arose was the contribution of seasonal influenza vaccine production, particularly with regard to fill and finish capacity. Vaccine manufacturing is specialized, and those who are producing the H1N1 vaccine are the producers of the seasonal vaccine as well. They use the same processes, facilities, testing, et cetera except the virus that starts this. This year seasonal vaccine production lasted longer than expected because of the inefficiency of production of one of the strains, and there cannot be a trivalent vaccine until all three strains are in it. Ironically, that problem also occurred with the H1N1 vaccine, which required some adjustments to improve that yield of that strain. The bottom line was that the production took longer than anticipated, which intersected with the production of H1N1 vaccine.

Since October, weekly projects of H1N1 vaccine for the US have been provided to state health officials. A major change in projections was made the week before this ACIP meeting based on several events. In early October, a more thorough analysis of the range of data from all of the manufacturers and the magnitude of the poor production yields for the lots manufactured over the summer were completely analyzed, which was responsible for the change in the projections. Also learned the week before this meeting was that some of the new fill / finish lines that were put in place to handle this greatly increased downstream processing for H1N1 and seasonal vaccine experienced brief interruptions in operations due to some of the initial start-up

problems. These issues have now been resolved and are back on track, but it takes a while to catch up. Also learned the week before this ACIP meeting was that vaccine formulation filling into vials by one of the manufacturers is facing some technical challenges that have not been solved to date. The availability of this vaccine, which was to be a small amount of the total for the US and was initially projected to be available in December may now be delayed until after the first of the year.

NVPO is hopeful that by early November, there will be another 43 million doses of vaccine. Through November and the rest of the year, the vaccine supply situation is expected to be greatly increased with widespread availability. It is important to remember how fortunate it is that multiple suppliers have been working on this. This provides insurance against a catastrophic problem that may be experienced, as has occurred with other vaccines. There are daily conversations with the manufacturers and others at all levels. The manufacturers have assured everyone that they are doing everything they can to meet this public health challenge. These delays are occurring across the globe, and the pandemic supply is testing the limits of present day capacity and manufacturing processes, which are being addressed in the long-term.

Discussion

Dr. Baker inquired as to how many doses were expected to be sent to states during the month of October.

Dr. Schuchat indicated that the Friday before this meeting, a press conference was held during which CDC offered an update regarding the challenges with production. By the end of October, they expected to be at 28 million doses versus the projected 40 million. Important to know is that projecting many weeks ahead will be challenging. It is very important for the states to have as much data as possible about those forward projections so that they can plan. CDC is trying to give the states everything they can, but the certainty with which each of those targets will be met is limited. CDC has committed to updating everyone when they know something new. More doses are being distributed each day.

Dr. Baker asked how much of the vaccine that had been distributed was inactivated.

Dr. Schuchat replied that more than half of the doses are injectable.

Ms. Ehresmann pointed out that many people were familiar with the vagaries of the influenza system and were not surprised by the current situation. However, a major challenge was that highly optimistic projections being made from higher up than CDC were creating major demand from the public for vaccines that will not be met. While she appreciated the various projections, she requested that in the future there be a moderated approach from levels above.

Dr. Sumaya pointed out that during earlier ACIP deliberations, there were discussions regarding demand and supply. Supply was a particular gauge for targeting priority groups. At this point, he wondered who was assessing that and whether there needed to be a change in priority groups.

Dr. Schuchat responded that they are trying to report weekly about the dose situation in terms of doses that would be the most meaningful for communities. Every Tuesday and Friday, CDC reports the aggregate number of doses available for order by states and the number of doses that have been ordered by states collectively. Every Friday state-specific information is included on how much has been shipped. The primary information the public wants to know is how much is in their states or cities. Prioritization has been formally assessed in a number of ways. When ACIP voted in July 2009, there was a strong focus on having national standards as well as local flexibility. CDC has re-evaluated that focus a couple of times and still believes that this is the appropriate approach. Formal decision analysis work has been done to sort out whether great sub-prioritizing could prevent more deaths. The concept that ACIP and the Work Group had about avoiding over-prioritization and having doses sit around was quite prescient. CDC is aware of some locations in which supply exceeds demand and other places where demand exceeds supply. The assumption moving forward is that the priority groups have been well-publicized. CDC plans to assist with the communications about setting expectations and let the states that are directing the doses use them as effectively as they can.

Dr. Englund agreed wholeheartedly with the prioritization. She thought that the ACIP Work Group, with a great deal of assistance from many experts, had assessed various and multiple options about how to prioritize. No one believed this could be regulated, particularly in a changing environment. Expectation and having no vaccine continue to cause hardships to many.

Dr. Neuzil emphasized that nobody on the Work Group wanted to prioritize. The situation had to do with responding to the delay in vaccine. It is known from past experience that by over-prioritizing, there is a risk of vaccine going unused. It is also known that there is not a clearcut ranking from top to bottom of people at highest risk. A large number of people are at risk of morbidity and mortality. They want to give the opportunity to as many people as possible to receive these vaccines. She thought that the delay placed the greatest stress during the earliest phase. Given that the pandemic is on-going, she noted that there were some potential and relatively simple alternatives to increase supplies that might include an Emergency Use Authorization (EUA) for LAIV that would allow for an expansion of the age groups, for example for healthcare workers who happen to have reached their 50th birthday or beyond, or even half dose vaccine for immunocompetent children and adults. She requested that the FDA comment on issuing EUAs for these alternatives.

Dr. Sun (FDA) responded that the FDA has been very much engaged in the issues related to H1N1 vaccines, and rapidly evaluated and approved the strain change supplement. While there are various scenarios in which EUAs can be used. They are typically for use of unapproved products or unapproved use of approved products. For example, a vaccination that does not have age indications in certain groups can be used under an EUA. However, that decision must be made by the Secretary. While the scenarios suggested by Dr. Neuzil could be entertained, they must be submitted, evaluated, and analyzed for risk-benefit. It is not for FDA to mandate that certain EUAs be brought about. This has to come from the department and from sponsors who are requesting these EUAs. This is worth discussing and FDA is prepared to assist in any possible, but this decision would not originate with FDA.

Dr. Baker emphasized that the epidemiology presented earlier in the day offered reassurance that ACIP's July prioritization was appropriate. However, vaccine can only be distributed when it is available. It was clear in her state that a healthy amount of supply went out proportionate to the rest of the states. However, many of the decisions are being made locally. While one may

agree or disagree with local decisions, she maintained that this was not CDC's job. CDC is doing an ample amount of work and had communicated wonderfully to the state and local health departments to do the best they could under a dynamic and difficult situation.

Dr. Duchin (NACCHO) agreed that while they may not want to prioritize, some people in some locations may need to do so. ACIP already offered a form of guidance in proposing a subset of initial target populations to consider when providers felt the need to do so. He proposed that they discuss including those between the ages of 25 and 64 who have the highest mortality rates and the highest number of deaths. They are currently not included.

As one who abandoned growing viruses in eggs 53 years ago and switched to cell culture systems, Dr. Katz wondered what incentives the US Government, which was paying for all of the vaccine this year, would impose on manufacturers to change to cell cultures systems in which viruses can grow much more rapidly, with much large numbers from much smaller input. This may be beneficial in future situations.

Dr. Gellin responded that significant incentives have already been offered, once of which is in Holly Springs, North Carolina where one manufacturer is building a cell culture facility. Unfortunately, this will not address this pandemic. Recognizing this years ago, a number of efforts were put in place, beginning with adjusting the egg supply so that there is a year-round supply of eggs, which did not used to exist. He thought Dr. Katz' comment was important with respect to the medium term for increased capacity and the longer term for new technology, particularly those that are more nimble that could shorten the time between when a virus emerges and when a vaccine is ready.

Dr. Iskander indicated that a sponsor for an EUA would be CDC. Some recently published survey data provides guidance about some of the communications and vaccine acceptance challenges that might accompany any use of a vaccine under an EUA. He agreed with Dr. Neuzil that it was important to consider a variety of solutions.

Regarding clear communication of the ACIP's recommendations, Dr. Schaffner (NFID) indicated that he had received several emails throughout the day asking him to bring to the attention of the committee the use of LAIV in healthcare workers, particularly those who work in neonatal intensive care units. His recollection of the discussions establishing those recommendations was that LAIV in healthcare workers was fine. The only intensive care unit or patient population for which concerns were expressed about LAIV regarded bone marrow transplant units. The Red Book affirms that as well. This question has come through the Emergency Operation Center and contrary information is now being provided to hospitals. He thought it would be beneficial if ACIP could reaffirm the original intent and what is currently in the recommendations in order to clear up this issue.

Dr. Baker agreed that this was causing a great deal of confusion, and stressed that it was a very important issue.

Dr. Fiore responded that CDC has heard from a number of healthcare facilities that have been very reluctant to use LAIV within the facility itself, not just within intensive care units. It was clear from the 2006 healthcare worker recommendations for not using LAIV was only for those healthcare workers who were in special protected hospital rooms, such as those for bone marrow transplant patients. This was in the absence of any evidence that this was actually a problem. It was strictly a precaution. Dr. Fiore indicated that he would work with the EOC to

ensure that the correct information was being disseminated. He thought it was clear in the ACIP guidance, and CDC has been trying to communicate in a variety of ways to get beyond their concerns about LAIV use in hospitals in general (e.g., Q & A on the website, et cetera). While it was somewhat of a surprise that this was an issue, he assured everyone that CDC would address it.

Dr. Baker summarized that except for bone marrow transplant units, LAIV use in healthcare workers is recommended.

Dr. Lett said she thought it was a miracle that vaccine was available so soon, and that everyone who deals with influenza understands the issues. She stressed the importance of continued communication and keeping everyone in the loop with respect to continued developments in vaccine production.

It was Dr. Keitel's understanding that a greater quantity of LAIV could be made available, but the delivery devices are limited. She reminded everyone that the development of these vaccines involved the use of droppers to administer LAIV, which got at an emergency use type of authorization and begged the question about what the trigger would be to begin pursuing alternative strategies. That is, how high does the case fatality rate have to be before instituting the use of adjuvants or EUAs.

Dr. Sun reiterated that the FDA was open to considering all options in this pandemic. While he could not specifically address the issue of the delivery device for LAIV other than to say that as a regulatory agency, the FDA is responsible for ensuring that all products are pure, safe, and potent even as urgent as the pandemic situation may be.

Dr. Pickering indicated that several of those present had just returned from the national AAP meeting where 12,000 pediatricians were gathered. He clarified a potential misconception heard there. Based on what Dr. Gellin reported, it appeared that the delay in H1N1 vaccine production was due to potency and filling issues and had nothing to do with safety. Nevertheless, concerns persist about the safety of H1N1 vaccine. Despite assurances that the vaccine is safe, the delay has further accentuated the concerns in some quarters.

Dr. Gellin responded that it was correct that the issues pertained to production versus safety.

Ms. Ehresmann pointed out that in discussing the vaccine safety monitoring that would be taking place, Dr. Vellozzi had used the term "We are concerned about the safety of this vaccine." She stressed that statements be made to reassure the public that because of the widespread use and promotion of this vaccine, existing surveillance systems are being enhanced to ensure that there is timely reporting in order to detect any signals quickly—not that there is anything about this particular vaccine that makes it less safe.

Dr. Schuchat clarified that CDC has no reason to believe that the safety of this vaccine will differ from seasonal influenza vaccine. About 100,000 million people receive seasonal influenza every year and they have a very good safety record. CDC knew that there were concerns in the community, and that a lot of vaccines would be administered in the fall, so they wanted to strengthen vaccine safety monitoring to ensure that if there were any unanticipated issues they could be found promptly and appropriate action could be taken.

Dr. Schaffner (NFID) pointed out that the words they use and their intentions can be heard differently. The use of the word “concern” is one problem and there has been a “rush” to produce this vaccine. “Rushing” to produce this vaccine in his mind meant “worked very hard” to produce it. However, this has sometimes been heard as “cutting corners.” Hence, they must be very carefully about language.

Dr. Hasbach (sanofi pasteur) reminded everyone that in June, he stressed that the numbers were optimistic and that he did not believe they were totally realistic, given that they counted on everything going perfectly. However, it is known that nothing goes perfectly from flu season to flu season. Regarding Dr. Katz’ position on cell culture and new technology, he thought egg technology has been belittled lately and unfairly so. All manufacturers are working on multiple new technologies, including universal vaccines, et cetera. If put head to head with the virus introduction into each of the facilities and their different production processes, they was only a week or two separating the ability of first lots of vaccine, lots in clinical trials, et cetera. Major savings are not gained by have cell culture facilities. There are other ways to make gains. Even with new technology for reverse genetics, they had to rely on the first seed strains coming out as the classic reassortant because there were some glitches with the new technology of reverse genetics. He believes that egg-based technology is a tried and true methodology. However, what is really needed for all of these vaccines is to work on release testing. That is where a lot of time is consumed. Being able to identify earlier in the process exactly how much antigen there is critical. Something different is needed, otherwise they will always be in this position.

Update: 2009 Influenza Vaccine Implementation

**Pascale Wortley, MD, MPH
CDC / NCIRD / ISD**

Dr. Wortley reported on 2009 influenza vaccine implementation to date. Regarding the funding disseminated through the Public Health Emergency Response (PHER) cooperative agreement, in late July and August, approximately \$1.5 million was distributed through Phase 1 (\$260,000) and Phase 2 (\$248,000). Those funds were for accelerated planning and early implementation. At the end of September the Phase 3 funding of \$846,000 was disseminated for implementation. By and large, the Phase 1 and 2 funding has made its way from states through the county level. The Phase 3 funds are in the process of doing so currently.

In terms of distribution, during the late July ACIP meeting, CDC was in the process of making a decision about the distribution process. Ultimately, a decision was made to implement centralized distribution. All products, including vaccine and supplies, are allocated across states pro rata according to population as they become available. All states receive daily updates and place orders against their allocation. Those orders first come to CDC where there is a verification process, and are then transmitted to the distributor. The distributor then fills and ships the orders. The minimum shipment size is 100 doses, which was necessary to limit the number of shipments due to capacity and cost issues. There has been an increase in distribution sites from 90,000 to 150,000 over the course of the campaign, and an accelerated shipping timeline was instituted on October 12th. That eliminated approximately 2 days from the process. For example, if a state places an order on Monday, it will ship out of the distributor Tuesday and arrive on Wednesday.

Ancillary supplies are being distributed along with vaccines, which creates some additional logistical issues. The ancillary supplies are kitted and sent to the same distributor dealing with the vaccine; however, the distributor ships the vaccine and the kits separately. Although programs are accustomed to ordering vaccine, ordering ancillary supplies is a different process. Learned over the past few days is that ancillary supplies are reaching points of administration, but there are some issues related to the fact that providers are receiving supplies they may not be accustomed to using, so there are some training issues involved. In addition, kits may contain multiple products. The first kits ordered included adjuvant mixing needles as a contingency measure. Although these will no longer be included, they created initial confusion at the start. The accelerated shipping timeline means that ancillary supplies and vaccine arrive the same day. Previously, ancillary supplies were meant to arrive before. As providers become accustomed to the routine, these are not anticipated to be continuing issues.

Vaccination financing has also been a major topic of interest. The goal of vaccination financing is to balance reasonable payments to providers with affordable access to individuals. While the vaccine itself is free, the clinical administration fees for providers come from several sources. Administration fees are supported by government health insurance plans, and at this point it appears that the private health insurance sector is supporting this as well. Many plans have waived or do not require cost-sharing. Private sector vaccinators may collect an out-of-pocket fee up to regional Medicare rate from individuals. In addition, PHER funding and insurance billing supports mass vaccination, school vaccination, and contracts with community vaccinators. Public health clinics and clinics associated with public health may not charge out of pocket fees to individuals, but may bill insurance. Two sets of Qs and As for financing and billing available on CDC's H1N1 web site, which took a while to develop due to the complexity of the issues.

Regarding doses allocated and ordered by day, although greater on some days than others, most days there have been increases. Over the three week period from September 30th to October 19th, there has been a catching up of ordering in relation to the allocation in terms of the national aggregate. When assessed state by state, there is some variation in patterns for a number of reasons that pertain to how states are operating their programs.

CDC has a collaboration with the University of Michigan with Sarah Clark, Gary Freed, and others to collect information on an on-going basis on implementation know as the Vaccine Implementation Tracking Project. Sarah Clark and her group make calls to states every 1 to 2 weeks focusing on emerging issues. Feedback is provided back to states through ASTHO and Association of Immunization Managers (AIM). This has been a useful project. States like to see how they stand in comparison to others, especially given the diversity of ways that this is being implemented. Some of the results from that project, collected from October 5 through 9 based on calls with 40 states and 4 separately funded cities, follow. Decision-making for the allocation of vaccine is occurring for 29 states at the state level, in 14 states at the local level, and in 3 states at the state and local levels. One of the implications for states in which decisions are made at the local level is that when a state receives allocations, they provide them to counties, counties make decisions, and return them to the state. That introduces a lag in distribution and differences in patterns.

CDC was also interested in knowing whether the initial allocations went. Based on data collected during the first two weeks of ordering (9/30-10/9) for 44 states and 4 cities, 33 states have established specific target populations at the state level, and 14 states delegated targeting to local health departments. States were largely targeting healthcare workers, pregnant women,

and children with some variation. Another recurring theme was resistance to the use of LAIV in healthcare workers and shifting of unused doses of LAIV from healthcare workers to other eligible groups. Also observed was that there has been infrequent targeting of caregivers of young infants.

Information has been collected from states regarding how many provider agreements have been signed. As of October 12th, over 72,000 providers were registered. A provider agreement is signed by a practice or an institution, so that number does not represent individuals. For example, a retail pharmacy chain might sign an agreement for all of its locations in a given state. The retail pharmacy sector has been widely engaged in most states. Almost all states are planning some degree of school-located vaccination, while some plan vaccination in every school district. However, the timing of school-located vaccination is in question due to supply issue. Communities are drawing upon a variety of staffing resources for clinics.

Challenges include the compressed timeline. It would have been beneficial for more timely transfer of funds to the local level. In addition, complex issues had to be resolved at the federal level with planning implications for state and local levels. Vaccine availability has been a major challenge in terms of uncertainty with regard to shifting projections, which has many implications for implementation. When the drops occurred over the last few weeks, a number of states reconsidered their plans to determine whether they were suitable based on the current supply. Many states had intended to move forward with the public and private sectors simultaneously; however, reduced supply in some areas is making this difficult to do. The initial allocations were quite small, with approximately 2.4 million doses of LAIV the first week. It is always challenging to allocate small amounts of vaccine. There was then an additional challenge of matching vaccine formulations to target populations. During the first week there was only LAIV. During the first two weeks combined, there was approximately 50 / 50 LAIV multi-dose vials for 6 months and older. Currently, the proportion of LAIV is decreasing. Communications and managing demand in relation to changing availability have also posed major challenges. These are just some of the glaring challenges of many challenges being faced at the state level.

A Harvard Opinion Research Program poll was conducted by the Harvard School of Public Health from September 14-20, 2009 regarding public attitudes about 2009 H1N1 flu vaccine. This poll was conducted with 1000 people. Of those asked whether they were concerned that someone in their immediate family may get sick from 2009 H1N1 during the next 12 months, on 6/28/09 38% said they were concerned, while on 9/20/09 52% said they were concerned. Of those asked whether they would get the 2009 H1N1 flu vaccine on 9/20/09 53% said yes and 40% were absolutely certain. Of those asked whether they thought they would get this vaccine for one or more of their children, on 9/20/09 70% said yes and 51% were absolutely certain.

Major reasons adults said they would not, were not sure, or may change their mind about getting the H1N1 vaccine included the following: 30% were concerned about side effects, 28% did not think they were at risk for a serious case, 26% thought they could get medication to treat H1N1, 21% were concerned about getting H1N1 from the vaccine, 20% thought getting the vaccine would be too expensive, 20% were concerned about getting another serious illness from the vaccine, 19% said they do not trust public health officials to provide correct information about vaccine safety, 17% did not think the vaccine would be effective, 16% said they do not like shots / injections, 14% said they planned to get seasonal flu vaccine and believed it would protect against H1N1 as well, 10% indicated that their healthcare provider said they should not get the vaccine, 8% thought it was too hard to get to a location for the vaccine [Harvard Opinion Research Program, Harvard School of Public Health, September 14-20, 2009].

Major reasons parents said they would not, were not sure, or may change their mind about getting the H1N1 vaccine for their children included the following: 38% were concerned about side effects, 33% were concerned about their child getting another serious illness from the vaccine, 31% said they do not trust public health officials to provide correct info about vaccine safety, 27% did not think their child was at risk for a serious case, 24% were concerned about their child getting H1N1 from the vaccine, 23% did not think the vaccine would be effective, 15% said their child did not like shots / injections, 13% thought that getting the vaccine would be too expensive, 12% who said they planned to get seasonal flu vaccine for their child believed it would protect against H1N1 also, 7% said their healthcare provider told them not to get it for their child, 4% thought it was too hard to get to a location for the vaccine, and 3% indicated that their child was less than 6 months old and could not get the vaccine [Harvard Opinion Research Program, Harvard School of Public Health, September 14-20, 2009].

Regarding American public views pertaining to the safety of H1N1 versus seasonal flu vaccine, 57% felt that seasonal flu vaccine was very safe for most people to take compared to 33% for H1N1 vaccine; 29% felt that seasonal flu vaccine was very safe for children 6 months to 2 years compared to 18% for H1N1 vaccine; 25% felt that seasonal flu vaccine was very safe for pregnant women to take compared to 13% for H1N1 vaccine.

A number of coverage monitoring systems are in place. The National 2009 H1N1 Flu Survey (NHFS) will provide national estimates of coverage and behavioral factors through weekly and monthly reports. The BRFSS will provide state-level estimates of coverage through monthly reports. SDI provider office claims data will provide weekly estimates at the state and local levels. To assess specific populations, a Rand internet panel survey will be conducted of healthcare personnel on a monthly basis. Pregnancy Risk Assessment Monitoring System (PRAMS) data will be available for selected states in the late summer to fall of 2010.

Results from National 2009 H1N1 Flu Survey Outcomes survey will be reported weekly once the weekly sample size has reached sufficient levels to reliably estimate H1N1 vaccination coverage and intent to be vaccinated. This was anticipated to be within 1 to 3 weeks following this meeting. Some outcomes will be reported monthly only. Unlike the BRFSS that will just provide coverage estimates, this will provide a number of pieces of information including: receipt of influenza vaccinations (H1N1, seasonal); type of vaccination (shot or spray); month of vaccination; place of vaccination; intent to be vaccinated; main reason for no intent to be vaccinated; provider recommendations for seasonal and H1N1 vaccination; opinions about effectiveness and safety of H1N1 vaccine; knowledge, attitudes, and practices related to H1N1 flu; and receipt of pneumococcal vaccination.

Next steps include assessment of doses administered / coverage data that are just beginning to come in; and identifying best practices and lessons learned that appear to be associated with success.

Discussion

Dr. Lett thanked Dr. Wortley and her team for their weekly conference calls with states, which have been incredibly beneficial.

Dr. Schaffner (NFID) joined Dr. Lett in her appreciation. He inquired as to whether ordering and shipping was a 7-day or 5-day operation.

Dr. Wortley responded that currently it is a 5-day operations, with no orders placed on Saturday or Sunday. However, shipping does occur on Sundays.

Dr. Schaffner (NFID) requested further information about the throughput from the manufacturers, to the distributors, to the states in terms of how much vaccine had been shipped to the distributor and how much was in the distributors' warehouses.

Dr. Schuchat responded that this is a pipeline and for consistency of communication, CDC had decided upon three points in the pipeline that are shared on a regular basis. One is the doses that are available for allocation to the states, which means that the product has come into the distributor, it has been checked out and does not need to be quarantined. The second number is the number of doses that states have actually ordered. The third number is the number of doses shipped out. CDC is not reporting what is leaving each manufacturer and how many days it takes to reach the central distribution depots. It seemed that selection and reporting of these three points in the pipeline, it would give everyone a good sense of how things were moving.

Dr. Baker reported that Houston knows how many doses in a week the State of Texas has received; however, the rest of the process is a great mystery.

Ms. Ehresmann pointed out that a challenge for local areas is that when states received an allocation that is far less than needed, determining where it goes is difficult. In order to reach out to pediatric providers, Minnesota had to allow a window of several days for providers to let the state know their needs, and then the state used a lottery system because they could not ethically choose between providers who were reaching equally high risk populations. Issues like this go into the timing, and people do not really understand some of the challenges.

Dr. Baker added that states are also identifying their own priority groups. For example, the first doses in Texas in terms of patients were allocated to 2- and 3-year olds. Not everybody had to follow that at the local level as a legal requirement, but it was a suggestion.

Dr. Christine Hahn (CSTE) reported that local health departments are struggling to some extent in every state. Some have moved toward the smaller priority groups, while others have followed the target groups. Predictably, this is causing the usual consternation among neighboring counties and states. While there was no formal vote anticipated during this session, she wondered whether it would be useful for the ACIP to issue some type of continued support for the philosophy of a national standard and local flexibility.

Dr. Baker reiterated that the epidemiology substantiated that ACIP's prioritization in July was appropriate. As more vaccine is received, the recommendations can be expanded. She stressed that vaccine distribution among states varies in any situation because of state laws. That is beyond the prerogative of ACIP and CDC, which recommend and advise. The philosophy of making recommendations, providing great data and communications, is being done. It must now trickle down to the local level.

Dr. Schuchat emphasized how prescient ACIP was in thinking about local flexibility. Influenza is extremely local and demand can be highly variable from week to week and location to location. Consumer interest and the flexibility of the private and public sectors will vary in the same state in the same week. CDC is aware of doses being unused in one local health department

targeted toward a relatively narrow population, while there are long lines in a neighboring area. Thus, local flexibility to understand the dynamics within the context of the target groups has been helpful.

Influenza Vaccine Work Group Discussions

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

Dr. Fiore indicated that the Influenza Vaccine Work Group has been meeting quite frequently since the 2009 H1N1 situation began, with teleconferences every 1 to 2 weeks, on-going email and telephone discussions, and an in-person Work Group meeting on October 20, 2009. He highlighted some of the Work Group topics that received a lot of discussion during the past three months.

Seasonal influenza vaccine effectiveness in preventing 2009 H1N1 influenza was a topic of great interest at the start of the pandemic. Initial epidemiologic and immunologic data suggested that seasonal vaccine was unlikely to provide any protection against 2009 H1N1 influenza. Studies conducted by CDC's public health colleagues in Canada identified in an initial study some preliminary data suggesting that receipt of seasonal vaccine might put some persons at higher risk of subsequently acquiring 2009 H1N1 influenza. As media reports of these preliminary findings came out, the Work Group wanted to further assess this issue. CDC's public health colleagues from Canada discussed preliminary findings from several Canadian studies during two teleconferences with Work Group. They indicated that persons who received 2008-09 influenza vaccine were at some increased risk for a medical visit with lab-confirmed 2009 H1N1 influenza during April to July 2009. No increase in severity of infection was observed amongst those persons who developed 2009 H1N1 influenza. Interestingly, these findings were consistent across several studies in Canada using a test-negative control or cohort design.

David Shay and colleagues at CDC were also conducting studies to examine this same issue in the US, and summarized their data in the same teleconferences. Using several different study designs, Shay and colleagues found that there was no association (e.g., vaccine effectiveness of 0 after receiving seasonal influenza vaccine). These included a study conducted in the FluVE sites conducted the same way this group has calculated VE of seasonal vaccine, using the test negative control approach. In addition, two ad hoc cohort studies were conducted on school campuses that had confirmed outbreaks, and one study compared vaccination rates among cases in 8 states with those from state level coverage data. None of these studies found any association. Similar studies conducted in the UK also showed no effectiveness.

Neither the Canadian nor the Shay et al studies are published. However, there are two published studies that have also examined this issue. One is from Australia [Kelly et al. *Eurosurveillance* 2009], which also used the test-negative controls approach, and found no significant effectiveness: 3% (95% CI = -56% to 40%) with a 95% confidence interval. The other is a small study conducted in Mexico among hospitalized cases [Garcia-Garcia et al, *BMJ* 2009], which found that those who had received the seasonal vaccine had significant protection from 2009 H1N1 of 73% (95% CI = 34% to 89%).

After hearing about all of these studies over the course of several conference calls in several weeks, the Work Group concluded that observational studies of vaccine effectiveness are difficult to perform and interpret, and may lead to conflicting results. There is no evidence of increased risk among those who received seasonal vaccine in the US or other countries. Given that, the Work Group does not believe there is any reason to change the recommendations for seasonal vaccine in US. Seasonal viruses are circulating elsewhere and may have considerable impact later this season; therefore, seasonal vaccine should continue. On-going studies in US and other countries will continue to monitor this issue. Additional Work Group discussion is expected on this matter and findings will be reported back to the full ACIP.

The topic that took up most of the Work Group's time over the last several months was the emerging immunogenicity and safety data from the on-going 2009 H1N1 monovalent vaccine clinical trials. With respect to how these were licensed, manufacturers submitted a supplement to their seasonal influenza biologics license analogous to a seasonal strain change supplement. The antigen content in the vaccines being tested was similar to one strain in the trivalent seasonal vaccine (7.5-15 mcg for inactivated vaccines and $10^{6.5-7.5}$ fluorescent focal units for live attenuated vaccine). This licensure pathway requires vaccine to be manufactured and tested in same way and in same facilities as seasonal vaccine.

Licensure progress has been quite good: CSL, sanofi pasteur, and Novartis all have licensure of their inactivated vaccines and MedImmune has licensure of LAIV. The dosing recommended in the approved prescribing information is similar to seasonal vaccine, which is 1 dose for persons 10 years or older and 2 doses for children 6 months through 9 years. The approved formulations are the same as for seasonal vaccines. All are unadjuvanted, and there are prefilled syringe single dose and multi-dose vial preparations. As with seasonal vaccine, the multi-dose preparations contain the preservative thimerosal. Single prefilled dose syringes do not contain preservatives. The age indications are the same as for seasonal influenza as well.

While not a requirement for licensure, the FDA laid out a basic design of the clinical trials that were expected. These included the usual seasonal dose of 15 mcg, but also lower and higher doses as well as a group that received an adjuvanted vaccine. The Work Group focused on the unadjuvanted vaccine data [Adapted from W Sun (FDA): ACIP Meeting, July 29, 2009]. The trial endpoints recommended were typical of previous trials and included immunogenicity endpoints such as hemagglutinin inhibition assay results ($\geq 1:40$), geometric mean titers, safety data, and a requirement for an extended 6- to 12-month follow-up period following the last dose of vaccine [Adapted from W Sun (FDA): ACIP Meeting, July 29, 2009].

Some of these trials are beginning to be published. Regarding the results of immune response at 21 days after one dose of a 15 mcg unadjuvanted influenza A (H1N1) 2009 monovalent vaccine (CSL Limited), as measured on hemagglutinin-inhibition (HI) assay, Greenberg et al showed that after one dose, 100% of 18 to 49 year olds, and 94% of 50 to 64 year olds, responded with increased HI titer to 1:40 or more, and substantial increases in the antibody titer. The GMT ranged from 8- to 14-fold. This is quite similar to what one would expect from a seasonal vaccine. These are preliminary results. This trial is on-going, with additional follow-up expected soon [Greenberg et al. N Engl J Med 2009].

Based on the findings from a vaccine used in China (e.g., 15 or 30 mcg split virus egg-derived vaccine made by Hualan Biological Bacterin Company), the safety profile also was similar to seasonal vaccines, with the most common adverse events reported mild, short-term pain or tenderness at the injection site, or mild, short-term systemic symptoms, most commonly headache and malaise. At day 21, a very high proportion of adults who received a 15 mcg dose showed an HI titer $\geq 1:40$. Among children, the 12- to 17-year olds looked similar to adults. However, the percentage of 3- to 11-year olds who had an HI titer $\geq 1:40$ was considerably lower at 74.5% for the 15 mcg dose. However, at day 35 (two weeks after the second dose) this group was at 98%, which is heartening news [Zhu F-C, et al. A novel influenza A (H1N1) vaccine in various age groups N Engl J Med 2009]. This is the first published data among younger persons.

Returning to the Greenberg data, almost all of the reported side effects were mild and consisted of those typically observed with seasonal influenza vaccine [Greenberg et al. Response after one dose of a monovalent influenza A (H1N1) 2009 vaccine—preliminary report. NEJM 2009]. There were only a few moderate and severe adverse events. Adverse events are illustrated in the following table:

Table 4. Proportion of 240 Subjects Who Reported Having a Solicited Local or Systemic Adverse Event within 7 Days after Receiving One Dose of the H1N1 Vaccine.

Adverse Event	Mild	Moderate	Severe	All Grades
	<i>percent (95% confidence interval)</i>			
Solicited local event				
Any	43.8 (37.6–50.1)	2.5 (1.2–5.3)	0	46.3 (40.1–52.6)
Pain	20.8 (16.2–26.4)	0.8 (0.2–3.0)	0	21.7 (16.9–27.3)
Tenderness	35.0 (29.2–41.2)	1.7 (0.6–4.2)	0	36.7 (30.8–42.9)
Redness	8.8 (5.8–13.0)	0.4 (0.1–2.3)	0	9.2 (6.1–13.5)
Induration	8.8 (5.8–13.0)	0	0	8.8 (5.8–13.0)
Ecchymosis	4.6 (2.6–8.0)	0.4 (0.1–2.3)	0	5.0 (2.9–8.5)
Solicited systemic event				
Any	35.8 (30.0–42.1)	8.3 (5.5–12.5)	0.8 (0.2–3.0)	45.0 (38.8–51.3)
Fever	2.1 (0.9–4.8)	1.7 (0.7–4.2)	0	3.8 (2.0–7.0)
Headache	27.1 (21.9–33.0)	4.2 (2.3–7.5)	0	31.3 (25.7–37.4)
Malaise	14.2 (10.3–19.1)	2.9 (1.4–5.9)	0.4 (0.1–2.3)	17.5 (13.2–22.8)
Myalgia	13.8 (10.0–18.7)	2.9 (1.4–5.9)	0.4 (0.1–2.3)	17.1 (12.8–22.4)
Chills	5.8 (3.5–9.6)	0.8 (0.2–3.0)	0	6.7 (4.1–10.6)
Nausea	5.0 (2.9–8.5)	1.3 (0.4–3.6)	0.8 (0.2–3.0)	7.1 (4.5–11.0)
Vomiting	0	0.8 (0.2–3.0)	0	0.8 (0.2–3.0)

The CSL results are quite similar to those observed in studies using the other vaccines, as the Work Group learned in a series of calls during which manufacturers discussed their preliminary results from early timepoints. Immunogenicity for inactivated vaccine looked similar to the published 2009 H1N1 monovalent vaccine data and LAIV was similar to seasonal LAIV.

The National Institute of Allergy and Infectious Diseases (NIAID) is conducting a number of studies as well. These studies were not intended to support licensure, but were meant to be complementary to the trials planned by the manufacturers. The studies underway include 1 versus 2 doses of unadjuvanted vaccine in healthy adults and children; and co- versus sequential administration of TIV and H1N1 monovalent vaccine in adults and children. Preliminary results will be available soon.

The NIAID trial results among children ages 6 months through 17 years using the sanofi pasteur vaccine (15 and 30 mcg) showed a safety profile similar to seasonal vaccine 8 to 10 days post-Dose 1 of a 15 mcg vaccine. The proportion of a hemagglutinin inhibition assay titers $\geq 1:40$ was 25% among subjects 6 months to 35 months, 36% in those 3 to 9 years of age, and 75% in those 10 to 17 years of age. It is important to remember that this is a very early timepoint. Additional 2009 H1N1 NIAID-sponsored vaccine studies underway that may answer some of the questions raised include: pregnant women, asthma (mild, moderate, severe), HIV infected persons (pregnant women, children, and youth), and additional seasonal influenza vaccine studies that also include a study of pregnant women.

Based on these early data, the Work Group concluded that the studies thus far indicate that the immunogenicity and safety of the 2009 H1N1 vaccine are similar to that of seasonal vaccine. The use of vaccine on the FDA-approved schedule appears to be reasonable, which is 2 doses in ages 6 months through 9 years and 1 dose in ages 10 years and older.

In view of the data presented during this session, Dr. Fiore revisited the planning assumptions that led to the current vaccine recommendations at the end of this session, with a checkmark placed by each one that appeared to still be true or at least not false:

- ✓ The severity of illness and groups at higher risk for infection or complications will be similar to what has already been observed
- ✓ The safety profile and antigen content of unadjuvanted novel H1N1 vaccines will be similar to that of seasonal influenza vaccines
- ✓ Adequate supplies of licensed unadjuvanted vaccine can be produced for all by approximately February 2010
- ✓ Enough vaccines for all will not be available before next pandemic wave, hence need for targeting of certain higher risk populations with initial vaccines
- ✓ Pandemic vaccine and seasonal vaccine availability will overlap and both will be recommended for many population groups
- ± 2 doses will be needed for protection (based on preliminary immunogenicity data, it appears that much of the population will only need 1 dose)
- ? Initial demand for vaccination approximately the same as for seasonal vaccine, but could increase quickly if community transmission increases
- ✓ Vaccine distribution will be timely
- ✓ Implementation will be challenging

The Work Group's conclusions are that the characteristics of cases, hospitalizations, and deaths caused by 2009 H1N1 influenza are similar to those observed in the first few months of the pandemic. No significant antigenic changes have been observed among novel influenza A(H1N1) viruses since April 2009. Trial data to date indicate that 2009 H1N1 vaccines are safe and immunogenic. ACIP's target / prioritization recommendations remain reasonable and are evidence-based. There should continue to be an emphasis on local decision-making and flexibility to provide vaccination to as many as possible as efficiently as possible, targeting those at higher risk. There should be continued use of seasonal vaccine as recommended.

Discussion

Dr. Sawyer inquired as to whether there was an established interval between the sequential administration of LAIV for both seasonal and H1N1 vaccine.

Dr. Fiore responded that the Work Group discussed this, and also consulted with a number of outside experts who conducted such trials in the past. The Work Group's conclusion was that there is not a clear data base to guide them. There was concern that if the vaccines were given too close together or were given simultaneously, there may be potential for the vaccines to interfere with each other and perhaps not engender a good immune response. While there are people who wish to use the LAIV for both types of vaccines, forcing a waiting period 4 weeks as is typically recommended for live vaccines made it impractical to use. The Work Group agreed that 4 weeks is quite a reasonable timeframe between the vaccines; however, they would accept as little as two weeks based upon expert opinion that suggested that concerns with interference largely pertained to the vaccines being given within two weeks of each other or simultaneously. On October 21, 2009 the 10 most frequently asked questions about the use of vaccines were posted on the CDC website.

Having been recently asked this question by 12,000 pediatricians during the recent AAP meeting, Dr. Baker inquired as to which vaccine should be given first in the scenario of a 3-year old child who has not had seasonal flu or H1N1 vaccine.

Dr. Fiore responded that in most seasons, the start of significant seasonal influenza does not typically occur until late in the year or the early part of January. There is currently a pandemic of 2009 H1N1, so it would seem reasonable to give H1N1 first.

Dr. Baker noted that this was a trick question, because included in the communication for healthcare providers, in this midst of this pandemic the answer is pandemic H1N1 first. She requested that Dr. Fiore verify that the minimal interval of 4 weeks was recommended, but it could be as soon as 2 weeks for the LAIV.

Dr. Fiore replied that this was between the two different formulations of LAIV. There is an option to use the inactivated vaccine for either or both. There is no interval necessary between those. One could receive an inactivated formulation of 2009 H1N1 and FluMist® or vice versa on the same day. This is only a dilemma for those who want to use only the LAIV for both vaccines.

Dr. Keitel indicated that she would like to go on record as being quite concerned about shortening the interval to two weeks in the absence of data to support adequate replication. It is clear from small studies conducted in the past that there is non-specific resistance in the airways after administration of a dose of LAIV as well as other respiratory viruses, and that this interference can persist for over a month. However, the studies have been conducted with an interval of 4 weeks, which is the licensed regimen. Therefore, she supported first administering pandemic H1N1 vaccine given the pandemic, and that if a provider felt compelled to administer a TIV dose, even though there is no seasonal circulation currently, it is available.

In terms of seasonal vaccine, Dr. Meissner noted that it appeared that the live attenuated vaccine was not as effective as TIV. He requested further information about this in regard to the monovalent 2009 H1N1 vaccine.

Dr. Fiore responded that he could not. The leading thought about why several studies have shown that TIV might be a better choice in adults than LAIV has pertained to the idea that there may be some pre-existing immunity that causes resistance to the LAIV taking hold in the nose. Because they were dealing with what appeared to be a new antigen, he did not believe this argument was compelling. Thus, he has been telling people that one or the other is fine and that both should be quite immunogenic.

Regarding the comments earlier in the day about secondary bacterial infections, Dr. Grabenstein (Merck) indicated that Merck had data from the current 2009 H1N1 pandemic based on autopsies and ICU admissions. He noted that one speaker had said, "Fortunately, we have a pneumococcal vaccine for adults." He cautioned against complacency because the uptake rates of pneumococcal vaccine in adults with underlying medical conditions is woefully low in the 20% to 40%, meaning that 70% or more are unprotected. This has persisted flat line since 2000, over a decade, with substantial racial and ethnic disparities. He encouraged CDC to show the full committee the NIS data on these points because it describes the struggling condition of adult immunization in the US. He suggested that when disseminating influenza messages to also encourage the "cheese on the hamburger" or the "French fries with the hamburger" of the pneumococcal vaccine with the influenza vaccine according to the ACIP recommendations. The Immunization Action Coalition has repeatedly issued this message, but it is one that will take a while to overcome the flat line experienced over the last decade.

Dr. Baker pointed out that a number of adult organizations had emphasized the woeful adult immunization situation in the US. If she was an internist, she would take the same approach as taken with a child presenting for H1N1 vaccine by taking that opportunity to catch the adult up on other recommended vaccines. There are no contraindications for doing so that she knows of.

Due to concern that the committee may not get to this issue, Dr. Duchin (NACCHO) again raised the issue of the higher mortality rates in the 24 to 49 and 49 to 65 age groups. If they were not going to add those individuals to the initial target groups for prioritization, he wanted to understand the logic for that decision.

Dr. Schuchat responded that they had never focused on that sub-set and it seemed to her they were included in the groups being promoted with local flexibility.

Dr. Fiore agreed, pointing out that many doses would go to providers who would administer the vaccine to those with chronic medical conditions or healthcare workers. Given that it appeared that the time window necessary for prioritization would be short, he did not believe this would be a major concern. He thought it was reasonable to emphasize that there is local flexibility and that internists should not hold onto vaccine waiting for the next iteration of when the recommendation will be expanded. The Work Group can continue to discuss this issue.

Dr. Baker reiterated that those with underlying conditions in those age categories with underlying conditions were already part of the prioritization list in large part.

Dr. Duchin (NACCHO) agreed that they were part of the target groups, but that ACIP had proposed a subset of initial target groups for people to consider when vaccine is in short supply. It currently is in short supply and many people are looking at that subset. It did not make sense to him to exclude from that subset people who have the highest mortality rates, when groups with lower mortality rates are included.

Dr. Baker replied that she did not disagree, but there is state and local flexibility. For example, in her children's hospital healthcare workers and EMS personnel are included in the reduced group. Among those in her area for which vaccine was delivered, 1% of vaccine orders for the children's hospital (the largest in the US) were filled in the first week. The pediatric practices in Houston received 10% of what was ordered; however, all 200,000 children except the 0- to 6-month olds would be eligible for a vaccine presumably. She thought it was too late to change the priority groups. A great deal of time has been spent messaging the priority group. There are going to be inequities no matter what.

Dr. Neuzil agreed that what they heard during this session about higher mortality in the 19 to 64 year olds with underlying conditions was a very important point. What she was hearing from other people was that communications, messaging, and changing priorities groups would be difficult in changing pandemic. She emphasized education. CDC has engaged in many conference calls and has disseminated numerous bulletins, which would be good places to emphasize the mortality in various age groups so that internists understand and can vaccinate accordingly. It is also important to remember that there are antivirals and that 2009 H1N1 remains susceptible to these, and early antiviral use should be implemented. This could also be emphasized through education. Dr. Neuzil also stressed that the assumption should not be made that all would go smoothly from this point forward. The more flexibility there is, the more prepared everyone will be. In that spirit, she encouraged the federal agencies and the manufacturers to act immediately on the issue of EUAs. While these may not be needed, she thought they must work in parallel in order to have as many options and as much flexibility as possible if necessary.

Dr. Baker added that early antiviral intervention is important for children and adults.

Day 2: Public Comments

Shannon Duffy Peterson Parent / PKIDS Member

My name is Shannon Duffy Peterson. I am a Disease Prevention Advocate for PKIDS and the parent of three children. My youngest are at home in Sleepy Eye, Minnesota and my oldest, Abigail, is up in Heaven with her grandparents. In 2001, my 5-year old daughter became a statistic when she died of a vaccine-preventable disease. Abigail became infected with chicken pox, and after battling that disease, became infected with the pneumococcal virus [*sic*]. When our children were born, my husband, Dwayne, and I were adamant about vaccinating our children. We wanted our children to be protected against everything. We wanted healthy children. At that time, we had a pediatrician who did not push vaccinations and did not recommend the most recent vaccines available. Consequently, my children did not have their chicken pox or pneumococcal vaccinations.

February 18, 2001 began as a normal Sunday. We took our children to Sunday School, went to church together, played throughout the day, dancing with them to music and then relaxing with them before bedtime by playing a board game. Abigail said she suddenly wasn't feeling well and had a headache. We had her lie down and took her temperature. It was 101.5. We gave her Motrin® for the pain and temp. She started to vomit up the medicine and we thought she had the flu. We thought this was strange because she had the same illness and a sinus infection two weeks earlier. But she was in kindergarten and we knew that the kids were passing around many germs. We became alarmed when a rash developed all over her body that we had never seen before, but suspected it to be a high fever rash. I called the emergency room, we don't have urgent care in rural Minnesota, and was told that the flu was going around with high fever, vomiting, and diarrhea, and just to treat the fever alternately with Motrin®, Tylenol®, and a tepid® bath if she continued to vomit the medicine. She was tired and we put her to bed, planning to check on her quite frequently, but hoping she would sleep off the flu. Throughout the night we kept changing her bedding, bathing her to break the fever, and even though she was pretty lethargic, ended up sleeping with her to comfort her. But we woke later to her call for mommy as she had fallen out of bed while attempting to make it to the potty. It was then while cleaning her up that my husband noticed the tremendous blotches on her skin and said, "This is not normal. We have to get her to the emergency room right away.

We woke up our little boy, got into the truck, and drove as fast as we could 21 miles to the hospital, called the hospital on the way to say we were coming, and prayed for the best. I sat in back with my children, comforting Abigail when she said to me, "Mommy, I hurt so bad all over." I assured her it was from the sickness and held her in my arms the best that I could while we were all buckled up. Those were the last words that I would ever hear from my beautiful little girl. She died in my arms while we were driving. When we arrived at the hospital, they called a Code Blue and attempted for one hour to revive her. Her heart never started and they were breathing for her. She was pronounced dead at 7:20, Monday, February 19th. Our hearts broke that day as our son, Abigail's little brother, witnessed all of this and we had to tell him that his playmate, his bedtime companion, had died and there was nothing mommy and daddy could do to save her. We rocked our Abigail for many hours afterward, and consented to an autopsy, and donated her beautiful eyes as the only organ that they could use.

Two hours after we arrived home from saying goodbye to our first born, our son started to experience some of the same symptoms as his sister, and we rushed him to the clinic. They got us in immediately and started running tests. While we were waiting for results, Samuel, our son, started to vomit. I couldn't believe this was happening all over again. I was holding him on the floor in our doctor's office when our pediatrician came in with Abby's preliminary autopsy results stating that she had overwhelming sepsis caused by *Streptococcus pneumoniae*, congenital asplenia, absence of the spleen, and hemorrhagic adrenal glands. They admitted Samuel immediately to the hospital and did an ultrasound to make sure he had a spleen. He did to our extreme relief; however, they held him in the hospital for two nights as his asthma was acting up and he was fighting the same virus that killed our daughter. I believe if Abigail had been given the vaccines available at the time, maybe, just maybe, they would have protected her. We will never know if this would have saved her, but it would have most certainly offered her some extra protection. I am asking that you make sure all kids are kept healthy, and to vaccinate children as new vaccines become available so that they will be protected from even more strains of pneumococcal. If we do this, we will save lives. It is our responsibility as parents and medical professionals to protect our children. Thank you very much for letting me speak.

Dr. Baker thanked Mrs. Peterson, expressing her sympathy for her loss, and requesting that she remain following the meeting so that she could speak with her.

Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the October 21-22, 2009 ACIP Meeting are accurate and complete.

____ January 22, 2010 _____
Date

Carol J. Baker, Chair
Advisory Committee on
Immunization Practices (ACIP)

List of Attendees

Last Name	First Name	Citizenship
Abu-Elyazeed	Remon	Egypt
ADENIKE TITILAYO	OSHO	Nigeria
Ajuma Mary	Sule	Nigeria
Ali-zade	Narguiz	Canada
ALLAVOINE	THIERRY	France
BABAJIDE MICHAEL	OLANIYAN	Nigeria
BOGAERTS	Hugues	Belgium
Bricks	Lucia	Brazil
Butt	Tausif	United Kingdom
Carreño	Roberto	Mexico
Cervantes	Yolanda	Mexico
Chatterjee	Arani	India
CHUKWUMA CHRISTIAN	OKONKWO	Nigeria
Dubi	Aweke	Ethiopia
Edelman	Laurel	Canada
Florez	Jorge	Colombia
GEORGE	ANI	Nigeria
Ghosh	Rajdeep Ghosh	India
Hayrapetyan	Armen	Armenia
Ismail (nee Virani)	Shainoor	Canada
Iwata	Kentaro	Japan
Kalam	Mohammed Abul	Bangladesh
KIMANI	JENNIFER	Kenya
KIMANI	GEORGE	Kenya
Langley	Joanne M	Canada
Lanteri	Jane	Australia
LeBlanc	Julia	Canada
Lee	Jennifer Wai	Hong Kong Special Administrative Region
LUCIDI	Bruno	Belgium
Luna	Expedito	Brazil
Manjarrez	Robert Carreno	Mexico
Merengwa	Enyinnaya	Saint Kitts and Nevis
Mesaros	Narcisa	Belgium
MIKE UNYIME	ANTHONY	Nigeria
Moses	Ogwang	Uganda
Nagendra	Murali Krishna	India
omar	abdiwahid	Somalia
Omer	Saad	Pakistan
Oselka	Gabriel	Brazil
Perombelon	Yves Francois	United Kingdom
Perron	Lina	Canada
Quintanar	Manjari	Mexico

Raina	Ajit pal Singh	India
Saddier	Patricia	France
Sever	Perica	Canada
Shindman	Judith	Canada
Sobanjo-ter Meulen	Ajoke	Germany
sollano-Carranza	leticia	Mexico
taan	ghazi	Lebanon
Tan	Litjen (L.J)	Singapore
taylor	martin	Nigeria
THUMU	ESTHER	Kenya
Weckx	Lily	Brazil
Wettendorff	Martine	Belgium
York	Laura	Canada
Yuan	Chuan	China-Taiwan
Abraham	Brian	United States
Advani	Aneel	United States
Ahuja	Ajay	United States
Alexa	Pam	United States
Alfano	Deborah	United States
Allen	Jennifer	United States
allen	john	United States
Ambrose	Karita	United States
Anzjon	Sarah	United States
Aponte	Fernando	United States
Araujo	Antonio	United States
Arenson	Michael	United States
Armstrong	Kris	United States
Arnold	Bill	United States
Arrindell	Deborah	United States
Arthur	Phyllis	United States
Ault	Kevin	United States
Baccarini	Carmen	United States
Baggs	James	United States
Baker	Debbi	United States
Baker	Carol J.	United States
Bandell	Allyn	United States
Barri	Michael	United States
Bawnatoppybon	Bawnatoppybon	United States
Bean	Sandra	United States
Benning	Eric	United States
Berg	Jeffrey	United States
Birkhead	Guthrie	United States
Blackmon	Lindsay	United States
Blalack	Gary	United States
Blazek	Nicole	United States

Bobba	Durga	United States
Bocchini, Jr.	Joseph	United States
Bonney	Loida	United States
Bowser	Andrew	United States
Bozof	Lynn	United States
Brady	Michael	United States
Bresnitz	Eddy	United States
Brown	Jean	United States
Buchanan	Anna	United States
Campbell	Stephanie	United States
Campos-Outcalt	Doug	United States
Cannon	Patricia	United States
Caporizzo	John	United States
Cary	Donna	United States
Chaney	Mike	United States
Cheek	Jim	United States
Chilton	Lance	United States
Cieslak	Ted	United States
Claxton	Isabelle	United States
Clover	Richard	United States
Coelingh	Kathleen	United States
Coit	Henry	United States
Colwell	Chris	United States
Conner	Penny	United States
Conway	Frank	United States
Cooper	Brian	United States
Counard	Catherine	United States
CREED	Carlisle	United States
Cullison	Mark	United States
Dahill	Noreen	United States
Daley	Ellen	United States
Dalrymple	Donald "Dack"	United States
Dana	Adrian	United States
Dasbach	Erik	United States
Decker	Michael	United States
DeNoon	Daniel	United States
derkay	craig	United States
Dinovitz	Richard	United States
Donnelly	Jessica	United States
Dormitzer	Philip	United States
Dougherty	Kelley	United States
Douglas	John	United States
Dubin	Gary	United States
Duchin	Jeffrey	United States
Duffy	Colleen	United States
Duggan Goldstein	Sarah	United States
dupont	lisa	United States
Dzubin	Shannon	United States
Edwards-Fortner	Angela	United States

Ehresmann	Kristen	United States
Ehrlich	John	United States
Elbasha	Elamin	United States
Elward	Alexis	United States
Englund	Janet	United States
Etkind	Paul	United States
Evans	Jim	United States
Evans	Geoffrey	United States
Feinberg	Mark	United States
FELDMAN	BRENDA	United States
Filipski	Brian	United States
Fix	Amy	United States
Folowoshele	Catherine	United States
Forsythe	Sarah	United States
Foster	Stephan	United States
Friedland	Leonard	United States
fries	louis	United States
fryhofer	sandra	United States
Furr	Christine	United States
Gaffoglio	Diane	United States
Gargano	Lisa	United States
Garrett	W. Matthew	United States
Gellin	Bruce	United States
gensheimer	kathleen	United States
Gershman	Mark	United States
Gesser	Richard	United States
gilmore	ruth	United States
Giuliano	Anna	United States
Goldstone	Stephen	United States
Gordon	Lili	United States
Gordon-Evans	Jill	United States
Goveia	Michelle	United States
Grabenstein	John	United States
Greenberg	David	United States
Groom	Amy	United States
Hahn	Christine	United States
Halsey	Neal	United States
Halstrom	Erik	United States
Hammer	Sandra	United States
Hannan	Claire	United States
Harder	Gina	United States
HASTINGS	DAVID	United States
Haupt	Richard	United States
Hazelwood	Kimberley	United States
Hemby	Lisa	United States
Hilbert	Kathleen	United States
Hill	Aretha	United States
Hinman	Alan	United States
Hodges	Sonya	United States

Hogrefe	Wayne	United States
Hosbach	Philip	United States
Howe	Barbara	United States
Huey	Michael	United States
Hughes	James	United States
Humphrey Franklin	Donelle	United States
Jain	Varsha	United States
James	Chuntiel	United States
Johnny	Shana	United States
Johnson	David	United States
Johnson	Anasa	United States
Kalish	Scott	United States
Kanesa-thasan	Niranjan	United States
Kattan	Randi	United States
Katz	Samuel	United States
Kaye	Bronwen	United States
Keenan	Richard	United States
Keitel	Wendy	United States
Keyserling	Harry	United States
Kimberlin	David	United States
Kingsley	Mary Lee	United States
Korch	George	United States
Kruzikas	Denise	United States
Kuter	Barbara	United States
Laird	Susan	United States
Law	Huay-Zong	United States
Lawson	Herschel	United States
Ledezma	Victor	United States
Lee	Lucia	United States
Leger	Marie-Michele	United States
lett	susan	United States
Lewin	Clement	United States
Lewis	Tamara	United States
Loehr	James "Jamie"	United States
Lowery	Kerry	United States
Malinoski	Frank	United States
Malone	Robert	United States
Mansoura	Monique	United States
Marcy	Stephan Michael	United States
Marlowe	Steven	United States
Mason	Dean	United States
Mast	Thomas Christopher	United States
Mazur	Marie	United States
McCubbins	John	United States
McKenna	Maryn	United States
Mclaughlin	Jeffrey	United States
McLoughlin	Sean	United States
Meigs	Wendy	United States
Meissner	Barbara	United States

Meissner	Cody	United States
Middleman	Amy	United States
Miller	Jacqueline	United States
Miller	Michael	United States
Milley	Frankie	United States
Mitteldorf	Darryl	United States
Moore	Kelly	United States
Muhammad	Riyadh	United States
murphy	linda	United States
Musey	LuwY	United States
Myers	Tanya	United States
NELSON	SUSAN	United States
Netoskie	Mark	United States
Neuzil	Kathleen	United States
Nicholson	Ouzama	United States
Obara	Timothy	United States
O'Brien	Scott	United States
Offit	Paul	United States
Ogilvie	Gina	United States
O'Neill	Kevin	United States
Paradiso	Peter	United States
Parikh	Shefali	United States
Penrod	Deborah	United States
Peters	Martin	United States
Peterson	Diane	United States
Peterson	Shannon Duffy	United States
Polack	Ellie	United States
Poland	Gregory	United States
Pugh	Pearl	United States
Quinn	Jane	United States
Randall	Lisa	United States
Ray	Jill	United States
Redwood	Lyn	United States
rennels	margaret	United States
Richards	Steve	United States
RICHARDSON	VESTA	United States
Robitz	Rachel	United States
Rodewald	Lawrence	United States
Ross	David J.	United States
Rozen-Adler	Nuphar	United States
Santoli	Jeanne M.	United States
Sapsis	Kari	United States
Sarecha	Dileep	United States
Saslow	Debbie	United States
Sawyer	Mark	United States
Schaffner	William	United States
Schechter	David	United States
Schlam	Everett	United States
Schmader	Kenneth	United States

Schneider	Jason	United States
Schofield	David	United States
Scott	Laura	United States
Seehafer	Darin	United States
Shapiro	Elana	United States
Shefer	Abigail M.	United States
SIEVERT	ALAN	United States
Silsbee	Jeffrey	United States
Silverstein	Leonard	United States
Skjeveland	Eric	United States
Smith	Parker	United States
Snyder	Patricia	United States
Solomon	Diane	United States
Splete	Heidi	United States
Stanley	Grogg	United States
Staples	J. Erin	United States
Steele	Robert	United States
Stein	Gary	United States
Stoddard	Jeffrey	United States
Strikas	Raymond	United States
Strutton	David	United States
Stuerke	Stacy	United States
SUAREZ	RICHARD	United States
Sullivan	Gina	United States
Sumaya	Ciro	United States
Swain	Christopher	United States
Sylvester	Gregg C.	United States
Talkington	Kathy	United States
Taylor	Jeff	United States
Taylor	Deb	United States
Taylor Jr.	Jerome	United States
Temte	Jonathan	United States
Thomas	Lonnie	United States
Thomas	Michael	United States
Tilley	Carol	United States
Trenet	Janet	United States
Trizzino	John	United States
Tsai	Theodore	United States
Turner	James	United States
Vaupel	Christine	United States
Vernon	Thomas	United States
Vigliarolo	Peter	United States
Wali	Mostafa	United States
Ward	Joel	United States
Warner	Amy	United States
Wassil	James	United States
Weiss	Holly	United States
Wexler	Deborah	United States
White	Laura	United States

Whitley-Williams	Patricia	United States
Whitman	Matt	United States
Whittenburg	Janette	United States
Wighton	Timothy	United States
Wimberly	Yolanda	United States
Yamada	Eileen	United States
Yamauchi	Terry	United States
youwakim	Michel	United States
Zacharyczuk	Colleen	United States
Zimmerman	Richard	United States