

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

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



**Summary Report
October 27-28, 2010
Atlanta, Georgia**

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FINAL – October 21, 2010
MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia
October 27-28, 2010

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, October 27, 2010			
8:00	Welcome & Introductions		Dr. Carol Baker (Chair, ACIP) Dr. Larry Pickering (Executive Secretary, ACIP; CDC)
8:30	Meningococcal Vaccine <ul style="list-style-type: none"> ▪ Introduction ▪ Considerations for people at high risk for meningococcal disease to receive 2-dose 1° series ▪ Cost-effectiveness of adolescent meningococcal vaccination ▪ Provider attitudes & practices regarding adolescent meningococcal vaccination ▪ Considerations regarding adolescent meningococcal vaccination 	Information Discussion Vote Information & Discussion Vote VFC vote	Dr. Cody Meissner (ACIP, WG Chair) Dr. Amanda Cohn (CDC/NCIRD) Dr. Ismael Ortega-Sanchez (CDC/NCIRD) Dr. Allison Kempe (University of Colorado) Dr. Amanda Cohn (CDC/NCIRD)
10:00	<i>Break</i>		
10:30	Hepatitis B Vaccine <ul style="list-style-type: none"> ▪ HepB vaccine coverage in high risk adults ▪ Work Group introduction ▪ Infection control initiatives ▪ Review of hepatitis B in adults with diabetes ▪ Policy considerations - HepB vaccination for adults with diabetes 	Information & Discussion	Dr. Kathy Byrd (CDC/NCHHSTP) Dr. Mark Sawyer (ACIP, WG Chair) Dr. Joseph Perz (CDC/NCEZID) Dr. Trudy Murphy (CDC/NCHHSTP) Dr. Trudy Murphy (CDC/NCHHSTP)
12:30	<i>Lunch</i>		
1:30	Pertussis Vaccines <ul style="list-style-type: none"> ▪ Update on Pertussis Vaccines Work Group activities ▪ Update on pertussis outbreak - California, 2010 ▪ Proposed recommendation for use of Tdap regardless of Td interval ▪ Safety and immunogenicity of Tdap in people ≥65 years of age ▪ Proposed recommendation for use of Tdap in people ≥65 years of age ▪ Proposed recommendation for use of Tdap in undervaccinated children 7-10 years of age 	Information & Discussion Vote VFC vote Information & Discussion Vote Vote VFC vote	Dr. Mark Sawyer (ACIP, WG Chair) Dr. Kathleen Harriman (CA Dept of Public Health) Dr. Jennifer Liang (CDC/NCIRD) Dr. Michael Decker - sanofi pasteur Dr. Wayne Weston - GSK Dr. Jennifer Liang (CDC/NCIRD) Dr. Jennifer Liang (CDC/NCIRD)
3:45	<i>Break</i>		
4:00	Evidence Based Recommendations <ul style="list-style-type: none"> ▪ Introduction ▪ Evidence-based format for ACIP recommendations: based on GRADE (Grades of Recommendation Assessment, Development, and Evaluation) 	Information & Discussion Vote	Dr. Jon Temte (ACIP, WG Chair) Dr. Faruque Ahmed (CDC/NCIRD)
5:15	Public Comment		
5:30	Adjourn		

FINAL – October 21, 2010**Thursday, October 28, 2010**

8:00	Unfinished Business		Dr. Carol Baker (Chair, ACIP) ACIP <i>Ex Officio</i> Members
8:15	Agency Updates (CDC, CMS, DOD, DVA, FDA, HRSA, IHS, NIH, NVAC, NVPO)	Information	
8:30	Human Papillomavirus (HPV) Vaccines	Information &	Dr. Janet Englund (ACIP Member) Ms. Julianne Gee (CDC/NCEZID) Ms. Shannon Stokley (CDC/NCIRD) Dr. Richard Haupt (Merck) Dr. Mandy Allison (University of Colorado) Dr. Harrell Chesson (CDC/NCHHSTP) Dr. Lauri Markowitz (CDC/NCHHSTP)
	<ul style="list-style-type: none"> ▪ Introduction ▪ HPV vaccine safety - Vaccine Safety Datalink ▪ HPV vaccine uptake in females and program issues ▪ HPV4 in males: clinical trial data ▪ Provider attitudes and practices regarding HPV vaccine use in males ▪ Review of cost effectiveness of male HPV vaccination ▪ Considerations for HPV vaccination recommendations in males 	Discussion	
10:20	Vaccine Supply	Information	Dr. Jeanne Santoli (CDC/NCIRD)
10:30	<i>Break</i>		
11:00	2011 Immunization Schedule - 0-18 years of age	Information Vote	Dr. Cody Meissner (ACIP, WG Chair) Dr. William Atkinson (CDC/NCIRD)
11:30	2011 Immunization Schedule - 19 years of age and older	Information Vote	Ms. Kris Ehresmann (ACIP, WG Chair) Dr. Abigail Shefer (CDC/NCIRD)
12:00		<i>Lunch</i>	
1:00	Rotavirus Vaccines	Information &	Dr. Lance Chilton (ACIP, WG Chair) Dr. Romulo Colindres, Director, GSK Biologicals Dr. Manish Patel (CDC/NCIRD) Dr. James Baggs (CDC/NCEZID) Dr. Christopher Mast, Dr. Colette Ranucci (Merck) Dr. Julie Bines (University of Melbourne, Australia) Dr. Margaret Cortese (CDC/NCIRD)
	<ul style="list-style-type: none"> ▪ Introduction ▪ Intussusception following administration of rotavirus vaccine (RV): GSK study, Mexico ▪ Intussusception following administration of RV: PAHO study, Brazil and Mexico ▪ US data on intussusception following administration of rotavirus vaccine (RV) ▪ Update: intussusception data; porcine circovirus ▪ Australian data on intussusception following administration of RV ▪ US analysis: benefits and risks of RV 	Discussion	
3:00	Influenza	Information &	Dr. Wendy Keitel (ACIP, WG Chair) Dr. Tim Uyeki (CDC/NCIRD) Dr. Jeanne Santoli (CDC/NCIRD) Dr. Tom Shimabukuro (CDC/NCEZID)
	<ul style="list-style-type: none"> ▪ Introduction ▪ Influenza activity worldwide ▪ Influenza vaccine availability ▪ Influenza vaccine safety 	Discussion	
3:30	Public Comment		
3:45	Adjourn		

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core surveillance system
ACHA	American College Health Association
ACP	American College of Physicians
ACIP	Advisory Committee on Immunization Practices
ACIR	Australian Childhood Immunization Register
AIM	Association of Immunization Managers
AEs	Adverse Events
AHIP	America's Health Insurance Plans
ALFs	Assisted Living Facilities
AMA	American Medical Association
AMBG	Assisted Monitoring of Blood Glucose
ANA	American Nurses Association
APSU	Australian Paediatric Surveillance Unit
ARRA	American Recovery and Reinvestment Act
ASH	Assistant Secretary for Health (NVAC)
ASPR	Office of the Assistant Secretary for Preparedness and Response
ASTHO	Association of State and Territorial Health Officials
BLA	Biologics License Application
BMI	Body Mass Index
BRFSS	Behavioral Risk Factor Surveillance System
BSRI	Blood Systems Research Institute
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CER	Comparative Effectiveness Research
CFS	Chronic Fatigue Syndrome
CISA	Clinical Immunization Safety Assessment Network
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
DHAP	Division of HIV and AIDS Prevention
DMSS	Defense Medical Surveillance System
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
EBRWG	Evidence Based Recommendations Work Group
ECDC	European Centre for Disease Prevention and Control
ED	Emergency Department
EGL	External Genital Lesions
EIP	Emerging Infections Program
EHR	Electronic Health Records
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EPO	Epidemiology Program Office
FAS	Full Analysis Set
FDA	Food and Drug Administration
FESA	Flexible Exact Sequential Analysis
FQHC	Federally Qualified Health Center
GAVI	Global Alliance for Vaccines and Immunisation
GBS	Guillain Barré Syndrome
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GRADE	Grades of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HCUP	Healthcare Cost and Utilization Project
HCW	Healthcare Workers

HepA	Hepatitis A
HepB	Hepatitis B
HET	High Risk Heterosexuals
HICPAC	Healthcare Infection Control Practices Advisory Committee
HHS	Department of Health and Human Services
HP2010	HealthyPeople 2010
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
ICD-9	International Classification of Diseases, Ninth Revision
ICU	Intensive Care Unit
ID	Influenza Division (of NCIRD)
IDSA	Infectious Disease Society of American
IDU	Injection Drug Users
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	Indian Health Services
IIS	Immunization Information Systems
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IOM	Institute of Medicine
ISO	Immunization Safety Office
JAMA	<i>Journal of the American Medical Association</i>
LLR	Log Likelihood Ratio
maxSPRT	Maximized Sequential Probability Ratio Testing
MenACYW-CRM	Meningococcal Conjugate Vaccine
MCO	Managed Care Organization
MCV4	Quadrivalent Meningococcal Conjugate Vaccine
MMR	Measles, Mumps, Rubella
MMRV	Measles, Mumps, Rubella, and Varicella vaccine
MMWR	<i>Morbidity and Mortality Weekly Report</i>
MSA	Metropolitan Statistical Areas
MSM	Men Who Have Sex With Men
NACI	National Advisory Committee on Immunization
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
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)
NEJM	New England Journal of Medicine
NHANES	National Health and Nutrition Examination Survey
NHBS	National HIV Behavioral Surveillance
NHIS	National Health Interview Survey
NICU	Neonatal Intensive Care Unit
NIOSH	National Institute for Occupational Safety and Health
NIP	National Immunization Program (Australia)
NIS	National Immunization Survey
NIS-Teen	National Immunization Survey-Teen
NMA	National Meningitis Association
NNDSS	National Notifiable Diseases Surveillance System
NNHS	National Nursing Home Survey
NREVSS	National Respiratory and Enteric Virus Surveillance System
N-SSATS	National Survey of Substance Abuse Treatment Services
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NVSN	National Vaccine Surveillance Network
OSHA	Occupational Safety and Health Administration
PAEDS	Pediatric Active Enhanced Disease Surveillance (Australia)

PAHO	Pan American Health Organization
PASS	Post-Marketing Authorization Safety Study
PATH	Program for Appropriate Technology in Health
PCR	Polymerase Chain Reaction
PCV	Porcine Circovirus
PEP	Post-Exposure Prophylaxis
PPACA	Patient Protection and Affordable Care Act
PPE	Per Protocol Efficacy Population
QALY	Quality-Adjusted Life Year
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RDD	Random-Digit-Dial
REST	Rotavirus Efficacy and Safety Trial
RSV	Respiratory Syncytial Virus Immunoprophylaxis
RTIMS	Real Time Immunization Monitoring System
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts (WHO)
SAM	Society for Adolescent Health and Medicine
SBA	Serum Bactericidal Antibody
sBLA	Supplemental Biologics License Application
SCCS	Self-Control Case Series
SES	Socioeconomic Status
SHEA	Society for Healthcare Epidemiology of America
SMBG	Self-Monitoring of Blood Glucose
SME	Subject Matter Expert
STD	Sexually Transmitted Disease
Tdap	Tetanus and Reduced Diphtheria Toxoids
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force
VA	Veterans Administration
VAERS	Vaccine Adverse Event Reporting System
VAU	Vaccine Analytic Unit
VFC	Vaccines for Children
VICP	National Vaccine Injury Compensation Program (HRSA)
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VPCI	Vaccine Policy Collaborative Initiative
VSD	Vaccine Safety Datalink
VSRWAG	Vaccine Safety Risk Assessment Working Group
VSWG	Vaccine Safety Working Group (NVAC)
VTE	Venous Thromboembolic Events
WG	Work Group
WHO	World Health Organization

Welcome and Introductions

Dr. Carol Baker
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Rima Khabbaz, MD
Deputy Director for Infectious Diseases / CDC

Dr. Baker called the October 2010 Advisory Committee on Immunization Practices (ACIP) meeting to order, welcoming those present. Dr. Pickering extended his welcome and called on Dr. Rima Khabbaz to offering the opening remarks. On behalf of CDC Director Dr. Tom Frieden, who was unable to attend, Dr. Khabbaz also welcomed everyone. She emphasized that ACIP is a very important advisory body for CDC, and offered gratitude to the members and liaison members for agreeing to serve. She extended a special welcome to three new ACIP members and offered a brief bio for each: Dr. Tamara Coyne-Beasley (who was approved, but was awaiting final paperwork before she could officially join the committee as a working member), Dr. Jeffrey Duchin, and Dr. Renee Jenkins. She also recognized and offered a brief bio of the new Editor-in-Chief for the *Morbidity and Mortality Weekly Report (MMWR)*, Dr. Ron Moolenaar, and the new Deputy Editor, Dr. John S. Moran. Dr. Pickering also recognized and thanked the outgoing *MMWR* Editor-in-Chief and Deputy Editor, stressing how hard the individuals in these positions work, Dr. Fred Shaw and Dr. Chris Casey, and thanking them for their diligence in publishing ACIP's recommendations.

Dr. Baker announced that earlier in October, the Section of Infectious Diseases of the American Academy of Pediatrics awarded Dr. Pickering the Lifetime Teaching in Pediatrics Award. She called for a round of applause for Dr. Pickering and said she hoped she could aspire to be as good a teacher someday.

Dr. Pickering delivered the administrative announcements, explaining that as with the last few ACIP meetings, the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web. He also welcomed those who could not attend the meeting in person. He then recognized several others in the room who were to be present throughout the duration of the ACIP meeting to assist with various meeting functions: Leola Mitchell, Committee Management Specialist for ACIP; Natalie Greene; Stephanie Thomas; and Tanya Lennon. Those with any questions were instructed to see him, any of these individuals, or Dr. Baker. Dr. Pickering noted that the complex agenda necessitated a full two-day meeting. 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 approximately one week after the meeting, while the meeting webcast will be posted on the ACIP website within two weeks, and the 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.

Ms. Lucia Helena deOliveira of the Pan American Health Organization (PAHO), and Dr. Pickering indicated that PAHO had committed to sending a member to each ACIP meeting. He also welcomed new Ex Officio member Dr. Jesse Geibe, Medical Corps Liaison Officer, Department of Defense (DoD); and new liaison members Dr. Matthew Zahn, National Association of County and City Health Officials (NACCHO); and Dr. Mike Brady, Chair, Committee on Infectious Disease, American Academy of Pediatrics (AAP).

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

Ex Officio Members

- Dr. Geoffrey Evans, Health Resources & Services Administration (HRSA), was unable to attend; Dr. Rosemary Johann-Liang attended in his place.
- Dr. Linda Kinsinger, Department of Veterans Affairs (DVA), was unable to attend; Ms Teri Murphy attended in her place.

Liaison Representatives

- Dr. Damian Braga, Pharmaceutical Research and Manufacturers of American (PhRMA) was unable to attend; Dr. David Johnson attended in his place.
- Dr. Stanley Gall, America College of Obstetricians & Gynecologists (ACOG) was unable to attend; Dr. Kevin Ault attended in his place.
- Dr. Christine Hahn, Council of State and Territorial Epidemiologists (CSTE) was unable to attend.
- Dr. Kenneth Schmader, American Geriatrics Society (AGS) was unable to attend.

To avoid disruptions during the meeting, those present were asked that all business not directly related to discussions of ACIP be conducted in the hall to avoid disturbing people in the audience, and were instructed to turn off all cell phones or place them in the vibrate mode to avoid disruption. Given that the meeting could not begin unless a quorum of members was present, all appointed members were asked to return from breaks and lunch in a timely manner to participate in the meeting.

Topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. In certain circumstances, a formal comment period may be scheduled during the deliberations of a specific agenda item rather than at the end of the day in order to be considered before a vote is taken. Those who planned to make public comments were instructed to visit the registration desk in the rear of the room to have Ms. Leola Mitchell 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. Mitchell 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 members' expertise while serving on the committee, CDC has issued limited conflict of interest (COI) waivers. Members who conduct vaccine clinical trials or who serve on data safety monitoring boards (DSMBs) may serve as consultants to present to the committee on matters related to those specific vaccines; however, they are prohibited from participating in deliberations or committee votes on issues related to those specific vaccines. Regarding other vaccines of the affected company, a member may participate in a discussion with a proviso that he or she abstains on all votes related to that vaccine company.

The following resource information was shared pertaining to ACIP:

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

Nominations: <http://www.cdc.gov/vaccines/recs/acip/req-nominate.htm>

The ACIP Secretariat solicits applications throughout the year for candidates to serve on ACIP. Detailed instructions for submissions of name of potential candidates may be found on the ACIP website. Applications may be submitted at any time of the year. Materials in support of the next cycle of applications for ACIP membership are due no later than November 19, 2010 for the term beginning July 1, 2011. Five positions are available. Interested parties were encouraged to complete an application and submit it by the deadline. Submit as e-mail attachments to: Jean C. Smith, MD, MPH: JSmith2@cdc.gov

Next ACIP meeting: February 23-24, 2011

Registration Deadlines: **Non-U.S. Citizens Feb 4, 2011 – U.S. Citizens February 11, 2011**

Vaccine Safety: www.cdc.gov/vaccinesafety/

Vaccine Abbreviations:

<http://www.cdc.gov/vaccines/recs/acip/vac-abbrev.htm>

Vaccine Schedulers: <http://www.cdc.gov/vaccines/recs/schedules/default.htm>

Childhood:

http://www2a.cdc.gov/nip/kidstuff/newscheduler_le/

Adolescent:

<http://www.cdc.gov/vaccines/recs/Scheduler/AdolescentScheduler.htm>

Adult:

<http://www.cdc.gov/vaccines/recs/Scheduler/AdultScheduler.htm>

Adult Vaccine Scheduler:

<http://www.cdc.gov/vaccines/recs/Scheduler/AdultScheduler.htm>

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

Vaccine Toolkit:

<http://www.cdc.gov/vaccines/spec-grps/hcp/conversations.htm>

The Vaccine Toolkit was also developed by NCIRD / CDC in conjunction with the American Academy of Family Physicians (AAFP) and the American Academy of Pediatrics (AAP). This is a providers' resource for vaccine conversations with parents.

Dr. Pickering indicated that Dr. Baker had requested an update on the status of ACIP provisional recommendations with regard to publications. Recommendations published since the last meeting as either policy notes or recommendations and reports (indicated by the RR under the *MMWR* reference) include the following:

Topic	Publication Date	MMWR Reference
Anthrax Vaccine	07/23/10	Vol. 59(RR06): 1-30
Yellow Fever Vaccine	07/30/10	Vol. 59(RR07): 1-27
Influenza Vaccine (seasonal and H1N1)	08/06/10	Vol. 59(RR08): 1-62
Policy Note: CSL Influenza Vaccine (Afluria)	08/13/10	Vol. 59(31): 989-992
Policy Note: PPSV23 Vaccine (adults)	09/03/10	Vol. 59(34): 1102-1106
http://www.cdc.gov/vaccines/recs/provisional/default.htm		

Status of publication of ACIP recommendations:

Vaccine	MMWR Weekly	Recommendations and Reports
Pneumococcal Vaccine (pediatric)	--	December 2010
Immunization Schedule 0 through 18 years of age	01/07/2011	--
Immunization Schedule ≥19 years of age	01/14/2011	--
General Recommendations (including combination vaccines)	--	January 2011
MMR: evidence of immunity in healthcare personnel (Joint ACIP/HICPAC – immunization of healthcare personnel)	--	May 2011
Influenza Antiviral Recommendations	2011	
Future Submissions (2011): <ul style="list-style-type: none"> ● Meningococcal Vaccines ● Pertussis-containing Vaccines ● Evidence Based Recommendations: Methods 		
http://www.cdc.gov/vaccines/recs/acip/		

The following conflicts of interest were declared:

- Dr. Janet Englund: Research support to her university from MedImmune, sanofi pasteur, Novartis, Admark, Adamas, and Chimerix
- Dr. Wendy Keitel: Her university receives clinical trial support from Novartis
- Dr. Cody Meissner: Payments made to Tufts Medical Center by MedImmune and Pfizer for participation in multi-center clinical trials
- The remainder of the ACIP members declared no conflicts

Discussion Points

Ms. Ehresmann pointed out that when she visited the ACIP Facebook page and chose to like it, she was the only person who liked the ACIP page at that time. When she checked the day before the meeting, there were still only five people who liked it. She encouraged everyone to visit this page and join her in liking ACIP.

Dr. Pickering responded that they would make sure that this information was disseminated widely so that many friends could join.

Meningococcal Vaccine

Introduction

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

Dr. Meissner recognized the members of the Meningococcal Work Group and thanked them for their participation, time, and effort in working through several very complicated issues. The meningococcal issues that were the focus of discussion during this session were as follows:

- Consideration for a 2-dose primary series for people at increased risk for meningococcal disease, including those with asplenia, complement component deficiencies, and HIV infection. Evidence suggests that a single primary dose with a meningococcal conjugate vaccine for people in these groups does not confer adequate immunity. The work group has proposed a 2-dose primary series for this small population.
- The second and more complicated topic pertained to the issue of reconsideration of the current adolescent vaccination schedule for meningococcus. Presentations during this session addressed the reasons the current schedule was being reconsidered and what changes might be made to optimize the adolescent meningococcal vaccine program. The advantages and disadvantages of each of several options were presented, as were the cost-effectiveness of adolescent meningococcal vaccination; provider attitudes and practices

regarding adolescent meningococcal vaccination; and considerations regarding adolescent meningococcal vaccination.

The work group has discussed the adolescent program for the past year. When the meningococcal conjugate vaccine was licensed in January 2005, data were not available regarding long-term efficacy, but the expectation was that protection would last for 10 years. Five years after a single dose of vaccine was first recommended for adolescents, evidence suggests that most vaccinees have a serum antibody concentration that is below the accepted surrogate of immunity. Thus, a single dose at 11 or 12 years of age may not offer protection against vaccine serogroups through the period of increased risk in the late teenage years and early in the third decade of life.

Most work group members agreed that the simplest solution would be to administer a second dose at 15 or 16 years of age. This would be least disruptive to the vaccine schedule and would offer the greatest reduction in the burden of meningococcal disease among the various options. The concern with this solution is the cost of a 2-dose schedule at a time when rates of meningococcal disease are at historically low levels and the future direction of these rates is unknown. Is it appropriate to almost double the amount of money spent on this program? The answer to this question regarding cost should be determined by the goal of the adolescent meningococcal program. If the goal is to prevent as many cases as possible, regardless of cost, then a 2-dose schedule appears to be the most reasonable approach. If the goal is to prevent as many cases as possible, but in a cost-efficient manner using the least number of doses, then a 2-dose schedule is unlikely to be the most reasonable approach and this leads to two other options.

The time of the 11- to 12-year old dose could be moved to 15 to 16 years of age, closer to the period of greatest risk. However, this would leave children in the 11- through 14-year old age group unvaccinated and the move would be disruptive to the established vaccine schedule. Another option is to leave the 11- to 12-year old dose unchanged until sufficient information is acquired on which to base a sound recommendation. However, this will take time and there is concern about waiting to see if disease rates rise. In terms of cost per quality adjusted life years saved (QALY), a single dose at 11 to 12 years of age is the most expensive option and is estimated to prevent the least amount of disease among the three options. However, even a single dose at 15 to 16 years of age will result in one of the highest costs per QALY of all routinely recommended vaccines. There is no easy answer to this conundrum. The work group has spent much effort on this issue and strongly supports changing the schedule at this time. The majority of members favor giving a booster dose at age 16 years, while some prefer moving the dose to later in adolescence or making no change at this time.

In closing, Dr. Meissner congratulated Dr. Cohn on her recent promotion to Commander.

Rationale and Proposed Recommendations for Two Dose Primary Vaccination for Persons at Increased Risk for Meningococcal Disease

Amanda Cohn, MD

**Meningitis and Vaccine Preventable Diseases Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Cohn reminded everyone that persons at increased risk of disease are currently recommended for a booster dose 3 to 5 years after primary vaccination, depending on age. However, these persons currently receive a one-dose primary series. HIV infected patients 11 through 18 years of age receive a single dose. Other persons with HIV may benefit as well, but are not considered high risk for meningococcal disease. There is evidence a single dose primary series may not be sufficient to confer protection in certain groups. Persons with HIV and asplenia have a suboptimal response to a single dose of meningococcal conjugate vaccine. In persons with complement component deficiency, high antibody titers can protect by enabling non-complement mediated killing.

The prevalence of complement deficiency is 0.03% in the population. HIV prevalence in adolescents is also very low. There are approximately 70,000 to 100,000 persons of all ages affected by sickle cell disease, but the prevalence of other types of asplenia is unknown. In short, the number of persons impacted by these proposed recommendations is small and is likely less than 50,000 persons a year.

N. meningitidis is the primary pathogen in persons with late component complement deficiency, including C3, properdin, factor D, and late component deficiencies. Often, meningococcal disease is the first indicator that they are complement deficient. Persons with complement deficiency are at 7,000 to 10,000 fold higher risk for meningococcal disease, 43% to 57% will develop disease, and half of these will have recurrent disease. There are data from polysaccharide vaccine that vaccination does confer protection [Figen et al, Clin Exp Immunol 1998]. Non-complement mediated killing can occur with high levels of functional antibody. Two doses will increase SBA titers, likely improving effectiveness and duration of protection.

Persons with functional and anatomical asplenia are at increased risk for meningococcal disease and have a high mortality rate of 40% to 70%. In a study in the United Kingdom (UK), 20% of persons with asplenia did not respond to a single dose of MenC vaccine. An additional 13% responded following a second dose of MenC 2 months later [Balmer, P., et al., *Immune response to meningococcal serogroup C conjugate vaccine in asplenic individuals*. Infect Immun, 2004. **72**(1): p. 332-7].

Adolescents with human immunodeficiency virus are recommended for meningococcal vaccination. In a study of adolescents with HIV, only 55% responded with a brSBA $\geq 1:128$ for serogroup C. Responses were higher for other serogroups, but are lower than responses in healthy adolescents. Adolescents with a low CD4 count and high viral load are at greater risk for not responding to a single dose [Siberry, G.K., et al., *Pediatr Infect Dis J*, 2010. **29**(5): p. 391-6].

There are examples of 2-dose primary series from other vaccination programs and clinical trials. Multiple doses in infants and 2 doses in toddlers are safe and highly immunogenic with Menveo® and Menactra®. A two-dose primary series for high risk groups has been adopted in the UK and Canada. In these countries, where most vaccine preventable disease is serogroup

C, one dose of MenC vaccine is followed 2 months later by a dose of MenACWY for persons with asplenia and complement deficiency.

The working group is strongly supportive of a two-dose primary series for persons with complement component deficiency, asplenia, and HIV. The potential benefits outweigh the low risk. The overall cost to the program will be low, and most persons in these groups receive specialized preventive medical care and therefore this recommendation should be straightforward to implement. These recommendations would appear in the updated ACIP recommendations for meningococcal vaccination in table format outlining the recommendations for persons at increased risk for meningococcal disease. Persons who are at increased risk to exposure to the organism, such as travelers to the meningitis belt or microbiologists, would not be recommended for a two dose primary series. The proposed language is as follows:

Proposed Recommendation: Part 1

- Persons with persistent complement component deficiency (C3, properdin, factor D, and late component deficiency) and asplenia who have not been previously vaccinated should receive a two dose primary series of MenACWY two months apart (0, 2 months)
- Persons with Human Immunodeficiency Virus (HIV) who elect to be vaccinated with MenACWY and all adolescents ages 11 through 18 years with HIV should receive a two dose primary series two months apart (0, 2 months)

Proposed Recommendation: Part 2

- Persons with complement component deficiency, asplenia, and HIV who have been previously vaccinated should receive a booster dose at the earliest opportunity, and then continue to receive boosters at the appropriate interval

Discussion Points

Dr. Englund expressed concern about the wording in the parentheses behind the complement deficiency, given that it seems too limiting. She has had a C2 complement deficiency patient.

Dr. Marcy agreed, noting that he had submitted a memo to that effect.

Dr. Baker's understanding was that C2 and C4 were not important in *N. meningitides*.

Dr. Cohn responded that they did not want to make the recommendation too general, which is why they chose the word "persistent" complement component deficiencies and included the specific ones that have been recognized as putting people at increased risk for meningococcal disease. They could add the word "including" before C3 in the parentheses, which would not limit it.

Dr. Sawyer raised the issue regarding whether there are existing recommendations for use in other immunodeficiencies, and whether the work group discussed others who are at risk like gamma globulin anemia patients and whether they should be included in this recommendation.

Dr. Cohn replied that persons with other immune deficiencies might be at slightly higher risk, but are not recognized to be at extremely high risk, as is the case for persons with late complement component deficiencies. Thus, they have not been previously recommended in this high risk group.

Dr. Keitel suggested including a comment about the age at which these vaccines should be administered.

Dr. Cohn responded that persons are recommended to receive these vaccines at diagnosis, at two years old at the earliest according to the licensed vaccines.

Dr. Judson wondered whether the definition of “deficiency” was an absolute, and what the range up to the percent of normal would be that would be included in this recommendation.

Dr. Cohn replied that the prevalence of these complement deficiencies is extremely low in the population, so there are very little data on the extent of deficiency. It tends to be people with familial complement component deficiencies who are at high risk.

Dr. Baker noted that about 30 years ago, the first recognition of this was a genetic deficiency of C5, C6, C7, C8, or C9. Any one of those components missing will not allow *N. meningitides*. The high risk is in people with congenital deficiencies. The way they are recognized is that they present with meningococcal disease, and people screen them because they are at risk for recurrence. As Dr. Cohn pointed out, it is believed that increasing the amount of antibody will help compensate for this defect. The other counseling is that if someone has a high fever, they need immediate medical attention rather than assuming it is another virus. She thought they were getting somewhat off of the mark because C2 and C4 have not been shown to be an increased risk. There are no data for B-cell deficiency that she knows of.

Dr. Temte wondered whether there was any safety information for revaccination at the proposed 2-month interval in this age group.

Dr. Cohn responded that in this age group, there are no data on a 2-dose primary series two months apart. There are some safety data on a second dose of vaccine in this age group at 3 years and 5 years apart, which suggest that it is very safe. Doses two months apart in infants and toddlers are safe.

Regarding the third bullet point, Dr. Middleman (SAM) inquired as to whether “persons who have been previously vaccinated” mean previously vaccinated and not yet boosted.

Dr. Cohn responded that this would be for persons who had received only one dose, and that this could be further clarified. A booster dose, at least among healthy persons, is extremely immunogenic and hopefully those who did not respond to a single dose will have responded.

Dr. Langley (NACI) mentioned that one of the considerations for Canada’s National Advisory Committee on Immunization (NACI) in giving a 2-dose schedule to this group was catch-up, and another was that the meningococcal C vaccine has a higher concentration of C than the quadrivalent. Since that is their highest case fatality rate, they wanted to be sure that this group was protected against C, and they did not believe that one dose of the quadrivalent would be sufficient.

Dr. Whitley-Williams (NMA) noted that the wording in the second bullet stating that “persons who elect to be vaccinated” was somewhat confusing.

Dr. Cohn responded that she could revise this to state “persons who are vaccinated.”

Dr. Marcy referred to an article regarding C2 deficiency primary meningococcal arthritis of the elbow by *N. meningitides* in a 12-year old girl.

Dr. Baker responded that one case was not proof of enhanced risk, although if a practitioner elected to vaccinate someone with a C2 or C4 deficiency, it would be acceptable.

Ms. Rosenbaum said that as a non-scientist hearing this discussion, she was also concerned about issues of coverage. Her sense was that if there are potential situations outside of the stated ones in the recommendations in which the judgment of the clinician is important, the recommendation should be drafted in a way that allows for flexibility. Otherwise, as ACIP standards take on new meaning in coverage, clinicians could face coverage exclusion prohibiting use of a vaccine in cases other than those identified. If the goal is to potentially reach populations other than ones for whom they are making formal recommendations, consideration must be given to flexible wording.

Dr. Cohn responded that one of the ways in which Dr. Santoli had been working on the Vaccines for Children (VFC) resolution for meningococcal vaccines is by having the recommendations be precise and provide clear guidance to practitioners. The VFC resolution can add some flexibility in terms of coverage from a VSD perspective.

Ms. Rosenbaum clarified that the law states that the recommendations of the ACIP will guide coverage. The VFC guidance may be very important in terms of what will be provided for purchase and distribution. However, ACIP’s recommendations are the binding recommendations for legal coverage decisions.

Motion: Meningococcal Recommendations for Two-Dose Primary Vaccination for Persons at Increased Risk for Meningococcal Disease

Ms. Ehresmann made a motion to accept the recommendation as presented, with the following revisions as suggested: 1) Add the word “including” before C3 in the parentheses following “Persons with persistent complement component deficiency; 2) Further clarify the third bullet point to make clear that it refers to persons who have received only one dose; and 3) Revise the wording in the second bullet stating that “persons who elect to be vaccinated” to “persons who are vaccinated.” Dr. Meissner seconded the motion. The motion carried with 12 affirmative votes, 2 abstentions, and 0 negative votes.

Cost-Effectiveness of Meningococcal Vaccination Strategies for Adolescents in the United States

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

Dr. Ortega-Sanchez reported on the analyses of the effectiveness and cost-effectiveness of three meningococcal vaccination programs in adolescents in the US under reduced disease incidence and duration of vaccine effectiveness, comparing 5 years of vaccine efficacy compared and contrasted with the 10 duration that were used in previous analyses. The three strategies under consideration include one dose at 11 years old (currently recommended), one dose at 15 years old, and two doses (first at 11 years old and second at 16 years old). A societal perspective was used, which means that both indirect and direct costs were included in the analyses.

For this purpose, a decision tree model was constructed to compare four strategies (the three just explained and one with no vaccination). A similar model was presented to ACIP previously. The decision tree is designed with Monte Carlo simulation analysis. The cohort consists of a hypothetical population of 4 million adolescents 11 years of age. The time frame is 10 years, the analytic horizon is age-specific life expectancy, the discount rate is 3% (0%-5%), and pre-vaccine epidemiological data were used from 1996 to 2005, the pre-vaccination era, so that the impact of the current vaccination program will not be included as a noise. The core model inputs include epidemiological data, vaccine characteristics, HCRU and cost data, indirect cost data, quality of life data after meningococcal disease, and other parameters. Epidemiologic data include age- year- and C+Y+W135 serogroup-specific incidence rates from 1996 to 2005, age- and serogroup-specific case fatality ratios, and the proportion of survivors with sequelae by condition after disease.


There are two important characteristics for economic modeling for adolescents. One is changes in the annual incidence in vaccine serogroups C, Y, W135 by age group per 100,000 (95% CI) [Active Bacterial Core Surveillance in Cohn et al CID 2010]. From 1998 to 1999 through 2004 to 2005, there was approximately a one-fourth reduction in incidence. The second characteristic is the incidence peak in the late teens. With regard to vaccination strategies, for simplicity, effectiveness and coverage were presumed to be the same for all age groups at 93% (range 73-98) with 72% coverage and a new scenario for efficacy duration of 5 years was utilized [Pichichero et al., *Pediatr Infect Dis J* 2005; Shepard et al., *Pediatrics* 2005; Snape et al., *JAMA*. 2008; For vaccine coverage among adolescents; Smith et al., *Pediatrics* 2009].

Vaccine cost was based on 2009 public and private sector prices. For adolescents using one dose of MCV4, \$90 per dose +\$AEs* +\$Adm** (= \$101) was used. Vaccine costs are varied from \$30 to \$120. For two doses of MCV4, \$189 per vaccine was used, which includes \$AEs* and \$Adm** discounted cost for the second dose [*Adverse event rates were taken from the UK experience with MCC: Trotter et al., *BMJ* 2002; Ortega-Sanchez et al., *CID* 2008; **Cost of vaccine administration among pediatric practices: Glazner et al., *Pediatrics* 2009]. Other benchmark elements include meningococcal disease incidence under vaccination; direct and indirect costs of meningococcal disease (e.g., acute phase costs and long-term costs, and productivity loss to deaths and sequelae); health related quality-of-life scores for estimating QALYs lost to sequelae; and cost-effectiveness ratios [Shepard et al., *Pediatrics* 2005; Ortega-Sanchez, et al., *CID* 2008].

With regard to the results for the baselines for the cohort of 4 millions adolescents with no vaccination, there were 305 cases, 36 deaths, 880 life years lost (discounted at 3%), and 4015 QALY's lost (discounted at 3%). Total cost of illness was \$143 million. One dose of vaccine at 11 years of age prevented 72 cases and 9 deaths, saved 233 life-years and 969 QALYs, and cost \$1 million per life-year and \$281,000 per QALY. One dose at 15 years of age prevented 120 cases and 14 deaths, saved 330 life-years and 2165 QALYs, and cost \$706,000 per life-year and \$121,000 per QALY. Two doses at 11 and 16 years of age prevented 193 cases and 23 deaths, saved 564 life-years and 3133 QALYs, and cost \$793,000 per life-year and \$157,000 per QALY. One dose at 15 years appears to be the most cost-effective. Base case comparisons are reflected in the following table:

Base case Comparisons \$/QALY in adolescent vaccines in the US		
Vaccine	Target group	Cost per QALY gained (compared to no vaccination)
Hepatitis B	College freshmen	<\$0 (cost-saving) to ≈ \$10,000
Hepatitis A	College freshmen	<\$0 (cost-saving) to ≈ \$15,000
HPV	12-year-old females	≈ \$3,000 to \$45,000
Influenza (LAIV)	12- to 17-year olds, high risk	≈ \$11,000
TDaP	All 11-year-olds	≈ \$21,000
Meningococcal (MCV4)	1-dose, all 15-year-olds	\$121,000
Influenza	12- to 17-year olds, healthy	≈ \$128,000
Meningococcal (MCV4)	2-dose, all 11 & 16-year-olds	\$157,000
Meningococcal (MCV4)	1-dose for all 11-year-olds	\$281,000

Source: Ortega-Sanchez et al. *Pediatrics* (2008), except new Meningococcal strategies
All figures were adjusted to Dec 2009 US\$



Sensitivity analyses were performed, one of which was sensitivity to vaccine price. When the price of the vaccine is lower, sensitivity is higher for one dose at 11 years old than for the other two scenarios. Otherwise, one dose at 15 years old is more cost-effective across the range of vaccine prices. Sensitivity analyses were also performed with a variety of outcome variables simultaneously (e.g., incidence at 16, 18, and 19, and 20 years; cost per dose; vaccine coverage; hearing loss; multiple amputations; et cetera) to determine which one ranked highest. Incidence of disease is always at the top as an indirect impact.

In conclusion, a 5-year vaccine effectiveness duration makes vaccinating at 11 years the least cost-effective strategy. The other two strategies cost between \$121,000 to \$157,000 per QALY saved. Vaccinating at 15 years would prevent the greatest number of cases per dose given, and is considered to be the most cost-effective. However, vaccinating at 11 years and revaccinating at 16 years would prevent the most cases. In all of the strategies, disease rates and vaccine cost drive the analyses.

Adolescent Meningococcal Vaccine: Physicians' Current Practices and Preferences

Allison Kempe, MD, MPH
University of Colorado

Dr. Kempe shared some brief results of a survey conducted with primary care providers regarding adolescent meningococcal vaccines. The objectives of the survey were to describe providers' current practices related to the meningococcal conjugate vaccine for adolescents; and providers' preferences regarding timing of meningococcal vaccine administration in adolescents.

Physicians in sentinel networks that are part of the Vaccine Policy Collaborative Initiative were surveyed. These sentinel practices are recruited from random samples of the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP). Respondents practicing less than 50% primary care are excluded from these samples. Quota sampling is done to ensure that the networks are similar to the overall AAP and AAFP memberships. A previous study compared this methodology of surveying sentinel network physicians to physicians randomly sampled from the American Medical Association (AMA). Sentinel networks are comparable to AMA with respect to physician demographics, practice characteristics, and most importantly, responses regarding vaccine-related issues [Crane LA, *Eval & Health Prof*, 2008].

In terms of the survey design and administration, the questions were developed jointly with CDC and were modified based on input from advisory committees comprised of pediatricians and family physicians from 6 representative states. The survey was pre-tested and was piloted among primary care physicians across the country, and was administered by Internet and email depending upon the preference of the physician December 2009 to January 2010. For the Internet survey, providers were sent a link to the survey via email. They received emails reminders every 3 days 7 times and then once a week 2 times. Subsequently, non-responders received one mailed survey. Mailed survey recipients were sent a pre-letter 4 days before the first survey, and up to 3 surveys were sent with an additional reminder postcard between mailings 1 and 2.

Dr. Kempe presented the results of one multivariate analysis. The dependent variable was providers who defer recommending meningococcal conjugate vaccine to adolescents greater than 12 years compared to providers who strongly recommend at 11 to 12 years of age. The independent variables include provider characteristics (e.g., specialty, year of graduation, gender), practice (e.g., region, urbanicity, practice type, VFC participation, patients' insurance status, and race / ethnicity), meningococcal vaccine supply, and provider level of concern about waning immunity. There was a 75% survey response rate overall, which was comprised of 63% (268/423) family medicine practitioners and 88% (367/419) pediatricians. Respondents were similar to non-respondents with respect to practice setting, region of the country, and urbanicity. Respondents were somewhat less likely to be male, and the mean age of the pediatric respondents was 3 years less than non-respondents.

In terms of current reported practices regarding administration of meningococcal vaccine, only 2% of pediatricians and 8% of family physicians said they do not currently administer the vaccine at all; 95% of pediatricians and 73% of family physicians said they routinely administer the vaccine; 1% of pediatricians and 6% of family physicians said they administer the vaccine only when required; and 2% of pediatricians and 13% of family physicians said they administer only to 11 to 18 year olds with high risk conditions [$p < .001$ for Kolmogorov-Smirnov test for comparison of distributions of responses between specialties].

Regarding the strength of recommendation for different age groups between pediatricians and family physicians, for both groups the percentage who recommend the vaccine strongly increases with increasing age of the adolescents. This is much more marked for family physicians than for pediatricians, largely because 83% of pediatricians say they already strongly recommend the vaccine at 11 and 12 years of age. Virtually all pediatricians recommend vaccination in the older age group. By comparison, 45% of family physicians are strongly recommending the vaccine at 11 and 12, 55% at 14 to 15, and only by 17 or 18 are the vast majority strongly recommending.

This question was posed in the survey exactly as worded here: How concerned are you about immunity wearing off if you immunize adolescents at age 11 to 12 years? Of pediatricians, 22% were not at all concerned compared to 26% of family practitioners; 54% of pediatricians and 42% of family practitioners were a little concerned; 19% of pediatricians and 24% of family practitioners were moderately concerned; and 5% of pediatricians and 8% of family practitioners said they were very concerned. In response to the question: Regardless of ACIP recommendation at what age would you prefer to have adolescents immunized? 68% of pediatricians and 35% of family practitioners said 11 to 12 years; 23% pediatricians and 31% of family practitioners said 14 to 15 years; 5% of pediatricians and 20% of family practitioners said 17 to 18 years; and 5% of pediatricians and 15% of family practitioners said they had no preference. This multivariate analysis also assesses the factors associated with deferring vaccination to mid or later adolescence. Family medicine physicians are more likely to defer the vaccine; however, even if specialty is control for, there are other differences as well (e.g., region of the country, proportion of Latino patients, vaccine supply in the office, concerns about waning immunity).

In terms of limitations, respondents may have differed slightly from non-respondents, but there was a high survey response rate. While sentinel physicians may differ from physicians overall, prior work suggests not. The survey results represent reported practice. Actual practice was not observed.

In summary, pediatricians are more likely to strongly recommend and administer the meningococcal vaccine for adolescents. Family Medicine physicians are more likely to prefer older age at vaccination. Characteristics associated with choosing to defer recommending the vaccine until mid or later adolescence include specialty (FM) and higher level of concern about waning immunity if vaccination occurs at 11-12 years of age.

Optimizing the Adolescent Meningococcal Vaccination Program

Amanda Cohn, MD

**Meningitis and Vaccine Preventable Diseases Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

During this session, Dr. Cohn discussed the working group rationale for changing the adolescent meningococcal vaccination program, including epidemiology, duration of protection, vaccine effectiveness, and programmatic considerations. She then reviewed the pros and cons of the potential options.

The current adolescent vaccination recommendation states that 11 to 12 year olds should be vaccinated at their pre-adolescence vaccination visit, and that 13 to 18 year olds who have not been previously vaccinated should be vaccinated at the earliest opportunity. There are currently two licensed quadrivalent meningococcal conjugate vaccines for 11 to 18 year-olds, Menactra® and Menveo®.

The meningococcal recommendations were driven by the goal to protect adolescents through the peak of disease incidences occurring in persons 16-21 years. In 2005, ACIP discussed where to place the dose prior to this peak, but the assumption at the time was that the vaccine would protect most adolescents for at least 10 years. Therefore, the preferred age of vaccination was placed at age 11 to 12 years in order to obtain high coverage before the increased period of risk, and to help with the development of the pre-adolescent vaccination platform. Meningococcal conjugate vaccine was the first of the three vaccines put at the 11 to 12 year old visit, and was an important part of successfully establishing the adolescent vaccination platform.

The question of the hour and for the past year of working group discussions is: Why change the program now? Data indicate that protection will wane within 5 years after vaccination. Most working group members do not want to wait for disease increases as we have done with other childhood vaccine preventable disease before adding a booster dose. They do not see attenuated disease in vaccinated persons, and the case-fatality ratio is similar in persons vaccinated compared to those who are not vaccinated. This vaccine was placed 4 to 5 years prior to the age of higher risk, and therefore we are missing protecting the group the recommendation was intended to protect—older adolescents. Importantly, changes should be made before additional states add mandates at middle school, since these mandates may be more appropriate for high school entry.

Regarding the current epidemiology of meningococcal disease among adolescents, rates of all serogroups have declined since 1999, and the US is currently at historic low rates of meningococcal disease [Active Bacterial Core Surveillance, estimated to the US population]. A direct impact of vaccination on meningococcal disease rates is beginning to be observed. In terms of Serogroup C, Y and W135 disease in 11 through 19 year-olds compared to persons 20 and older, declines were observed in among 11 through 19 year olds in 2008-2009 that were not seen in persons 20 and older. However, it appears this decline is primarily among younger adolescents. With regard to the average annual number of cases of meningococcal disease pre- and post-routine meningococcal vaccination, there was a 74% decline in disease among 11 through 14 year-olds, with approximately 12 cases annually since vaccination. However, 77 cases have been observed among adolescents ages 15 through 18 years—a 27% decline. In

the 2009 National Immunization Survey (NIS) teen data, large differences are not observed in vaccine coverage by age that would explain differences in declining disease. There was a 16% decline in persons aged 19 through 22 years, but there was likely impact on this age group of polysaccharide vaccine use on college campuses during 2000-2004. Importantly, during 2005-2009, an average of 141 cases of preventable meningococcal disease is still being observed among adolescents annually [Active Bacterial Core surveillance, estimated to the US population].

In summary, rates of meningococcal disease remain at historic lows. The peak of disease in late adolescence is predominated by serogroup C. An impact of vaccination in 11 through 14 year-olds is being observed, but declines are not as sharp among older adolescents.

There are three components that contribute to long-term protection with conjugate vaccines (e.g., persistence of functional antibodies, memory, and herd immunity). The antibody persistence data focus on serogroup C for two reasons. First, serogroup C causes the most disease among adolescents and has higher morbidity. Second, all serologic correlates are based on protection for serogroup C disease, so these correlates are bridged to presume protection with other serogroups. Using an assay that uses human complement as its complement source, serum bactericidal antibody (SBA) titers of $\geq 1:8$ are currently used as the Food and Drug Administration (FDA) measure of protection for licensure. Baby rabbit SBA of $\geq 1:128$ was used in the Menactra® clinical trials and data using brSBA were also presented. They are unable to compare SBA titers across assays even if they are using the same complement source.

Multiple small studies consistently showed decreasing antibody persistence over time. Two years after vaccination, only 62% of Menveo® recipients and 58% of Menactra® recipients had a human SBA $\geq 1:8$. In one study 3 years-post vaccination, only 35% of Menactra® recipients had a human SBA of $\geq 1:4$ and in another 75% of Menactra® recipients had a brSBA of $\geq 1:128$ [Gill et al, Human Vaccines, Nov 2010]. The differences in these two studies likely reflects the differences between the two assays.

Moving to 5 years, in one study of children vaccinated at ages 2-10 years 5 years previously, only 55% of persons vaccinated with Menactra® had titers above 1:128, and among persons vaccinated at ages 11-18 years 56% of persons vaccinated with Menactra® had SBAs $\geq 1:128$. At 5 years, persons vaccinated with Menactra® were the same as those vaccinated with polysaccharide vaccine. Each of these studies has a small sample size, but consistent results demonstrating waning functional antibodies are observed across studies [ACIP meeting, June 2009].

While antibody titers return to baseline 5 years after vaccination, conjugate vaccines have the advantage of priming the body to mount a larger response more quickly on exposure to the antigen, known as immunologic memory. Current data suggest a memory response takes 5 to 7 days after exposure. This comes from studies assessing how quickly titers boost after antigen challenge such as vaccination. Several studies have shown that it takes 5 days for antibody titers to increase after MenC booster dose [Snape et al, CID, 2006]. A study from the UK showed persons vaccinated with MenC vaccine who developed meningococcal disease (e.g., vaccine failures) did have a boost response, but it did not happen rapidly enough to prevent invasive disease. Invasive meningococcal disease typically occurs less than 4 days after exposure [Auckland et al, JID, 2006].

Conjugate vaccines also have the benefit of providing indirect protection through herd immunity, as was seen with the MenC vaccination campaign in the UK. Meningococcal vaccination coverage has increased to 53% in the Fall of 2009 from 10% in the Fall of 2006. Given the antibody persistence data and the slow rate of increasing vaccination, a high proportion of adolescents could not be expected to have antibody titers high enough to protect from carriage, although the immunologic mechanisms of protecting from carriage are unknown. There are no data to support an impact on nasopharyngeal carriage. Additionally, decreases have not been observed in unvaccinated age cohorts, which would be evidence of herd immunity.

In summary, the working group concluded that the proportion of vaccinated persons considered “protected” by accepted correlates declines with time since vaccination. Functional antibody is close to baseline 5 years after vaccination. Invasive disease develops rapidly, and memory alone cannot be relied upon for protection. Additionally, herd immunity cannot be relied upon for protection in adolescents, given the slow uptake in vaccination coverage and the multiple strains circulating in the US.

With respect to preliminary results of an evaluation of Menactra® vaccine effectiveness, Dr. Cohn presented results from a case-control study in which 4 controls per case are matched by age and geographic area. Enrollment began in January 2006 and is on-going. A case report form and phone questionnaire was completed, and 85% of subjects have a verified vaccination history from a provider or immunization registry. A case was defined as *N. meningitidis* serogroup A, C, Y, or W isolated from a normally sterile site, or detection by PCR (polymerase chain reaction). Conditional logistic regression, controlling for underlying condition (e.g., complement deficiency, asplenia, HIV, other immune disorder, cancer, diabetes, kidney disease) and current smoking history were used to determine vaccine efficacy estimates. Dr. Cohn emphasized that these are all preliminary data.

As of October 2010, there are 108 cases and 158 controls enrolled in the study. The demographics between eligible cases, enrolled cases, and controls were similar. Of note, the case-fatality ratio of eligible cases was higher than the case fatality ratio of enrolled cases. As might be expected, it was more difficult to enroll cases who died. Regarding the preliminary estimates for all persons enrolled in the study, vaccine efficacy is approximately 78%. The confidence intervals around the serogroup-specific estimates were wide, but the point estimate for serogroup C is 77% compared to a point estimate of 88% for the serogroup Y component. Vaccine effectiveness for those vaccinated less than one year from disease onset was 95%. Vaccine effectiveness for all persons vaccinated 1 to 2 years prior was 83%, which increased to 91% among well subjects. At 2 to 5 years after vaccination, vaccine effectiveness dropped to 58% among persons with no underlying illness. The confidence intervals are wide and cross zero, but the trend of the point estimates is convincing that protection wanes over time. In summary, low disease incidence and low vaccination coverage have contributed to limited power, and there are wide confidence intervals around point estimates. However, the trend in point estimates is consistent with serologic data, and estimates in persons without underlying conditions do not change the conclusion of waning immunity.

Data available on the safety and immunogenicity of a booster dose are all from studies with Menactra®. Two studies have evaluated the safety of a booster dose of Menactra® in adolescents, the first 3 years after the primary dose and the second 5 years after the primary dose. There were no serious adverse events in any group, and rates of local reactions were similar to those who received a primary dose at the time of the study [data courtesy of sanofi pasteur]. Large geometric mean titers (GMTs) were demonstrated for the serum bactericidal activity against serogroup C in response to a booster dose of Menactra®. The titers are more than 2-fold the titers generated in vaccine-naïve persons, and more than 10-fold the GMTs generated during the initial pre-licensure trials. In summary, the working group has no safety concerns for a booster dose, but safety should be monitored. This is based on limited data in 2 to 18 year olds, and several studies with both vaccines evaluating multiple doses in infants and toddlers which support safety. The boost response is greater than the response after primary vaccination, suggesting a booster dose may protect longer.

The working group recognizes the important role meningococcal vaccine has played to establish the adolescent vaccination platform. A major concern is that adolescents will not get vaccinated later in adolescence. There has been somewhat of a natural experiment answering this question with the recommendation for catch-up vaccination of 13 to 18 year olds with meningococcal vaccine for the past 5 years. Looking just at the 50% of vaccinated 17 year olds in the NIS from 2009, 17 year olds who were not eligible for vaccination at ages 11 to 12 were vaccinated throughout adolescence, with 30% vaccinated at age 15 and 25% vaccinated at age 16 [courtesy of Shannon Stokley].

Data on provider visits in adolescence are conflicting. An analysis at Marketscan data, which tracks visits of insured adolescents, shows approximately 80% of adolescents have a visit for any reason during a year, but far less, approximately 35% of these visits, are preventive visits where vaccines are typically given. Adolescent visits decrease as they get older, but visits at ages 11 to 12 are similar to visits at age 15 to 16 [Rand et al. Additional data courtesy of Fanjun Zhou, CDC]. Additionally, from the data presented by Dr. Kempe, providers are willing to give meningococcal vaccine throughout adolescence.

A number of states mandate for meningococcal vaccination prior to middle school entry. In the coming school year, there will be 10 states, including DC, with middle school mandates. An additional 17 states have mandates for education. The number of states with mandates in process is unknown, but by comparison there are 36 states with Td/Tdap mandates [www.immunize.org]. In summary, vaccinating with a first or second dose of meningococcal vaccine in middle adolescence is feasible. A middle adolescent platform would provide an additional opportunity for vaccination, including catch-up with other adolescent recommended vaccines. The working group recognizes vaccinating at this age would be challenging. Any change should be made prior to more states putting mandates at middle school entry.

The issues around the meningococcal vaccination program are complex. The working group remains committed to protecting adolescents through the peak risk of disease during 16 to 21 years old, even in the context of historical low disease incidence. The severity of meningococcal disease and the high morbidity in adolescents continue to have a strong influence on the working group. Current data indicate most adolescents are unlikely to be protected 5 years after vaccination. Additional immunogenicity data will be available on Menveo® vaccine in the next year, but are unlikely to be substantially different. In conclusion, a majority, but not all, of working group members agree program changes are challenging but necessary for optimal protection.

The working group requested that ACIP consider three major options at this time:

1. Vaccinate at age 11 through 12 years and recommend a booster dose at age 16 years.
2. Move the preferred age of vaccination to 14 through 15 years. Add to that recommendation to give a booster dose to all adolescents previously vaccinated at age 11 through 13 years. This option could include language for permissive vaccination beginning at age 11 years, with a booster dose recommended for those who are vaccinated earlier.
3. The third option is to make no changes to program at this time, and to monitor for increasing disease rates.

In terms of the cost-effectiveness analysis, the cost per QALY saved for all of these strategies is high, but the working group focused on the relative difference of these strategies rather than the absolute cost-effectiveness, given that there is already a meningococcal vaccination program. Assuming the duration of protection is 5 years, vaccinating at age 11 to 12 years and adding a booster dose prevents the greatest number of cases ($n = \sim 193$) and deaths ($n = 24$) annually. Keeping the program as is, continuing to vaccinate at age 11 years, has the highest cost per QALY saved (\$281,000) and vaccinating at age 15 years has the lowest cost per QALY saved (\$121,000).

However, none of the options that Dr. Ortega-Sanchez modeled in his analyses is absolute, and the reality of adolescent vaccination is that not all adolescents will be vaccinated at age 11-12 years. Therefore, while cost-effectiveness can be compared assuming each strategy on its own, actual program costs are more difficult to predict. Since the adolescent vaccination recommendation was expanded in 2007, each new cohort of 11 to 12 year olds has been vaccinated in addition to catch-up vaccination of older adolescents. Coverage was 53% in 2009, which means that if a minimum of 4.3 million adolescents are vaccinated per year for the past several years, this translates to a program cost of approximately the current program cost of \$387 million annually. If there is no booster dose, catch-up vaccination over time will continue to decline, and programmatic costs will decline to approximately \$270 million a year, assuming 75% coverage with a single dose. Costs rise incrementally with increasing use of the booster dose, but even if 50% of vaccinated adolescents receive a booster dose, costs will be approximately \$405 million, which is similar to the current program cost. Therefore, program costs with a booster dose at any level will not double the program costs, but will increase them somewhat.

The first option is to vaccinate at age 11 to 12 years, with a booster dose at age 16 years. The pros are that this scenario would prevent the greatest number of cases, the booster dose is more immunogenic than the primary dose, and it promotes early and middle adolescent platforms. The cons are the higher program costs, feasibility of attaining high coverage with dose at 16 years, and that this is off-label use and safety is not well-established. However, the third con was not a major concern of the working group. The second option is preferred vaccination at 14 to 15 years, with a booster dose for those vaccinated at age 11 to 13 years. This option could include language that allows providers to vaccinate as early as 11 years, with those vaccinated early recommended for a booster. The pros are that this is the most cost-effective strategy, there is potential to add permissive earlier vaccination with a booster dose, and state mandates would be placed at high school entry. The cons are that if there is no permissive language, persons age 11 to 13 years will no longer be vaccinated and that age group will no longer be protected. There is concern that a permissive option for vaccinating beginning at age 11 years will cause provider confusion. While moving the vaccination platform

to age 14 to 15 years is feasible, it may actually be more challenging than simply adding a dose onto the existing recommendation at age 11 to 12 years. Some adolescents vaccinated at ages 14 to 15 will not be protected through age 21 years. The final option to consider is to make no changes to the recommendations at this time, and to monitor for disease increases. The pros are that this is the least disruptive option, and because rates in all age groups are so low, observations of large increases in disease are unlikely to be observed even if protection wanes by middle adolescence. The cons are that adolescents who are vaccinated according to the recommended schedule are likely not protected during the period of highest risk, this is the least cost-effective option with a duration of protection of 5 years, and state mandates will continue for middle school entry.

In conclusion, a majority of working group members prefer adding a booster dose to the current adolescent program. The reasons are that it is programmatically more feasible, protection of the 11 to 13 year-old age group is not lost, and the boost response is strong. A minority of the members preferred moving to ages 14 to 15 years. The reasons include concern about program costs. There is support for this option from working group members who prefer Option 1 if the permissive vaccination language is included beginning at age 11 years with a booster. A few working group members prefer waiting for more data, including the working group Chair. Given the setting of the current low disease rates, changing the program at this time may be unnecessarily disruptive. While there was not unanimous support for any one option on the working group, members felt strongly that a decision must be made and that waiting for future meetings would not substantially improve the body of evidence. Ultimately, the working group felt that the decision would be judgment-based and that while a change should be made, the idea change remained unclear.

Option 1: Vaccinate at age 11 through 12 years, booster dose at age 16 years

- ACIP recommends routine vaccination of adolescents with MenACWY beginning at age 11 through 12 years at the pre-adolescent vaccination visit, with a booster dose at age 16 years.
- For adolescents vaccinated at age 13 through 15 years, a one-time booster dose should be given 3 to 5 years after the first dose.

Option 2: Preferred vaccination at ages 14-15 years (no permissive vaccination)

- ACIP recommends routine vaccination of adolescents with MenACWY, preferably at ages 14 through 15 years (high school entry)
 - Adolescents vaccinated at ages 11 through 13 years should receive booster dose 5 years after the first dose.

Option 2: Preferred vaccination at ages 14-15 years (permissive vaccination)

- ACIP recommends routine vaccination of adolescents with MenACWY, preferably at ages 14 through 15 years (high school entry):
 - Adolescents may be vaccinated beginning at age 11 years.
 - Adolescents vaccinated at ages 11 through 13 years should receive booster dose 5 years after the first dose.

Discussion Points

Dr. Cieslak expressed concern that the modeling was done with the assumption that immunity was at 93% at 5 years and then decreased to zero percent, because it seemed that this would result in an over-estimate of the amount of disease being prevented in the first 5 years and under-estimate any protection that might remain in years 6 through 10. With a 2-dose vaccination strategy, if the percentage of people who still have antibody at 5 years is as shown in the modeling on the order of 55%, half of those people do not even need a booster dose if it is believed that the antibody is predictive of disease. This is confounded by the fact that disease incidence rises with age rather than falls.

Dr. Cohn acknowledged this limitation in the cost-effectiveness analysis, and explained that they were attempting to conduct the simplest analysis in order to compare the three strategies. The problem with assuming that there is still 50% protection 5 years after vaccination is that the proportion of adolescents who had SBA activity who received Menactra® 5 years previously was very similar to people who had never received vaccination. In essence, the working group interpreted that data as being baseline prior to vaccination.

Dr. Baker emphasized that there are only 2, 3, and 5 year data at this point.

Dr. Judson noted that for most vaccines there is a period of 4 to 6 months in which antibodies are rapidly rising after a first, second, or third dose and then there is almost a straight line decay for antibodies. This may be a very narrow slope for Hepatitis B, but may be a fairly steep slope for meningococcal. The idea is that the slope of that decay curve should be reasonably protective, and they should not assume that there is one rate until 5 years and some other protective rate after that. One area of uncertainty is that antibody response in different years. The confidence intervals seemed to be extremely wide, and the percent protected ranged from 30% to 60% in one scenario. That is a very wide range for critical data.

Dr. Cohn responded that the working group recognized that much of the data had wide confidence intervals. The problem is that there will be no data available in a year that will close these confidence intervals substantially, so they felt that they needed to make assumption and use their judgment given the data there are. All of these studies were conducted in very small numbers of people.

Based on the data that Dr. Ortega-Sanchez provided regarding the coverage assumptions in the model for the cost-effectiveness analyses, Dr. Jenkins pointed out that the drop-off of adolescents who have a routine visit at 16 is substantial. She wondered how much it would vary the cost-effectiveness estimates if the range of coverage was reduced to what may be reasonable.

Dr. Ortega-Sanchez responded that for simplicity, the coverage used was the same across the three strategies. They understand that coverage is not the same, especially in late teens. The 15-year old strategy and the 2-dose strategy would show higher cost per QALY if the coverage is lower. They do not have any further information about what to assume in terms of coverage, but it can be assumed that for points of decrease in the coverage rate, there will be increases in the cost per QALY and that would make these less cost-effective than they are now.

Dr. Cohn added that the working group discussed 15 to 16 year old coverage extensively. She recognized that preventive visits are lower after this age, but there are multiple opportunities for vaccination. They do feel that it may take a couple of years, but there could be a successful middle adolescent vaccine platform.

Dr. Sawyer requested that “more cost per QALY” be translated into some ballpark dollar amount. He pointed out that the age range in which they would hope to administer a second dose was very narrow.

Dr. Ortega-Sanchez replied that they could do this, but not at this moment.

Dr. Cohn added that for almost everything they have modeled that has been within the range of \$100,000 to \$200,000 per QALY, she would not expect for it to be \$500,000 for example.

Dr. Chilton noted that they were also considering QALYs as a means of determining who should receive a particular product. He worried that an increase which looks small from \$121,000 to \$157,000 per QALY, which is about a 30% increase, would set the bar at that point for consideration of other products as well.

Ms. Ehresmann said her perspective has been that there is currently a situation in which they are willing to accept much higher costs with the existing schedule, so either one dose at 15 years or the 2-dose scenario would be more cost-effective than what there is currently. The 2 doses appear to offer the most benefit in terms of reducing morbidity and mortality.

Dr. Englund pointed out that ACIP needs to take the adolescent platform into account. This vaccine has been administered for 5 years. Based on her review of the literature, current vaccine uptake by the age of 15 is only 53% currently according to the *MMWR*. That is in the setting of a highly recommended adolescent visit in which a Tdap and HPV vaccine are supposed to be administered. The high school drop-out rate is as high as 40% among some groups. By moving vaccination ages up, she feels strongly that at-risk youth will be missed and that there will be a significant impact on other vaccinations.

Dr. Temte expressed concern that despite the fact that there were some clear recommendations to immunize at age 11, this is not occurring. In reality, a lot of adolescents are receiving this vaccine at older ages (14, 15, 16). Some guidance about when to revaccinate these individuals would be very important.

Dr. Cohn replied that adolescents who were born later are more likely to be vaccinated at 11 to 12 years of age, which is to be expected given that there are no supply issues. The language for Option 2 could state in the second bullet that for adolescents vaccinated at ages 13 through 15 years, a one-time booster dose could / may be given 3 to 5 years after the first dose.

Ms. Rosenbaum thought it was extremely important to not lose the connection of children with the healthcare system at 11 to 12 years of age. She thought that Option 2 was more of a transition than an option. It will last as an option as long as children have received vaccination at ages 11 to 12, but at some point everybody will fall under the grandfathering provision. Not having a good way to deal with access amongst middle adolescents is not a reason not to make the investment. It is important to think about what issues can be raised about the importance of strengthening the platform (e.g., through family planning, school health programs, et cetera).

Dr. Baker pointed out that while increased risk begins at 15, it lasts until 20 to 21. They must keep in mind that this issue affects adolescents and young adults.

Dr. Meissner reminded everyone that Dr. Ortega-Sanchez's model began with the assumption that there are a total of 305 cases of vaccine-preventable meningococcal disease between the ages of 11 and 21. The current one-dose schedule at 11 to 12 years of age prevents 72 of those cases, and a 2-dose schedule would prevent an additional 120 cases and an additional 15 deaths due to meningococcal disease. While these are fairly significant numbers, the total burden of disease in the US is relatively small in comparison to many other vaccine-preventable diseases. Shifting the dose to 15 to 16 years of age will leave a significant number of children vulnerable who enter the high risk period of dormitory life at 18 years of age. Perhaps a third of those vaccinated will no longer have the serologic correlate of immunity. In addition, little is known about the direction of meningococcal disease. A potential change was being recommended based on what has occurred in the past. The data on which they would be making this recommendation was relatively flimsy, and the cost-effectiveness is very dependent upon the incidence of disease.

With respect to incidence, Dr. Duchin noted that the rates in the data used in the model date back to 1996 and were about four times higher than currently. He wondered if any analyses were done using more recent incidence rates. Incidence rates in 11 to 12 years olds are similar to those in the 22 to 28 year old range. Prioritizing prevention of meningococcal disease in 11 to 12 year olds raises the issue of why other populations with comparable incidence rates are not being addressed.

Dr. Cohn replied that a large range of ages was used in order to account for potential increases in rates of disease. In many ways, this analysis under-estimates cost-effectiveness, which would be substantially higher if the years 2000-2004 and 2004-2005 are assessed. The incidence of 11 to 12 year olds in this analysis is similar to what is observed in older adolescents currently. This is one of the reasons that the working group had to consider this cost-effectiveness analysis in the context of the fact that vaccine is already being recommended. The actual cost of this program was not a major consideration for most people because we are already committed to that cost.

Dr. Ortega-Sanchez noted that point estimates and ranges were both provided. Incidence data from 1996 to 2005 were used, and there were changes in the incidence rates that will be reflected in those ranges. The same is true for vaccine coverage, which was from 40% to almost 80%. For every point estimate provided, the range and impact on cost per QALY is also shown.

Dr. Keitel suggested assessing infant disease rates as well.

Dr. Fryhofer (ACP) said that as a primary care physicians, internist were not included in Dr. Kempe's survey. As a member of the ACP Adult Immunization Advisory Board, any change ACIP makes in this recommendation to a later age group will probably mean that more insurance companies will need to get on board to vaccinate patients. ACP has mechanisms in place to get the word out to its members and is willing to help with this.

Dr. Turner (ACHA) pointed out that one concern about waning immunity would be if an emergence of disease was being observed on college campuses. He and Dr. Cohn coordinated a survey of schools last school year, although the data are very preliminary. They were able to get 207 schools representing about 2 million students to respond to this survey. Among those 2

million students, there were 11 cases of meningococcal disease, 5 of which were vaccine-preventable (4 group C, 1 group Y) and 3 of those cases are from one school where there was an outbreak. If those cases are consolidated into one, there were only 3 vaccine-preventable cases among 2 million students last year. Of the 11 cases, 3 died for a case mortality of 27%. Of the 4 cases of C, only 1 had been vaccinated and the Y had not received vaccine either. Of the 5 students, 2 were freshman in residents halls and 3 were living in apartments and were not freshman. The point is that an emergence of disease has not been observed among college students, so if there is waning immunity, it is not appearing as a manifestation of disease yet. Therefore, he is not terribly concerned about emerging disease at this point. While it may take a couple of years to observe this, it was not clear that there was urgency in deciding to give a booster.

While it is very encouraging that little disease is being observed on college campuses, Dr. Cohn pointed out that most cases who were in college this year were not vaccinated 5 years ago. Most of them were vaccinated within the last couple of years.

Dr. Turner (ACHA) added that 62% of students nationally are vaccinated, which is a fairly high vaccine rate. This rate was 4% in 2001.

Dr. Baker commented that 62% is still deplorable.

Dr. Schuchat felt that ACIP was doing a great job wrestling with the many uncertain elements of this issue. One of the drivers of this analysis was the price of the vaccine. She wondered if the manufacturers could speak to potential price changes in the future as well as supply.

Dr. Middleman (SAM) pointed out that this is a very difficult discussion because of the lack of data. She urged the ACIP members not to rule out 15 year olds and the potential for that platform, which must be built to know whether they will come. There has been a tremendous amount of success in the 11 to 12 year old age group. DPT has been available since the 1940s and it has taken 60 to 70 years to achieve a 90% coverage rate. The rates for meningococcal vaccine in adolescents have climbed astronomically quickly.

Dr. Keyserling (SHEA) pointed out that school mandates drive uptake and that perhaps the rate is only about 50% because only 32 states have mandates. It is virtually impossible to have a third mandate. Departments of Education and states are not going to institute a 10th grade entry vaccine review. If only one dose is given for 10th grade, there may be less uptake than one dose at age 11 to 12 or a 2-dose schedule.

Ms. Stinchfield (NAPNAP) said she was very proud to have participated in the original vote and set aside cost-effectiveness concerns at the time. That was less of an issue with the current discussion. Adding an additional dose rather than attempting to change the current age would be much more feasible and practical at the clinical level. People are used to the evolution of adding a second dose, and it would not be that difficult for practitioners to add a booster. Regarding the second sentence and the cohort of adolescents who were vaccinated at 13 and 15, some of them are approaching age 20 to 21. She thought it would be beneficial to include an end age on the second dose such as "through age 21" so that clinicians are very clear.

Dr. Salisbury (DOH, UK) pointed out that every aspect of the UK program differs from the US program. He also did not think the US understood some of the consequences. The UK has never used Menactra® in its program. They have used either tetanus conjugate or CRM conjugate vaccine, which is one of the important differences. They initially vaccinated infants

and did a catch-up through to at least 18 years, another substantial difference. They administered 3 infant doses with no booster initially and then changed to 2 infant doses, with a HibMenC booster and no further booster after that. However, they have observed a very rapid decay in antibodies. There is no doubt that antibodies fall extremely rapidly, as does efficacy. However, the UK has the same dilemma of very small numbers with very wide confidence intervals. Nevertheless, the first cohort that the UK vaccinated when they were less than one year of age are now age 11. The oldest cohort that was vaccinated, if counting the 18 year group, are coming upon age 30. There is a flat line of zero disease. A decade out without boosting, the UK still has effectively no Group C disease. They recently went two years without a single death in the under 18 group. He does not understand this because it is incongruous with the antibody responses. The UK has also grappled with the same dilemma of whether they should wait for an increase in cases before making a recommendation for a teenage boost. The view from their analysts is that it would require only a very small increase in cases to be cost-effective because the price the UK pays for MenC vaccine is a very significant order of magnitude different.

Dr. Grogg (AOA) indicated that Oklahoma experienced an outbreak of Group C, with two cases dying within 24 hours and significant publicity and attention. Thus, he is a major advocate for immunizing. Speaking as a pediatrician, he would want to continue to have a recommendation at 11 to 12 years of age because they are presenting at that age. It is much easier for him to add booster doses than to eliminate a dose and move it to a different time. Therefore, he thought Option 1 would be much more effective.

Dr. Baylor (FDA) commented that the booster dose is an off-label use. When recommendations are made for booster doses off-label, it is very difficult to collect the necessary data to support this in the package insert. The data are scant and it is important to conduct studies. Once recommendations are made for the booster dose, there is little incentive to conduct those studies. This is not an emergency situation and he believes data should be collected to determine whether adding a booster dose would even have an impact. These questions need to be answered so that the FDA can include the information in the label.

Dr. Campos-Outcalt (AAFP) said the aspect he had not heard discussed sufficiently regarded practical applications in practices. The greatest problems faced by AAFP's members are how complicated the vaccine schedule is already, and how vaccines have to be purchased, stocked, and refrigerated. That probably explains some of the data regarding the difference in administration of the vaccine between pediatricians and family physicians. AAFP's surveys show that almost all physicians who do not vaccinate refer elsewhere to acquire vaccines, particularly the newer most costly ones. This recommendation would be to add a booster dose of a newer costlier vaccine. While that complicates the schedule, it could make it easier to stock the vaccine. It was also not clear to him what it would mean for a state vaccine program.

Dr. Langley (NACI) indicated that Canada is also observing indirect protection and decreasing nasopharyngeal carriage from high coverage rates. The infant programs are being adjusted in most provinces to only have one dose at one year of age in lieu of infant programs because of the indirect protection. Dr. Cohn's reported that there are no data supporting impact on nasopharyngeal carriage in the US. She wondered if they estimated the effects of a higher coverage rate in the middle years group, and what the effect on nasopharyngeal carriage would be. That could be a test case for assessing this in adolescent years.

Dr. Cohn responded that there is evidence that MenC conjugate vaccine reduces nasopharyngeal carriage, but they do not have any evidence that quadrivalent vaccines do so. A large nasopharyngeal study was conducted a few years ago and the carriage rates were so low that they were unable to assess a pre- and post-vaccine impact.

Dr. Ward (UCLA) pointed out that there have been Meningococcal C vaccines for more than 30 years, and there has been an evolution in thinking over the years about how and when to use these vaccines. In the initial 10 to 20 years, the decision was not to use them because the benefit was not thought to be justifiable. More recently, with immunization experiences in Europe and the private use in teens and colleges forced more general recommendations. He expressed concern that ACIP seemed to be moving onto "thin ice." The argument for the second dose being considered derives in large measure from persistence of antibody, waning of immunity. That is using the standard for initial licensure and applying it over a period of time with the assumption that these levels of antibodies must be maintained in all people or a large proportion of people throughout their lifetimes, or at least within the period of defined risk. That is not a standard that is met with many vaccines such as pertussis and diphtheria. He thought applying such standards was a mistake, and cautioned ACIP that this may set a precedent for having to maintain high levels of antibodies and giving boosters for all vaccines. The program cost is more than the cost of two visits.

Dr. Hasbach (sanofi pasteur) commented that programmatically Dr. Cohn's estimates of costs were similar to sanofi pasteur's estimates. They will not exceed what the program has experienced over the past three years on average, and the cost of the doses might even go down with the booster added. Older adolescents are certainly observed to be more difficult to get in, but in terms of overall distribution, sanofi pasteur's distribution of meningococcal vaccine is 55% private and 45% public. That is very different from traditional routinely recommended pediatric vaccines, which is directly the opposite. Their working assumption is that while 11 to 12 year olds might be similar, public versus private probably skews more toward private as age increases. He pointed out there were antitrust implications in terms of discussing price with his competitors in the room; however, he said that when there is competition in the market place stabilization is observed. They should review historical data in the VFC program to determine trends.

Dr. Lewin (Novartis) reported that Novartis has a booster trial underway for which data should be available shortly that could potentially be included on the label. Supply is not an issue for Novartis.

Claire Hannan (Association of Immunization Managers) shared the results of a poll they conducted with their members about various recommended options. Of the 64 CDC grant recipients, 35 responded. Approximately 50% of respondents wanted the recommendation to be kept at 11 to 12 years of age with a booster at 16 due to strong concerns around confusion of other options, and logistically trying to change their mandates. About 50% of respondents stated that they use 317 for meningococcal vaccine. If a booster is added without additional 317 funding, that would mean that something is not being purchased. About 25% of respondents indicated that they use state funds. Given the state fiscal environment, something else would not be purchased unless funds were added here as well.

Regarding the cost issue, Dr. Decker (sanofi pasteur) thought with the disappearance of the catch-up cohort, the total number of doses of meningococcal conjugate vaccine used in the US will stabilize or decrease even if the booster dose is added, so program costs will not increase. Regarding off-label use and booster dose studies, sanofi pasteur faces the same dilemma as

ACIP and CDC of not being certain whether a booster is needed or when it should be indicated. This affected their organizing of the very expensive and time-consuming booster study. If ACIP elects to make a booster recommendation, that would provide the clarity that Sanofi Pasteur needs to begin immediate discussions with the FDA about inaugurating the study that would move that recommendation inside the label.

Lynn Bozoff (National Meningitis Association) indicated that the mission of the National Meningitis Association (NMA) is to raise awareness about meningococcal disease. In addition, NMA actively promotes the entire adolescent platform. Their pre-teen program is designed to encourage compliance with all of the recommended adolescent vaccines. They have heard from parents and providers that what gets parents into the doctor's office is meningococcal prevention. Parents have heard the stories and know how devastating this disease is. While they are in the office, healthcare providers have the opportunity to discuss all of the other recommended adolescent vaccines. NMA has a number of concerns about changing the recommended age. Most importantly, moving the recommended age to 15 would leave pre-teens and young teens unprotected. If there is concern about waning immunity in older teens, NMA believes that the recommendation should be to continue with the 11 to 12 year old vaccine and administer a booster to older teens. Otherwise, there will be less coverage and more avoidable disease. Parents are very comfortable with the notion of boosters. In addition, losing the adolescent platform will result in reduced meningococcal prevention since there is no established well-care visit at age 15. Having two adolescent immunizations, one at age 11 to 12 and one at age 15 will cause confusion and less compliance. It is also known that the older adolescents are, the harder it is to get them into a physician's office. By age 15, many have switched to gynecologists or practices that primarily treat adults and do not have a strong immunization infrastructure. Approximately 10 states have implemented middle school requirements for meningococcal immunization at 11 and 12. Changing this would cloud the picture. New educational programs at the state and school board level would have to be developed. Everyone has worked extremely hard over the last few years to increase meningococcal vaccination rates. A change in recommendations poses a great threat to this gain, which is essentially the lives of children who may not otherwise be here today. Two NMA representatives asked to join her during this session to share their personal experiences.

Lori Buher (National Meningitis Association) indicated that her son Carl contracted meningococcal meningitis when he was 14. One day he was a healthy, active teen and great student of 6' 4" playing basketball. She and his dad had dreams of him going to the Huskies. He was in perfect health and had antibiotics only once in his life before he contracted this disease. Within 24 hours of playing a football game, he was being airlifted to Seattle Children's Hospital not expected to live. His heart stopped three times en route. She and her husband were met at the door of the emergency room by a social worker who was prepared to help them deal with his death. However, the wonderful people at the hospital saved him. They spent 6 months in Seattle hospitals. He lost both legs below the knee, three fingers, all of his knuckles were destroyed, the skin was destroyed on 70% of his extremities, and he had 11 skin graft surgeries. It was 4 years before he began walking again as a freshman in college. She heard so much about cost throughout the morning. The financial cost to their family and insurance company was over \$2 million and continues. The personal costs to their family have been significant. Carl is a miracle and is a success story because he survived and will graduate Valedictorian in June. However, many parents have not experienced this same success. If they had been able to vaccinate him at 11, it would have made such a difference. Ms. Buher is also a school guidance counselor who has been with the school district for over 20 years. She knows how parents think and what they do. They vaccinate when their children are infants, 5,

and 11 and they understand boosters and can handle this. She advocated for leaving the recommendation as is and adding a booster.

Nick Springer (National Meningitis Association) indicated that he is now 25 years old. When he was 14 he was in a summer camp where he was hiking the Appalachian Trail with a group of his friends when within 16 hours he went from a healthy kid to being given a 10% chance of survival and having his last right read to him. No one should have to go through this. While he fortunately survived, it was at a price. He had his legs amputated above the knee, his hands amputated at the forearms, had about 15 surgeries and skin grafts, et cetera. He spent 9 months in the hospital and was told when he got out that there was a vaccine available that could have prevented this from occurring. Every day he meets new people and old friends who have been affected by this. Many voices have been silenced by this disease, so he wanted to speak up on their behalf. Even with the current recommendations, there are children who are still being affected by this every day in the 10 to 14 year old age range.

Marty Young (Meningitis Angels) indicated that their lives were changed forever on March 19, 2007 when they were forced to deal with an illness they knew little about. When their son was lying in a hospital be about to die, it was no time to learn about a vaccine-preventable disease. This disease was taking away their eldest son, Dante, and they could do nothing to stop it. He could not relate how this feels and he could only hope and pray that those hearing these words would never have to. Meningitis was a disease that they were told only affects those in college dorms and that there was no need for their children to have the vaccine yet. They placed a high level of trust in those who provide medical care (doctors, nurses, surgeons, et cetera). What they say is taken as wise advice because they spent so many long years at universities, they must know what is best for people. Doctors are not infallible. They are human and make mistakes, given incorrect advice, and prescribe the wrong medicine sometimes. Even with those mistakes, parents expect them to know what is best. Doctors receive direction and tutelage from peers, medical journals, studies, and CDC. They are constantly learning and looking for advancements in the science of medicine and the quality of the education and direction they receive. That is why it is so critical to give them the best information to protect and treat their patients. Mr. Young thanked CDC and all of its associates for continuing to protect citizens and its leadership in this area, as their hard work pays off every day for millions of families across the US. He urged them to consider the ramifications of any decisions made during this meeting. Had Dante received the meningitis vaccine, he may still be here today. Instead he stood before them a grieving father who will never know the joy of his eldest son graduating high school, getting his first car, marrying, or having children of his own. He stood there as a father who now has a lifetime of wondering: What if we had gotten him the vaccine? Why does Dante's family and all of the other families whose lives are shattered have to go through this? He advocated for keeping the recommended age for this vaccine as is or changing it to the two-dose options. He asked them to take to heart the words they heard today, and to search their souls—not just their brilliant minds for the right answer. He and all of the other families and advocates there implored ACIP to do the right thing to prevent another family from bearing this crushing burden.

Frankie Millie (Meningitis Angels) said that she came before them with a very heavy heart and a lot of fear. Many things had been discussed, such as economics. Meningitis Angels understands economics. They understand the economics of the hundreds of thousands and millions of dollars that it takes to care for one child through a lifetime. She personally understands the economics of having her perfectly healthy son, who had just reached pro-golf status, being taken to an emergency room with a fever and an earache and two hours later having blood come from every orifice of his body, and then being taken to a morgue to be

dissected and probed to determine what happened to him. She understands that the 2 hours in the emergency room cost them \$35,000. She understands that the same day they talked to a funeral director who cost them \$15,000. They understand economics and they know that ACIP has a hard job and appreciates what they do. This summer she spent two weeks on the ground assisting in the Oklahoma outbreak. They heard earlier that two children died, but what they did not hear was that seven children were involved in the outbreak. A toddler lost both arms. An 18-year old who contracted the disease did not understand why he did not know he should have been vaccinated. She introduced Jeremiah Mitchell who was in attendance with her, and whose presence spoke for itself. She begged ACIP not to change the recommendation other than to add a 16-year old booster. No child and no adult in this country should die from a vaccine-preventable disease. Can we put a price on the cost of a life? Can we put a price on her child who she will never see again? She will never be called "mom" again. She will never hold a grandchild and she will never have her son's help in her old age.

Dr. Baker expressed appreciation for the public comments and offered sympathy for the situations and heartbreak that families have experienced.

Dr. Sawyer asked for clarification regarding why the time of the booster dose differed for Options 1 and 2.

Dr. Cohn responded that they were trying to deal with the ability to give a booster through age 21 years. She preferred saying that specifically and suggested the following language for the second bullet, "For adolescents vaccinated at age 13 through 15 years, a one-time booster dose should be given 5 years after the first dose through age 21 years."

Motion: Adolescent Meningococcal Vaccination

Dr. Marcy made a motion to accept the Option 1 recommendation as presented, with an amendment to the second bullet stating, "For adolescents vaccinated at age 13 through 15 years, a one-time booster dose should be given 5 years after the first dose through age 21 years." Ms. Ehresmann seconded the motion. The motion carried with 6 affirmative votes, 5 negative votes, and 3 abstentions.

VFC Resolution Update: Meningococcal Vaccines

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

Dr. Rodewald indicated that ACIP is the sole authority for the VCP, and communicates to the program through the VFC resolutions that are voted upon separately. The resolutions must be updated if the size of a recommended population or number of doses is changed for a population. He reminded everyone that Ms. Rosenbaum alluded to something important in a statement she made earlier, which was that under the Patient Protection and Affordable Care Act (PPACA), ACIP's recommendations are now binding for private health insurance. ACIP's resolutions allow them to back their recommendations with access to vaccines for financially vulnerable children who are less than 19 years of age in the US. That includes 60% of infants,

50% of young children, and 32% of teenagers. CDC has contracts for these vaccines, such that a resolution that passed during this session for these vaccines would be in effect immediately.

The purpose of this resolution was to clarify eligible groups for meningococcal vaccination, update the primary vaccination recommendations for high risk children, update recommendations regarding vaccination of adolescents and revaccination, and clarify the use of conjugate versus polysaccharide meningococcal vaccines. Eligible groups include the following:

- ❑ Children aged 2 through 10 years who are at increased risk for meningococcal disease, including:
 - children who have complement deficiencies (C3, properdin, factor D, and late component deficiencies);
 - children who have anatomic or functional asplenia;
 - children with HIV infection;
 - travelers to or residents of countries in which meningococcal disease is hyperendemic or epidemic; and
 - children who are who are part of an outbreak of a vaccine-preventable serogroup.

- ❑ All children aged 11 through 18 years

Dr. Rodewald emphasized that the language will be modified to match the ACIP recommendation precisely. There was a modification in the ACIP recommendation that addressed the time from vaccination to the booster dose, changing it from 3 to 5 years to 5 years. That means that individuals who are vaccinated at 14, 15, 16, 17, or 18 years of age will fall outside of the VFC program. ACIP has the power to change that, so Dr. Rodewald wanted to call this to their attention. The two tables will be as follows:

Recommended Schedule, Intervals (1):

Age	Subgroup	Primary Vaccination	Booster Dose
2 through 18 years of age, with high risk conditions *	Children with complement deficiencies; functional or anatomic asplenia; or those with HIV infection	Two doses of MenACWY vaccine, two months apart	If first dose received at ages 2 through 6 years and remain at increased risk for meningococcal disease , should receive an additional dose of MenACWY vaccine 3 years after primary vaccination. Boosters should be repeated every five years thereafter.
	All others in this age group recommended for vaccination	Single dose of MenACWY vaccine	If first dose received at age 7 or older and remain at increased risk for meningococcal disease , should receive an additional dose of MenACWY 5 years after primary vaccination. Boosters should be repeated every five years thereafter.

Recommended Schedule, Intervals (2):

Age	Primary Vaccination	Booster Dose
ACIP Option A: All other children 11-18 years of age	Routine vaccination with MenACWY vaccine at ages 11 through 12 years	If vaccinated at age 11 through 12 years , should receive a one-time booster dose at age 16 years If vaccinated at age 13 through 16 years , should receive a one-time booster dose 3 to 5 years after first dose
ACIP Option B: All other children 11-18 years of age	Routine vaccination with MenACWY vaccine at ages 14 through 15 years	If vaccinated at ages 11 through 13 years , should receive a one-time booster dose 5 years after the first dose

Recommended Schedule, Intervals (3):

Table Notes

- (1) At the time of this resolution, there are currently two licensed MenACWY products. One product, Menactra® manufactured by sanofi pasteur, is licensed for use in persons aged 2 through 55 years of age; the second product, Menveo® manufactured by Novartis Vaccines and Diagnostics, Inc., is licensed for use in persons aged 11 through 55 years of age.
- (2) MenACWY is preferred for primary vaccination and booster doses, but MPSV4 is an acceptable substitute for persons with precautions or contraindications to MenACWY vaccine.
- (3) Includes children who have complement deficiencies (C3, properidin, factor D, and late component deficiencies), anatomic or functional asplenia, and children with HIV infection; travelers to or residents of countries in which meningococcal disease is hyperendemic or epidemic; and children who are who are part of a community outbreak of a vaccine-preventable serogroup.

Recommended dosage and Contraindications / Precautions:

Recommended dosage

- Refer to product package inserts.

Contraindications and Precautions

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

The statement regarding update based on published documents:

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

Discussion Points

Ms. Ehresmann inquired as to whether Dr. Rodewald was saying that they would have the ability in the VFC vote to state that children who received a primary dose later could still receive VFC doses later.

Dr. Rodewald replied that what he meant was that they needed to state that a booster dose could be given at 3 to 5 years, which would then put those vaccinated at 15 at 18 for the booster dose. It is a nuance that may be important. However, if they fall out of the VFC age range, they would fall into full insurance category. Thus, that is not necessary a reason to make a change, but he wanted to point this out.

Dr. Chilton wonder whether the PPACA applied to ACIP recommendations only for active immunizations, or does it refer to other forms of treatment that are recommended by ACIP.

Ms. Rosenbaum responded that she believed the language in the act states immunizations recommended by ACIP. Changes with immunization practices themselves should be covered.

Motion: VFC Adolescent Meningococcal Vaccination Vote

Dr. Sawyer made a motion to accept the VFC language as presented, with the revisions necessary to match the ACIP recommendation precisely. Dr. Temte seconded the motion. The motion carried with 12 affirmative votes, 0 negative votes, and 2 abstentions.

Hepatitis B Vaccine

Overview

Dr. Larry Pickering Executive Secretary, ACIP; CDC

Dr. Pickering explained why the vote was removed from this session. This topic has been presented three times to ACIP. One presentation regarded terms of reference, the second was a half an hour presentation, and the third was an extensive presentation of data during the June 2010 meeting. Therefore, it was decided that this session would be devoted to another extensive discussion on this topic. The economic analysis and vote will occur at a future meeting.

Hepatitis B Vaccination Coverage Among Adults Currently Recommended for Vaccination

Kathy Byrd, MD, MPH
Prevention Branch, Division of Viral Hepatitis
Centers for Disease Control and Prevention

Dr. Byrd indicated that a number of years had passed since there had been an update of hepatitis vaccination coverage among high risk adults. During this session, she shared data on three groups of adults with high risk behaviors, including a combined group of high-risk adults, as well as high-risk heterosexuals (HET), injection drug users (IDU), and men who have sex with men (MSM). She also discussed vaccination coverage among persons with high risk healthcare exposures, including hemodialysis patients and occupationally exposed healthcare workers. Two main data sources were used to determine estimates of vaccination coverage: 1) National Health Interview Survey (NHIS), in which a combined group of high-risk adults was assessed; and 2) National HIV Behavioral Surveillance (NHBS), in which high-risk heterosexuals, injection drug users, and MSM were assessed.

To begin, the NHIS was utilized to determine vaccination coverage among adults considered to be at high-risk for incident hepatitis B infection. NHIS is a cross-sectional in-home household survey that focuses on civilian non-institutionalized populations. In addition to other information, a standardized questionnaire is used to collect information about behavioral risks for hepatitis B and self-reported 1- and 3-dose hepatitis B vaccination coverage [Lu et al. CDC unpublished data].

In the NHIS analyses, high-risk adults were defined as persons who responded “yes” to any of the following: MSM, ever injection drug use, hemophilia with receipt of clotting factors, sex for money or drugs, HIV positive, having sex with any of aforementioned, has multiple sex partners, diagnosed with a sexually transmitted disease (STD) in the past 5 years, or that the respondent felt that their HIV risk was high. Low risk individuals were defined as a respondent with none of these risk factors. With respect to the demographics and characteristics of adults 18 through 49 years of age in the NHIS sample, there were slightly over 15,000 adults in the sample. Approximately 1,200 of these were considered “high-risk.” Approximately half of the sample was male (n=6800) and over 60% was non-Hispanic white (n=7802). The majority of the sample had above a high school education (n=8984), had health insurance (n=11,098), and lived at or above the federal poverty line (11,003).

Regarding the proportion of all adults 18 through 49 years who received 1 or more doses of hepatitis B vaccine by risk level and age group, a decline in vaccination coverage occurs as the age groups increase in both high and low risk adults. Overall coverage was 51% and 41% in high and low risk adults aged 18- 49 years respectively. The highest vaccination coverage is observed in persons aged 18 through 20 and 21 through 25 years, with coverage of 68% and 62% in high-risk adults, and 62% and 55% among low risk adults, respectively. The lowest coverage is seen in the oldest age group at 35% and 29% for high and low risk individuals, respectively. While point estimates were higher among high-risk adults in each of the age groups, on bivariate analysis there was a significant difference between high and low risk adults overall and between those adults 31 through 40 years of age [Lu et al. CDC Unpublished data].

Independent predictors of ≥ 1 -dose vaccination were determined by logistic regression. The model included adjustment for age, sex, race / ethnicity, risk group, number of physician contacts in the past year, and a number of other variables. Persons who were considered “high-risk” had increased odds of vaccination compared to non high-risk adults, with an odds ratio of 1.3. Odds of vaccination decreased with increasing age, and Hispanic adults were less likely to be vaccinated than adults of other races. There was no difference in vaccination coverage between white, black, and adults classified as “other” race. Of note, the odds of receiving 1 or more dose of vaccine increased with increasing number of physician contacts per year.

To determine whether vaccination of this combined group of high-risk adults had changed over time, ≥ 1 -dose vaccination coverage among high-risk adults was compared from the 2004 and 2009 NHIS samples. There was a statistically significant 5% increase in ≥ 1 -dose coverage between time periods. While overall coverage increased 5%, coverage in certain high-risk demographics encountered a greater increase. Coverage in black, non-Hispanic adults increased a significant 11% and coverage in Hispanic adults increased 12%, although this increase was not statistically significant. This increase in hepatitis B vaccination coverage represents an achievement in reaching a hard to reach population of high-risk adults for hepatitis B immunization [Lu et al. CDC Unpublished data].

There are a few limitations to this study. First, NHIS relies on self-reported data that has not been verified through provider records. Second, while NHIS provides an estimate of vaccination coverage among high-risk adults, we are unable to stratify individual risk groups and are, therefore, unable to determine vaccination coverage among specific high-risk groups such as men who have sex with men. In addition, the NHIS sample is largely white, non-Hispanic, fairly well educated and well insured and may not be generalizable to the general high-risk US population.

To determine vaccination coverage in individual risk groups the NHBS was used. NHBS is conducted by the Division of HIV and AIDS Prevention (DHAP) and involves rotating cycles of surveillance in three populations per cycle who are at high risk for HIV (e.g., HET, IDU, and MSM). Since some risk factors for HIV and hepatitis B overlap, participants of NHBS are also at risk for hepatitis B. Participants were sampled in up to 25 metropolitan statistical areas with high estimated AIDS prevalence. For each survey cycle, a standardized questionnaire was used to collect information about behavioral risks for HIV, HIV testing history, use of HIV-prevention services and programs, and self-reported hepatitis B vaccination coverage. Data were used from the first cycle of NHBS to determine vaccination coverage among heterosexuals. This cycle took place between 2006 and 2007. Data were used from Cycle 2 for MSM, which took place in 2008, and injection drug users, which took place in 2009. NHBS defined high-risk heterosexuals as adults 18 – 50 years of age living in high risk areas which were defined as census tracts with high rates of HIV and poverty. IDU and MSM were defined as ever injected drug use and ever male sex with men, respectively.

The unweighted proportion of adults who received 1 or more dose of hepatitis B vaccine by age group was determined, and each risk group was analyzed separately. Independent predictors of vaccination were determined by logistic regression. The unweighted sample size of each of the three groups was approximately 18,000 in the high-risk heterosexual sample, and approximately 9700 and 7400 participants in the IDU and MSM samples, respectively.

In terms of the proportion of high-risk heterosexuals who received one or more dose of hepatitis B vaccine by age group, each age group had a minimal of 1600 participants. As seen in the NHIS analysis, vaccination coverage among high-risk heterosexuals is highest among the younger age groups and declines as age increases. Overall vaccination coverage was 38% and ranged from 42% in persons 18 through 20 years of age to 21% in persons aged 46 through 50 years [CDC Preliminary data]

Regarding the proportion of IDU who received one or more dose of hepatitis B vaccine by age group, there were at least 300 participants in all age groups with the exception of the 18 through 20 year old group, and over 65 year age group in which there were a minimal of 50 participants. Again, vaccination coverage decreases with increasing age. Overall, coverage among IDU was 35% and ranged from 53% in 18 through 20 year olds to 11% in persons aged over 65 years [CDC Preliminary data]

With respect to the proportion of MSM who received one or more dose of hepatitis B vaccine by age group, there were a minimum of 200 persons in each of the age groups with the exception of the 61 through 65 and over 65 year age group, in which there were a minimum of 66 participants. The highest coverage among the three risk groups from NHBS was seen in the MSM group in which overall coverage was 61%. Persons between 18 through 35 years of age had coverage of approximately 60% and coverage ranged downward to approximately 30% in persons 61 years of age and older [CDC Preliminary data]

While there were no HealthyPeople 2010 (HP2010) targets for high-risk heterosexuals or IDU, the Healthy People 2010 target for hepatitis B vaccination among MSM was 60%. The HP2010 target in this NHBS sample of MSM from high AIDS prevalence metropolitan statistical areas (MSA) has been met, particularly among those individuals under 30 years of age [Preliminary data, CDC].

As a reminder, the most recent hepatitis B recommendations were made in 2006, in which universal vaccination was recommended in venues servicing high-risk adults such as STD clinics, jails and prisons, drug treatment programs, and HIV Counseling and treatment centers. While there are limited vaccination coverage estimates in risk venues, data from NHBS suggests that persons that might have been seen in risk settings are being vaccinated.

A variety of independent predictors of vaccination were observed in each of the three NHBS risk groups. Recall that these surveys were conducted in areas of high AIDS prevalence. For each of the 3 groups, being HIV positive, which is also a recommended group for vaccination, was a positive predictor of vaccination. For each of the 3 groups, having an STD diagnosed in the past year was a positive predictor of vaccination. Again, persons seeking evaluation or treatment for an STD are recommended for vaccination, as are persons in drug treatment. In both the high-risk heterosexual and IDU sample, ever receiving drug or alcohol treatment was an independent predictor of vaccination. Incarcerated individuals are recommended for vaccination; however, in this analysis, incarceration in the past year was not associated with vaccination in any of the 3 risk groups. One notable negative predictor of vaccination in each of the three risk groups was being a black, non-Hispanic adult. While data from NHBS do not distinguish where an individual was vaccinated, it is encouraging that being HIV positive, being diagnosed for an STD, and ever receiving drug or alcohol treatment are positive predictors of hepatitis B vaccination [Preliminary data, CDC].

There are a couple of limitations to this study as well. First, NHBS relies on self-reported data that has not been verified through provider records. Second, the findings of the studies are limited to individuals in metropolitan statistical areas with high AIDS prevalence and are not representative of all HETs, IDUs, or MSM.

Two additional groups of at risk adults include hemodialysis patients and healthcare personnel. In terms of the proportion of chronic hemodialysis patients who received 3 doses of hepatitis B vaccination by year, based on a 2002 national survey of dialysis-associated diseases in all US chronic hemodialysis centers and a survey of End Stage Renal Disease Networks in 2005 – 2006, vaccination coverage increased from 35% in 1995 to 56% in 2002. Vaccination coverage from the End Stage Renal Disease Network survey in 2005 – 2006 was 62% [Seminars in Dialysis Vol 18, No 1 (January–February) 2005 pp. 52– 61; Bond et al. *Am J Kidney Dis* 54: 86 – 94].

Regarding vaccination coverage among healthcare personnel, data from the 2004, 2008, and 2009 NHIS and a 2002 – 2003 national cross-sectional survey of American Hospital Association member hospitals reveal estimates of approximately 75% to 80% and 68% to 75% for 3-dose coverage. While vaccination coverage for neither healthcare personnel nor hemodialysis patients is at recommended levels and has not increased greatly, hemodialysis patients and healthcare workers (HCW) have higher coverage than most groups with high-risk behaviors who are recommended for vaccination. Increased coverage among these groups may reflect greater access to the healthcare system among HCW and hemodialysis patients which better enables these groups to access vaccination. In addition, most HCWs are provided vaccine at no or minimal cost, which may increase uptake [Lu et al. CDC unpublished data; Simard et al. *Infecti Control Hosp Epidemiol* 2007; 28: 783 – 790].

Hepatitis B vaccination of high-risk adults continues to be a priority. New proposed HP2020 targets are intended for both men who have sex with men and injection drug users, although the targets have not yet been determined. NHBS will be entering cycle 3 of data collection in 2011. Vaccination coverage from early cycles of NHBS will be able to be compared to the newest data for determination of vaccination coverage and trends over time.

This past summer a Health and Human Services Viral Hepatitis work group convened to formulate an action plan regarding viral hepatitis. The workgroup recommended that individual risk factor, risk behavior questions and hepatitis B vaccination questions be added to national surveys such as the NHIS, the Behavioral Risk Factor Surveillance System (BRFSS) and the National Survey of Substance Abuse Treatment Services (N-SSATS) in order to monitor both risk factors for hepatitis B infection and hepatitis B vaccine uptake. In addition, the working group recommended increasing the availability and utilization of hepatitis B vaccine to high risk adults by assisting states in gathering and assessing evidence (e.g., prevalence of high-risk adult groups, hepatitis B incidence) to support prioritization of adult hepatitis B vaccination, and by identifying opportunities in health-care reform for vaccination of high-risk adults.

In conclusion, there is some evidence that hepatitis B vaccination coverage among high-risk adults is improving. Persons with greater access to the healthcare system, such as healthcare workers and persons with frequent physician contacts have greater uptake of hepatitis B vaccination. Hepatitis B vaccination coverage, however, in most high-risk groups, including HCWs remains below desired levels. Continued efforts are necessary to reach at risk populations.

Introduction: Hepatitis B Vaccination for Persons with Diabetes

Dr. Mark Sawyer ACIP Working Group Chair

Dr. Sawyer reported that the specific term of reference for this working group was to review data from hepatitis B outbreaks among adults with diabetes in institutional care to determine whether vaccination is appropriate. The ACIP Hepatitis Working Group is a diverse group comprised of 25 members, including partners from infection control, diabetes, hepatology, primary care and geriatric medicine, nursing home management, public health, vaccine program, regulatory, and consultant economist.

This is a complicated topic, particularly with respect to discussion pertaining to cost-effectiveness. The Hepatitis Working Group has engaged in 27 teleconferences since February 2009, and delivered 3 presentations during ACIP meetings in June 2009, February 2010, and June 2010. The working group also delivered a presentation to the Healthcare Infection Control Practices Advisory Committee (HICPAC) in June 2010.

The Hepatitis Working Group has discussed a broad range of topics, including risks of hepatitis B infection, morbidity, mortality by age, and setting; infection control practice in diabetes care and management; characteristics of long-term care and oversight; diabetes and its relationship to chronic liver disease; vaccination factors contributing to seroprotection, revaccination, and duration of protection; and cost-effectiveness of the program and program implementation. Dr. Murphy assisted Dr. Sawyer in summarizing all of these discussions into three focused questions on which the group has reached some conclusions:

Focused Question 1

Q. Is adherence to infection control practice adequate to prevent most hepatitis B transmission among persons with diabetes?

A. Infection control is critical for preventing transmission of all bloodborne pathogens, but current levels of adherence are not sufficient to prevent hepatitis B among adults with diabetes.

Focused Question 2

Q. Are adults with diabetes outside of long-term care at sufficient risk of hepatitis B that they warrant hepatitis B vaccination?

A. Seroprevalence of hepatitis B is increased among non-institutionalized adults with diabetes in all demographic and risk categories examined.

Focused Question 3

Q. Would vaccination decrease hepatitis B morbidity and mortality among adults with diabetes?

A. Vaccination is likely to substantially reduce the risk of hepatitis B among adults with diabetes.

There is strong overall working group consensus and support of hepatitis B vaccination for all or at least most adults with diabetes. There is, however, significant diversity of opinion about the best approach, particularly with regard to vaccinating older adults with diabetes. There is interest in trying to maintain consistency with existing hepatitis B vaccine recommendations, and it is important to grapple with the issues of the cost-effectiveness of vaccination.

Through their deliberations, this working group identified what they believe to be a generic issue for ACIP. With regard to immunization in older populations, for the majority of vaccines, vaccine efficacy declines and cost-effectiveness also declines. It is difficult to know what to do with a recommendation that spans an age group from the very young to the elderly for whom there are very different calculations of vaccine efficacy and cost-effectiveness. Thus, the Hepatitis Working Group has asked the leadership of ACIP to consider providing some general guidelines, either through the formation of a new working group or by asking an existing working group to take up the topic of general immuno-senescence and decrease in cost-effectiveness with age; provide standard approaches for vaccination; provide standard language to advise practitioners; and offer guidance for updating existing statements.

The group recognizes that the original signal leading to the current term of reference stemmed from outbreaks of Hepatitis B in long-term care (LTC) facilities, and plans to develop guidelines specifically for vaccine use during hepatitis B outbreaks in LTC facilities, which will be a separate topic from the diabetic recommendations.

Update on Bloodborne Pathogen Transmission during Blood Glucose Monitoring and Recent Infection Control and Prevention Initiatives

Joseph Perz, DrPH and Nicola Thompson, PhD
Division of Healthcare Quality Promotion, CDC

Dr. Perz emphasized that blood glucose monitoring is an essential component to diabetes management. In the US, surveys show that among all people diagnosed with diabetes (Type I and II), about 66% measure their blood glucose at least once daily, and persons with insulin dependent diabetes will measure more frequently [CDC. Behavioral Risk Factor Surveillance System. MMWR 2007;56:1133-1137]. The American Diabetes Association (ADA) recommendation for Type I diabetes is at least 3 times / daily. The frequency of monitoring is usually determined in consultation with a physician. The monitoring procedure is as follows: a new test strip is inserted into a glucose meter; a fingerstick device containing a sharp lancet is used to draw a drop of blood; the blood is applied to a test strip and drawn into the meter, and within a few seconds a reading is provided; and based on the blood glucose level reported, a dose of insulin can be administered as needed.

There are some important features of hepatitis B virus that help facilitate its transmission, such as the high viral titer and high environmental stability. A lot of virus can be present in tiny or invisible amounts of blood, and dried blood on surfaces, equipment or devices can remain viable for at least seven days. Together these characteristics play an important role in healthcare-related HBV transmission, and specifically during diabetes care when equipment used for fingerstick procedures and measuring blood glucose levels are shared among multiple persons. HBV transmission has been associated with blood contamination of the end and barrel of spring-loaded finger stick devices, with blood contamination of blood glucose testing meters, and with failures by staff to wear or change gloves or perform hand hygiene between performing finger-stick procedures [CDC. MMWR 2005;54:220-23. www.cdc.gov/injectionsafety/blood-glucose-monitoring.html].

Blood glucose monitoring and insulin administration can be accomplished in two ways, one of which is when another person assists with or performs testing and insulin administration for multiple persons. To help distinguish the issues between self-monitoring of blood glucose (SMBG), a well-understood concept, the term assisted monitoring of blood glucose (AMBG) was recently introduced in response to safety concerns related to HBV infection outbreaks during AMBG. Settings where AMBG may occur include nursing homes; assisted living facilities

(ALFs); hospitals, clinics, and physicians offices; senior centers; health fairs; correctional facilities; and schools, camps, and shelters [Klonoff, Perz. *Journal of Diabetes Science and Technology* 2010;4:1207-31; www.cdc.gov/injectionsafety/blood-glucose-monitoring.html].

A number of outbreaks (n=26) of HBV infection associated with assisted monitoring of blood glucose have been recognized and investigated by state and local health departments and CDC from 1990 to the present. Of these 26 outbreaks, 2 were in hospitals, 8 were in nursing homes, and 16 were in assisted living facilities. A marked feature are the waves of activity originally in the hospital setting. The first outbreak of this type was detected in the US in 1990. Then there was a shift to the nursing home setting, followed by a shift to assisted living facilities, with the 16 outbreaks occurring in just the last 7 years in this setting [Thompson, Perz. *Journal of Diabetes Science and Technology* 2009; 3:283-88. CDC unpublished data (2009- 2010)].

The first outbreak was quite notable and was reported in the *MMWR* and the *New England Journal of Medicine (NEJM)*, and was followed by safety alerts from CDC and FDA. There have been many scientific and other communications pertaining to this topic. At the time the *MMWR* article was published in early 2005, three recent outbreaks were being described, including the first outbreak in the assisted living facility. The *MMWR* report included CDC recommendations regarding infection control practices for diabetes care procedures, and key recommendations included an emphasis on single use lancets and avoiding shared equipment including glucometers [MMWR 2005; 54:220-3].

The single use lancet recommendation echoed earlier recommendations from the 1990s. In this context, CDC engaged in some outreach activities to nursing home medical directors, nursing directors, FDA, and CMS. Despite those efforts, outbreaks have continued to mount. There have been 7 HBV infection outbreaks identified since January 2009, all of which were among residents of assisted living facilities undergoing AMBG. Under investigation are two recent outbreaks, one of which includes approximately 5 acute infections, with reports that the health department is investigating to substantiate that there were 4 deaths among those infected. Another outbreak includes 3 acute infections. This outbreak occurred in a state in which there have been numerous efforts on the part of the health department to provide outreach to facilities since about 2005; however, the problem persists. Among these 7 recent outbreaks, over 62 residents have been newly infected. The number of patients affected by each outbreak ranges from 3 to more than 20 per outbreak. Of these outbreaks, 2 occurred across multiple ALFs within a region. AMBG services in this setting are sometimes provided by the same home health nursing agency, and at least in one situation, the home health agency seems to be the vector carrying infection from facility to facility. At least 1 person was affected in the context of receiving AMBG at home.

Assisted living, also commonly referred to as residential care, is a group living arrangement where the goal is to maintain the individual's independence in a home-like environment. The hospitality industry has played a major role in the development of these facilities. These facilities developed as a long-term care option in the 1980s and 1990s, largely in response to consumer dissatisfaction with nursing homes as places to live. Provision of medical care is not the primary function of assisted living facilities. Rather, staff at these facilities provide residents help with activities of daily living and medication administration, including assisted monitoring of blood glucose. Facilities vary greatly in terms of size. Currently, about 1 million persons reside in assisted living facilities in the US. However, due to the ageing of the population and increasing life expectancy, it is estimated that the number of persons residing in these facilities will double to 2 million within the next 20 years [Assisted Living State Regulatory Review 2010: www.ahcancal.org].

Adverse events have not been limited to recognized outbreaks. Recent adverse events include 4 patient notification events in the last three years due to receipt of assisted monitoring of blood glucose or insulin administration. Two incidents occurred in hospitals, both involving the use of insulin pens that are designed and approved for single patient use only being used in multiple patients. In both of these hospitals, this was a routine practice. In the first incident, 908 patients were affected and 2114 were affected in the second incident. There also have been incidents involving reuse of fingerstick devices. A recognition of those risks resulted in patient notification advising patients that they were potentially exposed to bloodborne pathogens. One of those events occurred in a community health center, affecting 283 patients. The other occurred in the context of a health fair where 64 patients were affected. Because records were not kept of who received screening for diabetes during this health fair, it was difficult to reach the affected patients and media involvement was required [Guh et al. Patient Notifications for Bloodborne Pathogen Testing Due to Unsafe Injection Practices in U.S. Healthcare Settings, 1999–2009. [Abstract 633]. Presented at: International conference on healthcare associated infections 2010. Atlanta. GA].

Surveys of routine practices when providing assisted monitoring of blood glucose have also shown that unsafe practices are present outside of the outbreak context. In response to outbreaks that were being investigated in Virginia in ALFs in 2006, CDC worked with the health department to survey infection control practices in a sample of ALFs. They found conditions that are present in outbreak conditions in a substantial proportion of the sample. Of 45 facilities, 7 (16%) were using personal use fingerstick devices for more than one person. Of the 8 facilities where blood glucose meters were not dedicated to the individual patient, 4 (50%) did not clean and disinfect shared blood glucose meters between each use. Similar results were observed in a survey conducted the next year in Florida that involved ALFs and nursing homes where 17% (3/17) of ALFs and 7% (1/15) of nursing homes were using personal use fingerstick devices for more than one person; and 71% (5/7) of ALFs and 73% (11/15) did not clean and disinfect shared blood glucose meters between each use. Recently, a survey was conducted of infection control practices in ambulatory surgery centers (n=68) showed that these unsafe practices were present in that type of facility as well. In this setting, 21% (11/53) were using personal use fingerstick devices for more than person and 32% (17/53) did not clean and disinfect shared blood glucose meters between each use [Patel et al. Infect Control Hospital Epidemiology 2009;30:209-14. Thompson et al. Journal of the American Geriatrics Society 2010;58:914-18. Schaeffer et al. Journal of the American Medical Association 2010; 303:2273-79].

Information from a survey of 12 hospitals in the early 2000s illustrated the potential for transmission of bloodborne pathogens associated with blood glucose meters. In this survey, 609 blood glucose meters were tested for presence of hemoglobin. Overall, 30.2% (range 0 - 60.6%) meters had detectable blood contamination. Detection was higher in intensive care units (ICUs), with 48% in ICUs vs. 29% in non-ICUs being contaminated. Only 1 hospital cleaned meters between each patient use, while 50% (6/12) had no schedule for cleaning. Hospital location, and increased number of meter operators significantly associated with blood contamination [Louis et al. Point of Care 2005;4:158-163]

A recent survey of a single hospital in Florida illustrates the high frequency of blood glucose monitoring in hospitals. This was an assessment of glucose meter usage in a 214-bed acute care hospital in a single month in October 2008. The total number of tests performed at that time was 11,665, using 37 meters. That averaged out to 315 tests per meter per month. Tests were performed on 803 individual patients, for an average of 12.5 tests per patient. The electronic data that can be captured from the meters allowed the investigators to determine that

sequential use of meters occurred between different patients on 79.8% (9310) of these tests, nearly 100% of which occurred within 24 hours (99.9%; 9302); and 60.9% (5664) of which occurred within 1 hour. There is clearly a hazard here in terms of the potential for bloodborne pathogen transmission. Also notable is that the investigators determined that the time required to clean and disinfect meters following the manufacturer's instructions between uses was approximately 310 hours and would represent approximately 1.93 FTEs when annualized. This institution showed that by increasing its inventory of blood glucose meters and by emphasizing assignment of meters to individual patients, they were able to greatly reduce the sequential use between patients [Hellinger and Shalev. [Abstract 199]. Presented at: International conference on healthcare associated infections 2010. Atlanta. GA].

There have been a number of recent communication and prevention activities. Since January 2009, there have been 7 CDC co-authored publications on this topic highlighting the need for improved awareness of risks; improved adherence to infection control recommendations; enforcement of infection control recommendations; and improvements in device design / labeling and use of engineering controls. CDC organized and hosted meetings (9/2009, 5/2010) to raise awareness of the needs for improved infection control oversight and device regulation that included key federal partners (CMS and FDA) and other stakeholders, including device manufacturers, diabetes educators, health departments, et cetera. [www.cdc.gov/injectionsafety/meetings/stickingW/safety52010.html]. CDC has recently updated its infection control guidance around assisted monitoring of blood glucose. The key points remained the same in that fingerstick devices should never be used for more than one person. In settings where assisted monitoring of blood glucose is performed, single-use, auto-disabling fingerstick devices should be used. Whenever possible, blood glucose meters should be assigned to an individual person and not be shared. If blood glucose meters must be shared, the device should be cleaned and disinfected after every use [www.cdc.gov/injectionsafety/blood-glucose-monitoring.html].

CDC and FDA issued clinical advisories and product alerts for use of fingerstick devices, glucose meters, and insulin pens. FDA alerted manufacturers of a revised process for evaluating, approving blood glucose monitoring devices, and increased focus on addressing infection prevention. This is to include clear labeling of single patient use and validated instructions for cleaning and disinfecting meters [www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm227935.htm].

CDC has also worked closely with CMS, which recently issued new infection control guidance to its surveyors who conduct facility inspections. This guidance includes a review of blood glucose monitoring practices at nursing homes and ambulatory surgery centers. For nursing homes, this directive specifies clearly that sharing of fingerstick devices must be cited as "Immediate Jeopardy" and requires immediate steps to remove the jeopardy from the nursing home or risk termination from Medicare / Medicaid programs. "Immediate Jeopardy" is a situation in which the non-compliance with one or more requirements has or is likely to cause serious injury, harm, impairment, or death to a resident. The directive also initiates enforcement action and requires immediate steps to remove the jeopardy. Guidance is carrying over to other licensed settings (e.g., acute care hospitals and home health agencies).

Prevention in assisted living facilities remains challenging, given that these operate under a social model of care. Care is primarily provided by non-professional staff with limited professional oversight. Resources and expertise in infection control are poor and staff turn-over is very high, which limits the impact of education and training efforts. ALFs are not federally regulated and licensing and inspection at the state level are highly variable. These operate

outside the scope of CMS; however, home health agencies are regulated by CMS. That is one area in which CDC may be able to find some greater reach into the assisted living environment. CDC continues to work with the infection control community and federal, state, and local health partners to improve the standard of infection control within this setting. For example, the role of Medicare-certified home health agencies as providers of care to assisted living residents will be examined as a potential avenue for clarifying and enforcing appropriate infection control procedures in the context of assisted blood glucose monitoring.

In summary, shared use of blood contaminated equipment increases risk of exposure to bloodborne pathogens. There is an increasing frequency of HBV infection outbreaks associated with assisted monitoring of blood glucose, most recently in assisted living facilities. Routine misuse of equipment and failure to follow infection control recommendations have been identified in a variety of settings (e.g., acute care hospitals, ambulatory surgery centers, health fairs). Continued efforts are needed to increase adherence to recommended infection control practices. Recent changes made by CMS and FDA are expected to aid adoption of recommendations. Prevention in settings such as assisted living facilities remains challenging.

Adults with Diabetes and Hepatitis B: Information Requested by ACIP

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Dr. Murphy reported that in 2007, the US was estimated to have 17.7 million adults with diagnosed diabetes. About 1.6 million adults receive a new diagnosis of diabetes each year, with a median age at diagnosis of 50 years. In 2006, approximately 64% of adults with diabetes indicated that they monitor blood glucose one or more times per day, including 35% who were not taking any medication for diabetes. During this session, Dr. Murphy offered a brief overview of the burden of hepatitis B among adults with diabetes, diabetes liver and renal morbidity as it relates to hepatitis B infection, and pertinent information about hepatitis B vaccine responses in adults. In addition, she addressed questions posed by ACIP during the June 2010 meeting.

Regarding the morbidity and mortality associated with acute hepatitis B in adults, an estimated 30% of acute cases are symptomatic, patients are debilitated for 1 to 4 months, 28% to 43% of patients are hospitalized [NNDSS 2007, Sentinel Counties 2002-2005], and fulminant liver failure occurs in 1% to 2% of patients. The case fatality rate for reported cases is 0.5% to 1%, but this varies with age. Among reported cases 50 years and older, the case fatality rate is 2% to 4%. In 21 HBV outbreaks in long-term care facilities, the case fatality rate was approximately 18% [CDC published and unpublished data]. Symptomatic and asymptomatic Hepatitis B infection becomes chronic in 5% to 10% of otherwise healthy young adults. Progression to chronic hepatitis B is reported to be much higher among older adults with acute infection (45% to 59%) and among hemodialysis patients (43%). Accumulating years with chronic hepatitis B lead to cirrhosis, liver failure, or liver cancer and premature death in approximately 15% of adults. Chronic hepatitis B is the primary reservoir for continuing person-to-person transmission among adults with diabetes, as Dr. Perz reported.

The Hepatitis Working Group asked the question, "Do adults with diabetes, aside from those in long-term care, have sufficient burden of hepatitis B that vaccination should be considered?" In response to that question, Dr. Murphy briefly reviewed the evidence for an excess burden of hepatitis B among non-institutionalized adults with diabetes.

The first evidence comes from the seroprevalence survey of hepatitis B among adults with and without diabetes. The survey results from the National Health and Nutrition Examination Survey (NHANES) were examined from 1999 to 2008. NHANES is a large population-based survey that seeks to collect data from a representative sample of the US population on a wide variety of relevant questions. The survey only includes adults from non-institutional settings and, therefore, does not include adults in long-term care. Diabetes status is determined by asking respondents if they had ever been told by a doctor that they have diabetes, excluding diabetes during pregnancy. Past or present Hepatitis B was defined by positive serology for hepatitis B core antibody [CDC. Unpublished analysis].

In June, Dr. Hu showed data giving the overall seroprevalence of hepatitis B among adults 18 years and older, by diabetes status, which illustrated that 8.3 % of adults with diabetes had evidence of past or current hepatitis B; whereas, 5.2% of adults without diabetes had evidence of past or current hepatitis B. The prevalence ratio of 1.6 suggests that adults with diabetes had a 60% higher seroprevalence of hepatitis B infection than adults without diabetes [CDC Unpublished analysis].

The prevalence of hepatitis B with and without diabetes by age group was examined for the same period [NHANES 1999-2008]. The point estimates of seroprevalence for each age group, and the prevalence for the means for adults with and without diabetes were not statistically different, in part because the sample sizes were small. However, the test for the difference of the prevalence means was significant overall, suggesting that the prevalence of hepatitis B is higher among adults with than without diabetes across age groups, even without data collected from adults in the hepatitis B institutional settings such as long-term care. The National Health and Nutrition Examination Survey (NHANES) survey evaluates a number of other characteristics, but the sample sizes tend to be too small to allow controlling for other factors of interest. Nonetheless, the seroprevalences and the prevalence ratios for adults with and without diabetes are informative.

Regarding the effect of excluding adults who indicated injecting drug use or men who have sex with men, two groups at high risk for hepatitis B infection, , the point estimates for adults with and without diabetes were 8.1% and 4.1%, respectively, and the prevalence ratio increased to 1.8. This suggests that adults with diabetes had an 80% higher seroprevalence of hepatitis B than adults without diabetes after removing the two highest risk groups [CDC.Provisional data.]. This was the pattern found for all characteristics examined (e.g., poverty income ratio, education, place of birth, marital status). The prevalence ratios for hepatitis B in each of these categories were elevated by 30% to 90% for adults with diabetes. For race / ethnicity and body mass index, the prevalence ratios for hepatitis B were elevated by 30% or more for adults with diabetes. These data do not provide direct evidence that exposure to blood during diabetes care and management is the key factor associated with higher hepatitis B seroprevalence among non-institutionalized adults with diabetes. However, they strongly suggest that adults with diabetes are at greater risk of HBV in the context of the widespread lapses in infection control practice and the stability of hepatitis B virus on the surface and its high infectivity, as was shown by Dr. Perz.

Ideally, the incidence of acute hepatitis B among adults with diabetes from national passive surveillance or emerging infections surveillance sites would have been examined. However, these surveillance systems do not routinely collected information about diabetes status from acute case interviews. In June, Dr. Hu described a catalytic model he and others developed to estimate the incidence and number of hepatitis B cases among adults with diabetes aged 25 years and older. The model incorporated seroprevalence data from NHANES, and acute

disease surveillance data from 2007 and 2008. The modeled estimate of incident acute hepatitis B among adults with diabetes was 1 to 4 cases per 100,000 persons for cases likely to be reported, and almost 23 per 100,000 persons after accounting for under diagnosis and under reporting. The modeled estimate of the number of acute hepatitis B infections was more than 4000 annually for adults with diabetes in each of 2007 and 2008, or about 10% of the overall estimated cases of hepatitis B among adults 25 years of age and older in the US [CDC Unpublished data analysis]. The modeled estimates were then compared with data provided by the directors of 4 Emerging Infections Program Sites that gathered diabetes status prospectively during case interviews (3 sites), or when determined in a retrospective review of cases in one site thanks to Dr. Paul Cieslak. Cases among persons with diabetes constituted approximately 10% of acute cases of hepatitis B reported, similar to the percentage for the modeled estimate [Unpublished data, used with permission].

With regard to the incidence of reported cases of acute hepatitis B by age group from 1999 to 2008 (updated from data shown in June 2010 by Dr. Jiles), the most significant decline in acute hepatitis B (88%) was among persons younger than 20 years of age, the group most affected by universal vaccination recommendations starting in 1991. Among adults 20 to 49 years, reports of acute hepatitis B declined by 52%. However, attack rates remain the highest in this age group, which includes slightly less than half of persons with new diabetes diagnoses. Among adults 50 years and older, the age group with slightly more than half of persons with new diabetes diagnoses, the decline in hepatitis B cases was only 35% [NNDSS].

In summary, higher point estimates were found for hepatitis B prevalence among adults with diabetes in all NHANES characteristics examined. Knowledge has been gained about lapses in infection control practice related to blood glucose monitoring and in administering insulin in multiple settings. The smallest declines in acute hepatitis B reports have been among adults 50 years and older, the age group when 50% of new diabetes diagnoses are made and with the highest prevalence of diagnosed diabetes. Adults with diabetes are estimated to account for at least 10% of all new hepatitis B cases in the US.

Other reasons to consider hepatitis B vaccination for adults with diabetes are liver and renal morbidity. Non-alcoholic fatty liver disease (NAFLD) is a spectrum of fatty liver disorders that ranges from simple steatosis to non-alcoholic steatohepatitis (NASH). NASH is associated with inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma. Studies were conducted that estimated the prevalence of non-alcoholic fatty liver disease among adults with diabetes using ultrasound or CT scan. (Ultrasound is not a routine procedure for adults with diabetes.) The prevalence of NAFLD ranged from 49% to 74% in these patients in contrast to 15% to 30% of adults without diabetes. Diagnosis of progression to NASH, the severe form of steatohepatitis, requires a liver biopsy. In one study that performed liver biopsy on 54 adults with diabetes, NASH was found to be present in 22% of the patients.

For a cohort study examining the incidence of chronic non-alcoholic liver disease and hepatocellular carcinoma by diabetes status, investigators used a Veterans Administration (VA) database to identify more than 170,000 (173,643) adult patients with diabetes, and a comparison group of more than 650,000 (650,620) patients with no diabetes from 1985 to 1990. Outcomes for patients without pre-existing diagnoses of liver disease were observed through 2000, excluding the first year of follow-up. Using a Cox proportional hazard model to adjust for other factors, these investigators found approximately a 2 times higher incidence of chronic non-alcoholic liver disease and 3 times higher incidence of hepatocellular carcinoma among patients with diabetes than among patients with no diabetes [El-Serag HB Gastroenterology 2004]. Using the same cohort study the authors examined the cumulative risk of acute liver

failure by diabetes status. Adults with diabetes had significantly higher cumulative incidence of acute liver failure than adults without diabetes (0.3% versus 0.19%; <0.0001) using Cox proportional hazard survival analysis. These two studies demonstrate the overall higher risk of chronic non-alcoholic liver disease, hepatocellular carcinoma, and acute liver failure among patients with diabetes compared with patients with no diabetes [El-Serag HB, Gastroenterology 2002].

Since the last ACIP meeting, CDC examined the National Inpatient Sample to determine the rates of chronic liver disease hospitalizations among adults with diabetes 18 years and older in the US. The National Inpatient Sample is a nationally representative survey of hospitalizations conducted by the Healthcare Cost and Utilization Project (HCUP) in collaboration with the participating states. It is the largest all-payer inpatient dataset in the US. Chronic liver disease-associated hospitalizations were determined by ICD-9 code in the top 15 discharge diagnoses, by age, diabetes status and diagnostic category. The prevalence of diabetes from NHANES was used for the population denominators to calculate hospitalization rates and 95% confidence intervals. The case definition for chronic liver disease included the following conditions: hepatitis B; hepatitis C, which has been associated with the development of diabetes; unspecified viral hepatitis; alcoholic liver disease; chronic hepatitis and cirrhosis; sequelae of chronic liver disease; and malignancy of liver and bile ducts.

Total rates for chronic liver disease-associated hospitalization were 4 times higher for adults with diabetes than without, more than 1500 (1586) versus almost 400 (392) hospitalizations per 100,000 population. Chronic liver disease-associated hospitalizations were increased in all age groups for persons with diabetes. Hepatitis B-associated hospitalizations were 3 times higher for adults with than without diabetes, 73 versus 26 per 100,000 population, a highly significant difference. Hepatitis C, chronic hepatitis and cirrhosis and malignancy-associated hospitalizations were all 3 to 7 times higher among adults with diabetes. These data show the substantial increase in hospitalizations associated with chronic liver disease and malignancy among adults with diabetes. They also show that hepatitis B and C each contribute significantly to the burden of liver disease-associated hospitalizations among adults with diabetes [CDC. Unpublished provisional data].

In a study from Hong Kong, all-cause mortality was increased among persons with diabetes who also had chronic hepatitis B compared with diabetes alone. Almost 3000 (2,838) patients with Type 2 diabetes were recruited from 1995 to 1999 and were followed for a mean of 3.5 years. Of these patients, 10% also had chronic hepatitis B infection. The other characteristics of the patients were similar. Shown on a Kaplan-Meier curve and using Cox proportional hazard model to adjust for other factors (controlling for age, sex, duration of diabetes, blood pressure, BMI, WHR, fasting plasma glucose, HbA1-c, TC, HDL-cholesterol, LDL-cholesterol, TG and estimated glomerulo-filtration rate at baseline), the cumulative frequency of death was 60% higher among patients with diabetes and chronic hepatitis B than among patients with diabetes and no chronic hepatitis B (7.3% versus 4.3%) [Cheng AYS. Diabetologia 2006].

In addition, a preliminary report of new analysis suggests that factors independently predicting liver-related mortality among Hispanic adults in the US were diabetes and chronic hepatitis B. The investigators used the NHANES database from 1988 to 1994 linked to the National Death Index to identify patient outcomes. In a Cox proportional hazard analysis, adjusting for major confounders, the factors independently predicting liver related mortality were age, diabetes (an almost 4-fold increase in mortality), and chronic hepatitis B (adjusted hazard ratio of 19.2) [Younossi ZM et al. AASLD 2010 (Online abstract)]

Diabetes is the leading cause of renal failure in the US. In 2007, approximately 530,000 US residents received hemodialysis and approximately 200,000 (37%) were persons with diabetes. Diabetes is the leading cause of new cases of renal failure, accounting for 44% of new cases in 2007. Limited data suggest that chronic hepatitis B might accelerate progression to renal failure among adults with diabetes. In the cohort of almost 3000 Chinese patients with diabetes followed for 3.5 years, a significantly greater proportion with chronic hepatitis B than without chronic hepatitis B had decline in renal function (8.7% versus 6.4%) [Cheng AYS. *Diabetologia* 2006].

In summary, increased acute liver failure, cirrhosis, and hepatocellular carcinoma occur with both diabetes and chronic hepatitis B. Liver-associated hospitalizations, including hepatitis B-associated hospitalizations, are increased among adults with diabetes. Chronic hepatitis B is associated with increase in liver-related and all cause mortality among at least some adults with diabetes.

Between 49% and 75% of adults with diabetes have NAFLD, and approximately 44% of new hemodialysis patients are persons with diabetes. Hepatitis B vaccination is recommended for persons with chronic liver disease and renal failure. Most adults with diabetes already or in the future will fall under current recommendations for hepatitis B vaccination, although there is under recognition of the chronic liver disease among persons with diabetes.

Protection against hepatitis B infection is indicated by the presence of antibody to hepatitis B surface antigen (anti-HBs). A level ≥ 10 mIU/mL after vaccination generally is accepted as the level that predicts protection. Published data from the US and Asia demonstrate having a response to vaccination of at least 10 mIU/mL predicts healthy adults have at least 22 years duration of protection against symptomatic illness and chronic infection [McMahon et al. *J Infect Dis* 2008].

During the June 2010 ACIP meeting, Dr. Philip Spradling presented a detailed review of clinical trials with a primary series of hepatitis B vaccine by age, that overall gave an impression of the effect of increasing age on seroprotection after vaccination, by diabetes status, and unspecified diabetes status. Each point on the accompanying graph represents a midpoint for an age range for seroprotection in a given study, age, or subgroup analysis. Some studies had multiple points determined by the number of age groups included, and some groups had small sample sizes. Most hepatitis B vaccines were recombinant formulations, and these trials included various schedules and follow-up periods. Laboratory assays were done in a number of different laboratories over several decades. CDC asked GSK and Merck to review their databases for information on older adults and adults with diabetes. Trials were designed for other purposes, and sub-analyses among adults with diabetes were retrospective, exploratory, and included small numbers of subjects.

The data show that seroprotection is high among young adults, including those with diabetes (>90%), and remains relatively high until approximately age 55 or 60, after which seroprotection decrease. Seroprotection was lowest in 3 published studies of older adults in nursing homes where mean ages were in the 70s and 80s and a few subjects were in their 90s. [Limited data suggest seroprotection is lower among adults with diabetes than without diabetes, especially in older age groups.

Given declining seroprotection with age, the Hepatitis Working Group explored whether higher proportions of older adults might achieve seroprotection with combination hepatitis A/B vaccine (Twinrix™) than after monovalent hepatitis B vaccine. Most trials with the combination vaccine were sponsored by the company and assays were done in the manufacturer's laboratories. Some of the data came from retrospective, exploratory analyses and included small numbers of subjects drawn from trials designed for other purposes. The combination A/B vaccine appeared to induce the same or higher seroprotection proportions than monovalent vaccines in ages through approximately 60 years [After 60 years of age, data for Twinrix™ were scarce and the working group concluded that they were insufficient to draw conclusions regarding an advantage of any specific vaccine type for older adults, or for schedule or dosage, based on additional data presented in June 2010.

The working group also assessed whether the observed lower seroprotection among older adults with diabetes related to diabetes or to obesity. Obesity affects about 50% of adults with diabetes. In 2007, the highest rate of obesity was among persons 45 to 64 years [CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics/comp/table7_3a.htm (from BRFSS)]. Hepatitis B vaccine is approved for intramuscular injection in the US. Early in the vaccine's history, it was appreciated that seroprotection was better after injection in the deltoid than in the buttocks, because vaccine antigen was more likely to be deposited in the muscle than in the subcutaneous fat. A number of studies demonstrated since then that needle length has to be adjusted to reach the muscle in obese adults [Weber DJ. JAMA 1985; Shaw FE. Vaccine 1989; Poland GA. JAMA 1997; Zuckerman JN. Lancet 2000. Koster MP. Pediatrics 2009].

In a study led by Amy Middleman, obese teenagers were randomized to receive hepatitis B vaccine at 0, 1, and 6 months using a 1 inch needle or 1.5 inch needle for injection. The characteristics of adolescents in the 2 groups were similar. The titers achieved by 24 subjects who completed the study and had a response to vaccine were significantly higher among obese adolescents whose vaccine was administered with the longer needle; All subjects seroprotected. [geometric mean titer was not reported. [Middleman AB et al. Pediatrics 2010;125(3): e000]. A review of published literature revealed that the effect of Type 2 diabetes on the immune response to hepatitis B vaccine is not well-defined apart from aging and obesity. Studies of needle length for an intramuscular injection indicate that appropriate needle length will optimize vaccine seroprotection among obese adults with diabetes. Guidelines for appropriate needle length are available in the General Recommendations on Immunization, *MMWR* 2006;55 [RR-15].

Data from studies of adults achieving seroprotection after 3 doses of hepatitis B vaccine suggest that most adults with diabetes (> 90%) could be vaccinated before age 70 years, albeit with declining rates of seroprotection [Data from vaccine literature; *MMWR* 2006; 55 (RR-16)]; Adapted from: CDC. Diabetes Data and Trends. Available at: <http://www.cdc.gov/diabetes/statistics/age/fig1.htm>].

With respect to revaccination for adult non-responders, a topic reviewed in detail during the June 2010 ACIP meeting, seroprotection among non-responding adults increases with up to 3 additional doses after the primary series, using a 0, 1, 6, or 0, 2, 4 month schedule. Limited data suggest similar increases in seroprotection after revaccination among older adults with and without diabetes, without increase in adverse events. Thus, available data do not confirm a clear advantage to higher dosage, type of vaccine, or schedule for revaccination.

In summary, there are limitations of the available data on seroprotection among adults. The working group reviewed the literature for hepatitis B vaccination among adults with and without diabetes, and found a large number of clinical trials among healthcare workers. Some trials included adults 60 years and older, but few included adults over the age of 70. A few trials focused exclusively on adults with diabetes, but the number and depth of these data were not optimal, particularly for revaccination studies. There were no published data on the duration of vaccine protection among older vaccine recipients. These are areas that would benefit from additional research.

Given the suboptimal responses by older adults to available hepatitis B vaccines, ACIP asked "Are hepatitis B vaccine candidates with improved immunogenicity in clinical trials?" Dr. Murphy indicated that Bill Heyward from Dynavax Technologies provided the following information. HEPLISAV™ is a candidate hepatitis B vaccine with a novel adjuvant currently in Phase III trials among persons 11 to 55 years of age. The vaccine combines 20 ug of hepatitis B surface antigen with 3000 ug of 1018 ISS (immunostimulatory oligonucleotide sequence), which is a toll-like receptor 9 agonist, a potent adjuvant for Th1 T-cell responses, and inhibits Th2 T-cell development. In the Phase III trial, subjects were randomized 3:1 to either a 2-dose regimen of HEPLISAV™ at 0 and 1 month, and placebo at 6 months, or a 3-dose standard series with monovalent hepatitis B vaccine (Engerix-B™) 20 ug at 0, 1, and 6 months. The 2-dose HEPLISAV™ regimen achieved earlier and higher proportions of subjects who were seroprotected at all time points in the per protocol analysis than the monovalent vaccine, including at the primary endpoints at 3 and 7 months. The safety profile of HEPLISAV™ was similar to that of Engerix-B™ for local and systemic events, adverse events, and serious adverse events. Two cases of ANCA-associated vasculitis (anti-neutrophil cytoplasmic antibodies-related vasculitis) occurred during the study; one in each vaccine group. Dynavax recently presented an abstract at IDSA looking at a sub-analysis of subjects with diabetes that showed favorable results. The Dynavax hepatitis B candidate vaccine with a novel adjuvant is highly immunogenic in a Phase-III trial using a 2-dose schedule among adolescents and adults to age 55 years. More information will be provided as it becomes available. In conclusion, the working group asked, "Would hepatitis B vaccination decrease the morbidity and mortality of hepatitis B infection among adults with diabetes?" Adults with diabetes experience excess morbidity and mortality from acute and chronic hepatitis B infection. Hepatitis B vaccination has the potential to substantially reduce hepatitis B among adults with diabetes. Most adults with diabetes will fall under current recommendations for hepatitis B vaccine during their life-time either from progressive liver disease or renal disease.

Discussion Points

Dr. Keitel requested an estimate of the prevalence of diabetes in the adult population.

Dr. Murphy responded that this depends upon which statistics are reviewed. The data posted from diabetes colleagues at CDC state 7.7% diagnosed diabetes for 2007, which are the latest data available. Rates quoted in the newspaper state 10%, but this includes undiagnosed as well as diagnosed diabetes.

Dr. Judson said he would accept the association, and probably no more than that, between diabetes and hepatitis B infection. The only reported outbreaks for the last 7 years have been from assisted living facilities. That seems to be clearly where they should concentrate. The problem is multiple punctures, blood-to-blood, which he would also accept. Meters were also emphasized. Having a wife with juvenile onset diabetes who has been involved with a number of meter studies, he understands these pretty well. He did not see how a meter could contribute

to blood-to-blood transmission of hepatitis B. He would accept that they would be contaminated with the blood on the test strip, but beyond that it should be a dead end. He worries about a broad recommendations for which people with meters are instructed to disinfect them after every strip. As far as he knows, a number of these meters could easily be damaged if this was not done correctly. One incentive for assisted living facilities to do the right thing is to ensure that they understand the medical liability and the potential lawsuits. This is clearly negligent healthcare behavior. Regarding the association versus causal relationship between diabetes and hepatitis B, without correcting for race, especially for black race, they can only go so far because all of the other primary causes of hepatitis B are more prevalent in blacks. Age and race must be adjusted for. The rates in Colorado diabetics versus the rates in New York City or Baltimore make him believe that this is going to be important.

Dr. Perz responded that the data do point to issues in assisted living facilities; however, he cautioned them not to think that the problems with risk or actual transmission are limited to that setting. Some detection bias is certainly occurring. In a captive population, the odds of detecting transmission and recognizing an outbreak are higher. Regarding the meter issue, approximately two-thirds of the outbreaks described involved shared fingerstick devices. In the other one-third of outbreaks, fingersticks were performed using safety lancets, and that leaves the meter as a possible vehicle. There is some good evidence that the meter can act in this manner. When there is blood carryover, even if a healthcare worker or other person assisting with monitoring is conscientious about their hand hygiene and glove use, picking up that contaminated meter now contaminates their hands and fingers and when they are manipulating the fingerstick wound, he expects there is some potential for transmission as a result. The cleaning and disinfection recommendations are in the context of this assisted monitoring where multiple persons require assistances, and that recommendation does not apply to diabetics who are individually conducting self-monitoring using meters that are designed for person use not institutional use. That is an area that requires more attention. He agreed that this represents negligent behavior, and that it is important to emphasize that reuse of fingerstick devices is not only not recommended, but also, it is unacceptable.

Dr. Jenkins requested further hypotheses about the observation regarding the difference in seroprevalence between adults with > 30 and < 30 body mass index (BMI).

Dr. Murphy responded that while this is fascinating and they could speculate on a number of things, this would not be a substitute for providing data..

Dr. Schuchat commented that many of the associations of higher seroprevalence are one-way looks. It was unclear to her whether any of the data sources could be adjusted for other risk factors among people with diabetes.

Dr. Murphy replied that this is a question with which they struggled. Because the surveillance system has not collected data on diabetes status, it has not been possible to assess the role of other risk factors in acute hepatitis B cases with diabetes. There may be some data from New York City eventually, and some other states are now interested in collecting those data. However, she did not know whether there would be enough cases to do multivariate analyses.

Dr. Foster agreed with Dr. Judson. In 2000, Congress passed the Needlestick Safety and Prevention Act, which had to address all of these issues and involved the Occupational Safety and Health Administration (OSHA). Almost every state has its own OSHA branch. There are significant penalties for non-compliance. CDC's National Institute for Occupational Safety and Health (NIOSH) is also involved with this.

Dr. Murphy reiterated that assisted living facilities have unique oversight by state or even locality. That has been a major part of the problem in getting anything introduced.

Dr. Perz added that the devices in question often qualify as safety devices. When they talk about reuse of the lancet device, it is often in the context of changing out the end cap with the lancet being integrated, or changing the lancet. When a healthcare worker actually has to manipulate and change an individual lancet, that is against sharps safety good practice. There is more of a role to work with OSHA, but that agency's emphasis is on worker protection. In the surveys, they found that awareness / uptake of OSHA bloodborne pathogen standards in the context of assisted living is lacking. Work can be done to improve this, and it would also be worthwhile to pursue more training in terms of patient risks as part of the annual training required under the bloodborne pathogens standard.

Dr. Keitel asked whether diabetic patients in the NHANES survey were asked about multiple sexual partners. In the footnote for the provisional data, the weighted results do not include that question, which would be significant.

Dr. Murphy responded that in the NHANES survey, all participants were asked all of the questions. They should have been, and she will check on this.

Dr. Temte requested a diagram showing age and the rate at which people acquire disease. Practices deal with five stages of kidney disease, and many people are Stage 2, which has very little meaning. They only know about diabetics with fatty liver disease if they happen to do an ultrasound or CT scan, which is a rare event. It would be helpful in their deliberations to know at what age these become significant with problems.

Dr. Pickering pointed out that the NIS 2001-2008 data pertaining to liver disease-associated hospitalizations among adults by diabetes status raised the issue of hepatitis C. He wondered where hepatitis C fell in relation to the disease produced by hepatitis B.

Dr. Murphy responded that while they are interrelated, because hepatitis C is often associated with the development of diabetes, additional analyses would have to be conducted to sort that out.

With respect to the issue regarding the strength of the evidence for a cause-effect relationship between transmission of hepatitis B and blood glucose monitors, Dr. Elward (HICPAC) pointed out that a number of Hill's Criteria for causality are being met. There are fairly strong associations between diabetes and blood glucose monitoring use in some of the case-control studies that have been conducted in some of these facilities. There is good biologic plausibility in terms of bloodborne pathogens with a low infectious dose that survives for long periods of times on surfaces, and people who are having repeated exposures from these devices over time in a community setting. There is also reproducibility because a number of outbreaks in similar settings have similar results. Regarding regulatory oversight and infrastructure, in settings where infection control has been successful initiatives there has been the "perfect storm" of stakeholder buy-in, solutions, and checks and balances on the system. As noted, this is a unique setting in that it does not have the same kind of oversight and reimbursement. Many of these facilities fall outside of the scope CMS. A major hook for regulatory oversight is linking it to reimbursement.

Dr. Duchin inquired as to whether any cost-effectiveness or other analyses were planned to assess various strategies to understand the results of various approaches in the context of reducing burden hepatitis B among diabetics who do not already have other indications for vaccination.

Dr. Murphy replied that an initial review has been done with respect to cost-effectiveness. A cost-effectiveness analysis will be presented during a future ACIP meeting. She noted that if there were specific requests, they would try to include those in the model.

Policy Considerations: Hepatitis B Vaccination for Adults with Diabetes

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After many months of review, an overwhelming majority of the working group members preferred a recommendation for vaccinating most or all unvaccinated adults with diabetes as soon as feasible after diagnosis in addition to enhanced efforts to improve implementation of infection control practice. The rationale for hepatitis B vaccination is to decrease the burden of acute hepatitis B; decrease the burden of chronic liver disease, hepatocellular carcinoma, and liver mortality among adults with diabetes who might develop chronic hepatitis B; provide protection before the onset of complications related to diabetes that will decrease vaccine effectiveness; and reduce the reservoir of chronic hepatitis B that contributes to continuing transmission.

An approach to vaccinating older adults with diabetes presents additional challenges. Major areas of working group discussion included declining seroprotection and cost-effectiveness among older adults, whether to have age criteria for recommending vaccination, and how to provide flexibility in decisions about vaccinating frail elderly adults. As reported previously, available data suggest seroprotection can be achieved after a 3-dose primary series in 75% to 90% of adults less than 60 years of age, and 50% to 75% of adults ages 60 and 70 years. In 2007, two-thirds of adults with diabetes received a diabetes diagnosis before age 60, and approximately 92% received a diagnosis before age 70 years. A decline in cost-effectiveness occurs with aging, in part because of declining vaccine seroprotection; fewer cumulative life years at risk for hepatitis B infection; and because the cost of hepatitis B vaccine and reimbursement fees for vaccine administration remain high. In addition, because of a lack of data, the incident risk of hepatitis B among adults in institutional settings and the public health cost of controlling outbreaks have not been included in the initial cost-effectiveness models.

The working group deliberated about the advantages and disadvantages of having specific age criteria that would signal a conditional recommendation for vaccination. For example, the wording of a recommendation might state that "Hepatitis B vaccination is recommended for all adults < 60 years. For adults ≥60 years, hepatitis B vaccination would be appropriate in the following circumstances." The possible advantages of age criteria might include simplicity in defining a change in recommendation from "universal" to "conditional," which could also highlight declines in seroprotection and declines in cost-effectiveness. Another possible advantage would be to focus vaccination efforts on adults with diabetes with the greatest potential benefit from vaccination. A possible disadvantage of having age criteria might be that the recommendation would be inconsistent with all other hepatitis B vaccine recommendations, which have no age criteria. For example, there is no age at which hepatitis B vaccine would not be recommended for healthcare personnel, patients with renal failure, chronic liver disease,

HIV, MSM, or for adults whose sex partner has chronic hepatitis B. Another possible disadvantage is that declining seroprotection is not uniform for all members of an age cohort. Declines are affected by both the general health of the adult and by immuno-senescence. Some healthy older adults might respond better to vaccination than some younger adults who have major co-morbid conditions. Some working group members were concerned that tying declines in cost-effectiveness to a specific age might result in excluding some adults with diabetes from insurance coverage. Another possible disadvantage might be having a more complex recommendation.

A third important area of the working group's discussions regarded how to provide flexibility for deferring vaccination for frail elderly adults who would likely have little or no benefit from vaccination. The concern applies primarily to the increasing subset of short-stay residents of long-term care with severe disability, terminal illness, or short expected longevity. The working group favored wording that would encourage use of clinical judgment to defer vaccination when medically appropriate.

Taking into consideration these 3 discussion areas, and after initial review of cost-effectiveness data, the working group majority favored vaccination for all unvaccinated adults with diabetes, regardless of age, while encouraging clinician judgment for decisions about vaccinating frail elderly adults with diabetes. The working group also favored post-vaccination serology for older adults only if revaccination of non-responders would be medically appropriate; that is, revaccination would be permissive rather than recommended. A substantial minority of working group members favored vaccination for most unvaccinated adults with diabetes in younger age groups, but for older adults favored limited vaccination based on individual decisions that consider the risk of hepatitis B, the risk of complications of hepatitis B, expected longevity, and likelihood of responding to vaccination. The working group minority felt that it was important to stress that it is safe to vaccinate at any age, but favored no recommendation for revaccination.

Future working group activities will emphasize continuing infection control initiatives; completion of the cost-effectiveness analyses with sensitivity analyses; and review of considerations for implementing a program of hepatitis B vaccination for adults with diabetes.

Discussion Points

Dr. Baker pointed out that this disease is vaccine-preventable as well as infection control-preventable. While she was unclear regarding what action to take about assisted living facilities, her local experience is that such facilities are caring for increasingly sicker patients in this competitive economy. Therefore, it is likely that the risk to the people these facilities take care of with little regulation will continue to increase. She thought that a more extensive cost-analysis would be very helpful. It also remains unclear is how much liver disease is being contributed to by hepatitis C versus hepatitis B.

Dr. Brian McMahon (Anchorage, Alaska) indicated that he was a member of ACIP Hepatitis Working Group and the Institute of Medicine (IOM) committee that made the recommendation about hepatitis B and C in the US. He suggested that there were two issues they should consider accomplishing: 1) How to prevent these outbreaks in nursing homes and extended care facilities; and 2) Patients with diabetes have chronic liver disease, which causes a substantial amount of morbidity and mortality later in life, and hepatitis B contributes to and makes that mortality excessive over not have hepatitis B, so prevention is key. It is known from the studies that have been conducted that 50% to 70% of diabetics have fatty liver demonstrated by ultra sound or CT. However, it is important to remember that ultrasound and

CT have a sensitivity rate of 50% for detecting fatty liver. When more sophisticated MRI studies are used, that percentage is much higher. In fact, 30% of liver cells at a minimum have to have fat in them before the ultrasound becomes positive. Therefore, most of these patients would already qualify under the current recommendations for vaccination. With that in mind, he thought it made sense to vaccinate all of the younger patients. The question is: What do we do about older people to prevent outbreaks? It was not clear to him that it really matters so much what contribution hepatitis C made, although it does contribute to overall morbidity and mortality. There are epidemiologic studies that illustrate the association between having hepatitis C and a higher risk of acquiring diabetes. Moreover, if hepatitis C is cured, which can now be accomplished with antiretroviral therapy, insulin resistance can disappear if the individual has no other factors associated with insulin resistance.

Pertussis Vaccines

Update on Pertussis Vaccines Work Group Activities

Dr. Mark Sawyer ACIP Pertussis Vaccine Working Group Chair

Dr. Sawyer explained that the Pertussis Vaccine Working Group had three terms of reference. The first was to review existing statements on infants and young children (1997), adolescent (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate them into a single statement. The second was to review new data on Tdap including the effectiveness of ACIP recommendations; the interval between Td booster and Tdap; use of Tdap in adults ages 65 years and older; use in pregnant and breastfeeding women, as well as cocooning strategies; and use in vaccinated healthcare workers and the need for post-exposure prophylaxis. The third was to review updated epidemiology pertaining to tetanus and diphtheria. Most of these deliberations were well under way when pertussis began to receive increased attention in 2010 due to outbreaks in California and a number of other states.

After reviewing the agenda for this session, Dr. Sawyer shared several maps to illustrate US incidence data reported to CDC. In 2009, there was a high variability of pertussis incidences across the country. At that time, California's incidence was relatively low (0-2.7). By week 41 of 2010, California's incidence had increased to a range of 3.6-5.7 according to CDC data, and 5.8-13.0 according to state health department data. While some states have had decreased rates of pertussis, the majority of states are experiencing increased rates. Reported pertussis-related deaths by age-groups in the US from 1980 to 2009 are reflected in the following chart, with California having an unusually high number of deaths in infants:

Age-Group	¹ 1980-1989	¹ 1990-1999	² 2000-2009
0-1 month	38	68	152
2-3 month	11	16	24
4-5 month	5	5	2
6-11 month	7	4	1
1-4 years	13	2	2
5-10 years	1	6	3
11-18 years	0	0	3
>18 years	1	2	8
Total	[†] 77	103	195

¹ Vitek CR et al. *Pediatr Infect Dis J* 2003; 22(7):628-34.
² National Notifiable Diseases Surveillance System, CDC, 2009
[†] Includes one case with unknown age

While the vast majority of deaths occur in children less than 12 months of age, it is the rest of the population who transmits disease to them. Therefore, much of this session was devoted to immunizing the population prevent transmission to this highly vulnerable group.

2010 California Pertussis Epidemic

Kathleen Harriman, PhD, MPH, RN
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Dr. Harriman reported that California has 12 children's hospitals, all of which are monitoring for pertussis and keeping track of their numbers. In late March, the California Department of Public Health (CDPH) was notified by the Children's Hospital of Central California of an increase in pertussis cases similar to that seen in early 2005, the last peak year for pertussis. The hospital was concerned enough to contact CDPH, which was very important because like many states, California has a decentralized public health department in that the state is a repository of reportable disease information, but it is really the local health departments that conduct case investigations, et cetera. Often, there is quite a lag in reporting to the state even though cases are being investigated.

The early alert prompted CDPH to query other local health departments. CDPH has an email listserv for all local health departments and all hospital infection preventionists. Many responded that they were observing an increase in the number of cases of pertussis. The last pertussis outbreak was in 2005 in California and nationally. Pertussis is cyclical, so it was not unexpected that 2010 might be a high incidence year. Fortunately, the early warning allowed them to begin planning mitigation efforts much earlier than they would have been able to do otherwise. A significant difference in 2010 that was not a factor in 2005 was Tdap. Tdap was first licensed in 2005, but it was not much of a factor during the 2005 outbreak. CDPH decided immediately to make use of this tool. The primary goal was to prevent deaths in infants. At least as far back as 1998, all deaths due to pertussis in California were in infants 3 months of

age or younger. In order to prevent deaths in infants, it was important to vaccinate people to whom infants might be exposed.

Mitigation efforts began immediately, with the primary goal to prevent infant deaths. Although the cocooning strategy has been recommended for a few years, there has not been a lot of evidence to suggest how effective it is. Therefore, in April 2010 CDPH conducted a survey of hospitals through which they were able to obtain evidence that the cocooning strategy and post-partum Tdap vaccination was effective. Extensive communications were made to clinicians, hospitals, and local health departments regarding early diagnosis and treatment. Dr. Jim Cherry, an expert in pertussis, helped CDPH develop recommendations for infants with severe pertussis that were quickly disseminated throughout the state.

The April 2010 survey revealed that about 25% of California's 250 birth hospitals had a Tdap post-partum policy or program; however, even in these hospitals implementation was another issue and a number of barriers were discovered. Tdap cost was cited as a barrier to postpartum Tdap because unless Tdap vaccine pricing is negotiated into the contracts that hospitals have with payers, hospitals implementing such a strategy would have to pay for Tdap themselves. Most hospitals bundle charges for labor and delivery and they receive one set amount for every labor and delivery. If Tdap was not included in the bundle, the hospitals would be paying those costs themselves, which was a significant barrier. The other issue in terms of the implementation of a cocooning policy was that ACIP's recommended interval between Td and Tdap was very confusing to providers, as well as patient uncertainty about the date of their last Td. Practitioners were afraid to vaccinate in such cases due to the concern that some harm might come to that vaccinee. This also led to missed opportunities for Tdap. In addition, Tdap is not licensed for those aged 7 through 9 or older than 64, and there are no pertussis-containing vaccine for these age groups. Differing recommendations on the use of Tdap in pregnant women by ACIP, AAP, and ACOG was also problematic, and most emergency departments were unfamiliar with Tdap for wound management. They were using either tetanus toxoid or tetanus diphtheria vaccine. Moreover, Tdap costs more so there were reimbursement issues.

Using American Recovery and Reinvestment Act (ARRA) funds, hospitals were offered free Tdap for postpartum women and other infant contacts, including families of neonatal intensive care unit (NICU) infants. Of the 250 birth hospitals, 180 have applied for vaccine. The offer was expanded to over 500 community health centers due to hospital difficulty in vaccinating non-patients. Approximately 147,000 doses have been provided to date through the ARRA mechanism. In July 2010, the recommendations were expanded on the use of Tdap issued. In August 2010, support to local health departments for vaccine clinics resulted in 35,000 doses being administered.

CDPH Tdap recommendations are to immunize those ≥ 10 years of age who have not yet received Tdap, especially women of childbearing age, preferably before, or else during or immediately after pregnancy; others with close contact with young infants; persons >64 years of age; and for wound management to replace Td. Use of Tdap was also recommended for under-immunized 7 through 9 year olds. There is also no minimum interval between Td and Tdap.

The rationale for the recommendations was that the safety of Tdap in children 7 through 9 years is suggested by two studies, and Tdap is licensed in Canada for children down to four years of age. Local and systemic events after ADACEL® vaccination was less frequent in adults <65 than adolescents, suggesting the safety of Tdap in older populations (FDA Clinical Briefing Document). Td is safely given to pregnant women. No theoretical risk of harm to mother or fetus exists from Tdap. AAP recommends use in pregnancy. While use during pregnancy is not

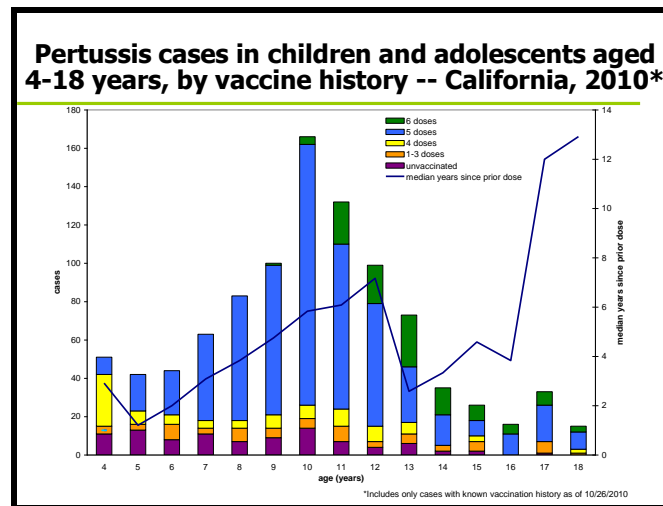
cited as a contraindication by ACIP and ACOG, preconception or postpartum administration preferred. Tdap given after previous Td or DTaP is well-tolerated at intervals of 1 to 18 months. There is no minimum interval between doses for all of the stated intervals in ACIP guidance [Halperin et al. *Pediatr Infect Dis J* 2006;25:195-200, Scheifele et al. *Pediatr Infect Dis J* 2005;24(12): 1059-1066, Beytout et al. *Hum Vaccines* 2009;5(5): 315-321].

As of October 27, 2010, California has had over 6200 cases of pertussis reported. Most have been diagnosed by PCR. The last year close to that number was 1950 when there were over 6600 cases. That is just case numbers. The numbers are now up to the 1959 incidence rate of a little over 16 cases per 100,000 population. Unfortunately and tragically in 2010, there have been 10 pertussis deaths to date in infants ≤ 2 months of age at disease onset. The case fatality rate for infants < 3 months of age is 1.8%. Of these 10 infants 9 were Hispanic infants and 1 was White. The California birth cohort is 50% Hispanic and is 500,000 infants per year. One premature infant received one dose of DTaP two weeks prior to illness onset, while all of the other infants were too young to be vaccinated. It was extremely frustrating to read some of these medical records. Many of the fatal cases had multiple contacts with healthcare providers before pertussis was diagnosed. One infant was taken in 5 times in 8 days before he was diagnosed with pertussis. Several had family members with cough illness. One had an ill 9-year old sister whose fifth dose of DTaP was in 2006. One had an ill 4-year old sibling who was due for the fifth dose of DTaP. The immunization status of other ill contacts of fatal cases is under investigation.

Regarding incidence of pertussis cases by race / ethnicity and age in California in 2010, in infants under 6 months of age, there is very much a disparity in terms of Hispanic infants being highly over-represented. That disparity disappears after about 6 months of age. It is hypothesized that these infants have larger numbers of contacts, large household sizes, et cetera. Once they have been vaccinated, that is not longer such an issue. Very few cases have been reported in anyone over 18 years of age, although that is probably due to under-reporting. Outside of infancy, 10 year olds have the highest incidence of pertussis.

In terms of susceptibles and disease transmission, there is a large pool of susceptible. National Tdap coverage in adults is 5.9%. At first they wondered whether the outbreak occurred because California has not had a Tdap mandate for middle school students like many other states have had for some years. However, California adolescent Tdap coverage is 53.1% and national coverage is 55.6%. There are primary vaccine failures and waning immunity as well. In California, most young children continue to be immunized. About 93.1% of 2009 kindergarten entrants had had five doses of DTaP. There is a smaller number of intentionally unvaccinated children compared to the pool of susceptible adolescents and adults; however, in some counties there are quite high rates of intentional unvaccination. Some of these areas have experienced school outbreaks over the years, and certainly in a couple of counties the intentionally unvaccinated children have probably played more of a role than in other areas. Rates of immunization in Hispanic infants and adolescents are comparable to Whites. In September 2010, a middle school Tdap vaccine mandate was signed into law that will take effect in Fall 2011 and includes all students entering grades 7 through 12. This marks the first time that California has ever implemented a vaccine strategy for more than one year of school entrance.

Pertussis cases in children and adolescents aged 4 through 18 years by vaccine history in California in 2010 is reflected in the following graphic:



In conclusion, Dr. Harriman indicated that they had had three Epi Aids thus far and that the California local health departments and infection preventionists in hospitals have done extensive work. She expressed gratitude for all that everyone has done, including their colleagues at CDC.

Tdap Following Td: Removing a Barrier

Dr. Jennifer L. Liang
ACIP Pertussis Vaccine Working Group
CDC / NCIRD

Dr. Liang presented information that the working group used to discuss the use of Tdap regardless of timing since last Td vaccine, and presented the proposed recommendations for discussion and vote. During the pre-vaccine era, the number of pertussis cases culminated to about 270,000 in the mid 1930s, with more than 10,000 deaths. Since the introduction of whole cell vaccine, DTP, in the late 1940s, the number of reported pertussis cases has fallen dramatically. Despite this decrease, pertussis continues to be endemic. Since 1980, there has been an increase in the number of reported cases from approximately 2,000 cases per year to over 10,000 cases per year [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service].

Tdap coverage among adolescents has increased since 2006. In 2009, coverage was reported to be over 55%. Compared to adolescents, coverage of Tdap among adults was reported to be less than 6% in 2008 [CDC. National, State, and Local Area Vaccination Coverage among Adolescents Aged 13-17 Years - United States, 2009. MMWR 2010; 59(32) 1018-1023; CDC. National, State, and Local Area Vaccination Coverage Among Adolescents Aged 33-17 Years - United States, 2008. MMWR 2008; 58(36) 997-1001; CDC. Vaccination Coverage Among Adolescents Aged 13-17 Years - United States, 2007. MMWR 2008; 57(40) 1100-1103; CDC. Vaccination Coverage Among Adolescents Aged 13-17 Years - United States, 2006. MMWR 2007; 56(34) 885-888].

The primary objective of the adolescent and adult pertussis vaccination policy is to protect vaccinated adolescents and adults against pertussis, while the secondary objective is to reduce the reservoir of pertussis in the population by decreasing exposure of persons at increased risk for complicated infection and reducing the cost and disruption of pertussis in health-care settings. The current language addressing interval in the adolescent statement is not specific. The 2005 ACIP adolescent recommendation for Tdap interval reads as follows:

“An interval of at least 5 years between Td and Tdap is encouraged to reduce the risk for local and systemic reactions after Tdap vaccination. However, an interval less than 5 years between Td and Tdap can be used.”

Language around interval in the adult Tdap statement is also not specific:

“Intervals <10 years since the last Td may be used to protect against pertussis. Particularly in settings with increased risk for pertussis or its complications, the benefit of using a single dose of Tdap at an interval <10 years to protect against pertussis generally outweighs the risk for local and systemic reactions after vaccination. The safety of an interval as short as approximately 2 years between Td and Tdap is supported by a Canadian* study; shorter intervals may be used.” [*Halperin SA, et. al. How soon after a prior tetanus-diphtheria vaccination can one give adult formulation tetanus-diphtheria-acellular pertussis vaccine? *Pediatr Infect Dis J.* 2006 25(3):195-200.]

The current language creates a perceived barrier to use of Tdap. Several examples illustrate how the current language addressing interval has created a barrier to Tdap vaccination. In a survey among primary care physicians on the interpretation of the adolescent recommendations, 48% indicated that 5 years would be the shortest acceptable interval before providing Tdap, 44% would wait at least 2 years, and 27% of HCW did not plan to receive Tdap because they had received a Td booster within last 2 years. The major barrier to vaccinate with Tdap is not knowing the date of recent Td booster, with 74% of obstetrician / gynecologists reporting that the major barrier for postpartum vaccination and / or vaccination of pregnant women was not knowing date of Td booster. Most parents with infants in the NICU could not recall their last tetanus booster [Dempsey AF, et. al. Adolescent Tdap vaccine use among primary care physicians. *J Adolesc Health.* 2009 Apr;44(4):387-93; Goins WP, et. al. Healthcare workers' knowledge and attitudes about pertussis and pertussis vaccination. *Infect Control Hosp Epidemiol.* 2007 Nov;28(11):1284-9; Clark SJ, et. al. Attitudes of US obstetricians toward a combined tetanus-diphtheria-acellular pertussis vaccine for adults. *Infect Dis Obstet Gynecol.* 2006;2006:87040; Dylag AM, Shah SI. Administration of tetanus, diphtheria, and acellular pertussis vaccine to parents of high-risk infants in the neonatal intensive care unit. *Pediatrics.* 2008 Sep;122(3):e550-5].

With regard to the rationale for changing the language, additional data are now available since the 2005 recommendations. Language addressing the interval between Td and Tdap is confusing. Current language is a perceived barrier to vaccination and is a problem for persons who require protection against pertussis, but who have a recent or unknown history of Td booster. Individual practitioners make risk assessments. Since the 2005 recommendations, post-marketing Tdap safety data are available. Analysis of data from the Vaccine Safety Datalink (VSD) have shown that medically-attended local reactions are uncommon and risk of those reactions is generally comparable to that expected following Td. In a pairwise comparisons of Td, Tdap, MCV4, no significant difference in risk of a validated local reaction was observed and there was no evidence of an association between Tdap and five predefined

adverse events. Through the Vaccine Adverse Event Reporting System (VAERS), there were no increases in reports of adverse events [Jackson LA, et. al. Risk of medically attended local reactions following diphtheria toxoid containing vaccines in adolescents and young adults: a Vaccine Safety Datalink study. *Vaccine*. 2009 Aug 6;27(36):4912-6; Yih WK, et. al. An assessment of the safety of adolescent and adult tetanus-diphtheria-acellular pertussis (Tdap) vaccine, using active surveillance for adverse events in the Vaccine Safety Datalink. *Vaccine*. 2009 Jul 9;27(32):4257-62].

The 2005 recommendations refer to a Canadian study which supported the safety of an interval as short as approximately 2 years between Td and Tdap. To summarize the data from that study by Halperin and colleagues, as the interval from previous vaccination became shorter, rates of adverse events did not increase. There were with no differences from 2 through 10 year intervals. The 2-year interval was defined as >18 months to <30 months. Severe adverse events, including Arthus reactions, were not observed in the study [Halperin SA, et. al. How soon after a prior tetanus-diphtheria vaccination can one give adult formulation tetanus-diphtheria-acellular pertussis vaccine? *Pediatr Infect Dis J*. 2006 25(3):195-200].

After review of published literature including the Halperin study, both Canada and Australia Tdap recommendations include language around not delaying the use of vaccine. The Canadian recommendation states "Tdap, must be used whenever there is a need for a pertussis booster in adolescents and adults who have recently received Td vaccine." The Australian recommendation states "A single dose of Tdap can be administered at any time after a dose of a vaccine containing tetanus and diphtheria toxoids. The benefits of protection against pertussis are likely to outweigh the risk of an adverse event." The Canadian recommendation is within context of a catch-up program [National Advisory Committee on Immunization (NACI). Interval Between Administration of Vaccines Against Diphtheria, Tetanus, and Pertussis. *CDCR* 2005; 31(ACS-8 and 9):17-22]

Since the Halperin study, there have been two published studies looking at the safety on the use of Tdap at intervals less than two years between Td and Tdap. The Beytout study looked at intervals 25 to 35 days between combined Td-IPV vaccine and combined Tdap-IPV vaccine. The Talbot study compared intervals <2 years to 2 or more years. To summarize those two studies, for persons who received Tdap at intervals less than 2 years after Td, the most commonly reported adverse events were pain (67.9% – 82.6%), redness (20.2% – 25.2%), and swelling (19.4% – 37.8%). Systemic adverse events included headache, fever, and myalgia. Serious adverse events related to the receipt of Tdap were not observed or reported. These data are similar to what was reported in the Halperin study [Beytout J, et. al. Safety of Tdap-IPV given 1 month after Td-IPV booster in healthy young adults: a placebo controlled trial. *Hum Vaccin* 2009;5(5); Talbot EA, et. al. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. *Vaccine* (2010), doi:10.1016/j.vaccine.2010.09.034].

In keeping with other vaccines including Td and TT vaccines, reported adverse events from Tdap are comparable:

Td vaccine¹

- Local: pain /redness/swelling (79%)
- Systemic: headache, fever/myalgia (10%)

TT vaccine¹

- Local: pain /redness/swelling (68%)
- Systemic: headache, fever/myalgia (16%)

Meningococcal conjugate vaccine (MCV4)²

- Pain (59.4%)
- Severe systemic reactions (4.3%)

Hepatitis A vaccine³

- Pain at injection site (53%-56%)

[¹Deacon SP, *et. al.* A comparative clinical study of adsorbed tetanus vaccine and adult-type tetanus–diphtheria vaccine. *J Hyg Camb* 1982;89:513–9; ² CDC. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2005 May 27;54(RR-7):1-21; ³ CDC. Prevention of Hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(No. RR-7):1-23].

The Working Group’s interpretations were that in general, reported adverse events from receipt of Tdap at intervals less than 2 years is same as greater than 2 years. While additional data do not rule out serious adverse events, it is reassuring not see an increase. The current language pertaining to interval is a perceived barrier. Increased incidence of pertussis warrants a change in recommendation. The benefits of protection against pertussis are likely to outweigh the risk of an adverse event. Providers should not miss an opportunity to vaccinate. The working group concluded that pertussis immunization, when indicated, should not be delayed, and strongly and unanimously agreed to the removal of language regarding interval. Because the overall goal of the working group is to create one statement for pertussis-containing vaccines, the following statement merges the existing adolescent and adult Tdap recommendation with no changes:

“For routine use, adolescents ages 11 through 18 years who have completed the recommended 5-dose childhood DTP / DTaP vaccination series and adults ages 19 through 64 years should receive a single dose of Tdap in place of one tetanus and diphtheria toxoids (Td) vaccine dose. Adolescents should preferably receive Tdap at a preventive care visit at 11 to 12 years of age.”

The following is the proposed working group recommendation on the use of Tdap regardless of interval for vote.

“Adolescents or adults who have not received a dose of Tdap should be immunized as soon as feasible. Tdap can be administered regardless of interval since the last tetanus or diphtheria containing vaccine.

Discussion Points

Dr. Chilton pointed out that most people will not know whether they last received a Td or Tdap. A decision will have to be made regarding whether someone should receive a second Tdap if they have had one before or whether they should not be given a new vaccine.

Dr. Baker indicated that they have been running a program in Houston since January 2008, through which they have realized that women only know whether they received a shot. During influenza season, they do not know whether they received Td or Tdap. Until there is a robust adult immunization registry, she does not believe they can count on adults having a clue about vaccines they have received in the past.

Dr. Harriman replied that their advice to hospitals and others has been that unless someone provides a piece of paper stating that they had Tdap, they should be given Tdap.

Dr. Chilton requested confirmation that they were assuming that a second dose is not dangerous.

Dr. Harriman replied that this is the assumption. There is no evidence to suggest that it would be.

Dr. Baker added that since January 2008 in Houston, either providers or their post-partum program have inadvertently re-immunized about 30 women, all of whom are fine.

Dr. Englund congratulated and applauded the working group for helping those in the trenches who have to deal with pertussis vaccine. She requested that another high risk group, transplant patients, be added for whom they are trying to immunize contacts because it is impossible to find out their immunization history. She expressed concern regarding whether the recommendation went far enough by stating routine vaccine in those 11 to 64 years of age, given that this also applies to those over the age of 64. It would be nice to have a one concise recommendation rather than bullets for each age group.

Dr. Liang replied that the next topic that she would present applied to that age group, and while they could combine the recommendations, the direction the working group was headed was to be more permissive for that age group.

Dr. Baker added that the reason these were separated was because they did not want to get entangled in different issues. However, she thought that if there was an affirmative vote on the next issue, these recommendations could be rolled into one.

Dr. Chilton wondered whether a statement was needed such as, "If it is no known whether a patient had received Tdap in the past, Tdap should be administered at the next opportunity."

Dr. Liang responded that from what she understood, within the general recommendations for vaccination, if someone has an unknown history, the assumption is that they have not received the vaccine and they would, therefore, receive Tdap.

In terms of the routine recommendation of Td every 10 years, Dr. Judson asked whether they were committing to use Tdap every time for most people since they often would not have a record. He also inquired about the difference in cost at this point.

Dr. Harriman responded that Tdap is more expensive at about \$35 per dose government price. That issue was raised by emergency departments who were concerned about reimbursement. Ms. Ehresmann emphasized the value of an adult immunization information system. She recognized that not every jurisdiction has a robust registry, but as registries further develop with increased use electronic health records (EHRs), that will become a wonderful tool in these situations.

Dr. Fryhofer (ACP) reiterated Dr. Chilton's comment. It is confusing to determine what patients have already received. She has spent hours trying to determine this. If a patient received a tetanus shot in the emergency department because they have been injured, it is difficult to find out whether it was Td or Tdap. Not giving physicians "permission" to give another Tdap if the patient may have already had one will result in missed vaccination opportunities. She agreed with Dr. Chilton's suggested language.

Dr. Thomas Clark (SME) indicated that the working group understands that it will need to adjust for previous vaccination in the future. The earliest vaccinees are just 5 years out.

It was Dr. Baker's understanding that in addition to the AAP recommending Tdap during pregnancy, ACOG also recommends this.

Dr. Kevin Ault (ACOG) responded that there is a permissive recommendation to vaccinate a pregnant woman if there is a reason to do so.

Dr. Marcy added that the current ACOG guidelines from July 22, 2010 state that "Pregnant women (including women who are breastfeeding) who have not been immunized with Tdap should receive it after delivery and before discharge from the hospital if two or more years have lapsed since Td vaccination (ACOG Committee Opinion 438).

Ms. Rosenbaum noted that if the delivering woman is of VFC age, there should be some mechanism for CMS to rapidly let states know that vaccine should be reimbursed in addition to the bundled payment. There is an argument to be made that it would fall under a pregnancy-related service. It is not just advisable to provide hospitals with the vaccine and expect that they will administer it, but also it is a covered benefit for the Medicaid population.

Dr. Baker noted that the Medicaid population is state-variable. Texas is currently deciding whether to bundle it with Measles, Mumps, Rubella (MMR) vaccine post-partum as part of the package. There is no question that women under 21 years of age are VFC-eligible, but that requires that the obstetrics department at a hospital has VFC status. However, many are not willing to do this.

Ms. Rosenbaum clarified that there are two ways in which vaccines are covered under Medicaid, one of which is through the VFC and the other of which is that it simply is a covered benefit for those under 21 years of age. Upon learning that there is a public health problem, CMS and states should have way to quickly send an automatic update to every hospital to bill under the regular Medicaid program because it is a covered benefit. Getting people to submit claims is a problem, but it is very tragic that in the California case it was partly a financial issue. In response to Dr. Schuchat's clarification that the VFC covers those aged 19 and under who are uninsured, Ms. Rosenbaum noted that this is an entitlement in the law for those up to 21 years of age as a regular benefit under Medicaid. This is a tension in the law that is the subject of a great deal of confusion. Many states believe that there is simply no coverage for the 18 to

21 year old population. The coverage itself is part of coverage entitlement. The financing is VFC up to age 19.

Dr. Grogg (AOA) recommended removing “5-dose” from the language that states “recommended 5-dose childhood DTP / DTaP vaccination series” because 4 doses of DTP may be sufficient as long as the 4th dose was after 4 to 6 years of age.

Dr. Sawyer proposed the following wording for the removal of interval language: “Adolescents or adults who have not received a dose of Tdap, or for whom vaccine history is unknown, should be immunized as soon as feasible.”

Motion: Revised Recommendation for Routine Tdap Vaccination (11-64 year olds)

Dr. Chilton made a motion to accept the language as proposed. Ms. Ehresmann seconded the motion. The motion carried with 13 affirmative votes, 0 negative votes, and 1 abstention.

Motion: Use of Tdap Regardless of Td Interval

Dr. Marcy made a motion to accept the language as proposed, with the suggested interval language stating, “Adolescents or adults who have not received a dose of Tdap, or for whom vaccine history is unknown, should be immunized as soon as feasible. Tdap can be administered regardless of interval since the last tetanus or diphtheria containing vaccine.” Ms. Ehresmann seconded the motion. The motion carried with 13 affirmative votes, 0 negative votes, and 1 abstention.

Safety and Immunogenicity of Adacel® Vaccine among Persons Aged 65 Years and Older

Michael D. Decker, MD, MPH
Vice President, Scientific & Medical Affairs
Sanofi Pasteur USA

Dr. Decker presented information on the safety and immunogenicity of Adacel® vaccine among persons aged 65 years and older. A clinical trial titled Td515 was conducted. Td515 was an active-controlled, randomized, modified double blind trial conducted at 19 sites in the US. Participants (n=1561 total) were randomized at a 3:1 ratio to receive either a single dose of Adacel® vaccine (n=1170) or Td adsorbed (DECAVAC®) vaccine (n=391). Overall, 1/3 of the study subjects were ≥ 75 years of age (Adacel® n=780; Td n=262), and 2/3 were 65-74 years of age (Adacel® n=390; Td n=129).

Comparing the Adacel® to the Td for solicited injection-site reactions days 0 through 14, there was little if any difference in the two vaccines for pain, erythema, or swelling. For solicited systemic reactions during the first two weeks after vaccination with either of these vaccines, fever was nil and there was essentially no difference in rates of headache, malaise, and myalgia. Detailed data on the safety overview after vaccine injection for time periods ranging

from 20 minutes for immediate reactions through 6 months for severe adverse reactions (SAEs) are reflected in the following chart:

Participants with at least one:	Time Period	Adacel			Td		
		n/N	%	95% CI	n/N	%	95% CI
Immediate Unsolicited Event	20 min	1 / 1170	<0.1	<0.1; 0.5	2 / 391	0.5	<0.1; 1.8
Immediate Unsolicited Reaction		1 / 1170	<0.1	<0.1; 0.5	1 / 391	0.3	<0.1; 1.4
Solicited Reaction	14 days	720 / 1153	62.4	59.6; 65.2	246 / 387	63.6	58.6; 68.4
Solicited Injection Site Reaction		615 / 1153	53.3	50.4; 56.3	200 / 387	51.7	46.6; 56.8
Solicited Systemic Reaction		420 / 1151	36.5	33.7; 39.3	155 / 387	40.1	35.1; 45.1
Unsolicited Event	35 days	269 / 1170	23.0	20.6; 25.5	108 / 391	27.6	23.2; 32.3
Unsolicited Reaction		71 / 1170	6.1	4.8; 7.6	30 / 391	7.7	5.2; 10.8
Unsolicited Injection Site Reaction		47 / 1170	4.0	3.0; 5.3	20 / 391	5.1	3.2; 7.8
Unsolicited Systemic Reaction		27 / 1170	2.3	1.5; 3.3	14 / 391	3.6	2.0; 5.9
AE Leading to Study Discontinuation	6 mon	2 / 1170	0.2	<0.1; 0.6	0 / 391	0.0	0.0; 0.9
Serious Adverse Event *		49 / 1170	4.2	3.1; 5.6	20 / 391	5.1	3.2; 7.8
Death *		3 / 1170	0.3	<0.1; 0.7	2 / 391	0.5	<0.1; 1.8

* No serious adverse event or death was considered related to study vaccine
n/N: Subjects reporting event / subjects exposed

The bottom line is that there is no material difference in any rates for any events between the Adacel® to the Td groups.

Given that these are individuals over the age of 65, some SAEs occurred within 6 months of vaccination. There was also no difference in the rates of those between the Adacel® and the Td groups and no SAEs were considered to be related to vaccination:

	All n	%	Adacel (N=1170)			All n	%	DECAVAC (N=391)				
			95% CI	Related n	%			95% CI	95% CI	Related n	%	95% CI
Subjects with at Least One Such Event	49	4.2	(3.1; 5.5)	0	0.0	(0.0; 0.3)	20	5.1	(3.2; 7.8)	0	0.0	(0.0; 0.9)
Death	3	0.3	(<0.1; 0.7)	0	0.0	(0.0; 0.3)	2	0.5	(<0.1; 1.8)	0	0.0	(0.0; 0.9)
Life Threatening	3	0.3	(<0.1; 0.7)	0	0.0	(0.0; 0.3)	0	0.0	(0.0; 0.9)	0	0.0	(0.0; 0.9)
Required or prolonged inpatient hospitalisation	44	3.8	(2.7; 5.0)	0	0.0	(0.0; 0.3)	18	4.6	(2.8; 7.2)	0	0.0	(0.0; 0.9)
Persistent or significant disability/incapacity	2	0.2	(<0.1; 0.6)	0	0.0	(0.0; 0.3)	0	0.0	(0.0; 0.9)	0	0.0	(0.0; 0.9)
Congenital anomaly/birth defect	0	0.0	(0.0; 0.3)	0	0.0	(0.0; 0.3)	0	0.0	(0.0; 0.9)	0	0.0	(0.0; 0.9)
Other important medical event	4	0.3	(<0.1; 0.9)	0	0.0	(0.0; 0.3)	1	0.3	(<0.1; 1.4)	0	0.0	(0.0; 0.9)

With respect to immunogenicity, the seroprotection rates (e.g., the proportion of people having at least ≥ 0.1 IU of antibody / mL of serum for tetanus or diphtheria) did not materially differ between the Adacel® and the Td groups following vaccine, nor did the booster response rates or the geometric mean concentrations (GMC) of antibody to each of the vaccine components. Comparing the pertussis response pre- and post-vaccination, a 4- to 15-fold rise was observed in the antibody levels to each of the 4 pertussis components in the vaccine.

In order to interpret the likely efficacy of the vaccine, sanofi pasteur took advantage of the Storsaeter et al study, which is nested household contact study that was nested within the pivotal Sweden I efficacy trial. During this study, blood was draw periodically from the persons in the household with a vaccinated child and then monitored for disease. Once pertussis was detected in the household, blood was again draw to determine who developed pertussis disease. A regression was then done against the last known pre-exposure serum levels and antibodies to determine which sera levels were actually protective [Storsaeter J, *et al.* Levels of anti-pertussis antibodies related to protection after household exposure to *Bordetella pertussis*. Vaccine 1998;16(20):1907–1916]. It is a general truism that protection cannot be predicted from pertussis antibody levels, given that so many different antibodies are used in vaccines.

For example, the US has licensed 1-, 2-, 3-, 4-, and 5-component vaccines. Obviously, the 1-component vaccine has no antibody to the other components, yet it still protects. Based on all of the studies taken together, protection is based not only which component, but also on how much of each component and how they are made. This is quite complex, but within a given family of vaccines, antibody levels can be correlated within protection. This study provides those correlations, and similar correlations can be made based on the original efficacy trials for other vaccine types. Kohberger and colleagues subsequently worked with Storsaeter and colleagues to generalize their regression equations to apply them to other studies, and those have been published. When applied to the Storsaeter et al data, the projected efficacy among the > 65 population with a single dose of Adacel® is 80%.

Thus, sanofi pasteur concludes that the safety profile shows no material difference from the standard licensed Td vaccine. In terms of tetanus and diphtheria immunogenicity, there is no material difference from standard licensed Td vaccine. Regarding pertussis immunogenicity, there were robust responses (4.4- to 15.1-fold GMC increases) to all pertussis antigens contained in the vaccine.

Immunogenicity and Safety of Boostrix® in Subjects 65 Years of Age and Older

**Wayde M. Weston, PhD
GlaxoSmithKline**

Dr. Weston reported on the immunogenicity and safety of Boostrix® administered to subjects 65 years of age and older. Boostrix® is GlaxoSmithKline's (GSK's) Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine. It is licensed in 64 countries worldwide. This vaccine was first approved in the US in 2005 for use in those 10 through 18 years of age. In 2008, the upper age limit was raised to 64 years. Over 28 million doses have been distributed globally since the first approval in 1999, and over 16 million doses have been distributed in the US since that time. As head throughout the day, the age for pertussis does not end at age 64. Individuals 65 years of age and older are also susceptible to pertussis infection and illness and can transmit the disease to infants who are not yet completely protected through vaccination. Therefore, GSK has investigated the safety and immunogenicity of Boostrix® vaccine in adults 65 years of age and older. The goals of the development of a program for those aged 65 years and older are to demonstrate seroprotection against diphtheria and tetanus comparable to currently available Td vaccine; demonstrate the immunogenicity of pertussis components and assess with respect to disease protection through immunobridging to the infant efficacy study; and evaluate reactogenicity and safety relative to the currently available Td vaccine.

Data on the immunogenicity and safety of Boostrix® in subjects 65 years of age and older are from two clinical studies. The data presented during this session were primarily from Pivotal Study 011, which was a randomized, observer blind, multicenter study comparing Boostrix® to a US-licensed Td vaccine (Decavac® manufactured by sanofi pasteur). Pivotal Study 011 was comprised of a total of 887 subjects 65 years of age and older who received Boostrix®. The study design and all study objectives discussed with and agreed to by the Center for Biologics Evaluation and Research (CBER) prior to study initiation. A second study, Supportive Study 008, was a randomized, open label study of Boostrix® co-administered with influenza vaccine in subjects 19 years of age and older. The primary analysis cohort for this study was comprised of 19 through 64 year olds. Data from this age group is included in the current Boostrix® label. In addition, 217 subjects 65 years and older received Boostrix® in this study. These subjects

provided proof of concept data for this age group. A total of 1104 subjects 65 years of age and older received a single dose of Boostrix[®] between these two studies.

With regard to the design of Pivotal Study 011 (randomized, observer blind, multicenter study comparing Boostrix[®] to Decavac[®]), subjects were healthy individuals 65 years of age and older who had never received a Tdap vaccine and who had not had a Td booster in the previous 5 years. Subjects were randomized at a 2:1 ratio to receive either Boostrix[®] or Decavac[®]. All subjects had blood draws prior to vaccination on Day 0. Subjects reported local and general solicited symptoms on diary cards for 4 days following vaccination, and reported on unsolicited symptoms for 30 days following vaccination. About one month after receiving study vaccine, subjects returned for a post-vaccination blood draw and there was an additional 5-month safety follow-up period for collecting information on serious adverse events.

For Study 011, the vaccine composition for Boostrix[®] was 5Lf tetanus toxoid, 2.5Lf diphtheria toxoid, 8mcg pertussis toxoid, 8mcg filamentous hemagglutinin, 2.5 mcg pertactin, and ≤ 0.39 mg / dose aluminum. The vaccine composition for Decavac[®] was 5Lf tetanus toxoid, 2Lf diphtheria toxoid, and ≤ 0.28 mg / dose aluminum. Both are given intramuscularly and have the T antigen content and a similar D antigen content. Boostrix[®] also contains the three pertussis antigens. There are no pertussis antigens in Decavac[®], and both vaccines contain aluminium as an adjuvant.

Study 011 enrollment was comprised of 1332 subjects (887 Boostrix[®], 445 Decavac[®]). The mean age was just over 72 years of age, with an age range from 65 through 93 years of age. Approximately 25% of the subjects were 75 years of age and older. Of the subjects, 53.7% were female and 95% were White-Caucasians of European heritage. There were no apparent differences in subject characteristics between the vaccine groups.

In terms of the immune responses to diphtheria and tetanus antigens contained in both vaccines, similar proportions of subjects in both the Boostrix[®] and Td groups had seroprotective concentrations of anti-diphtheria and anti-tetanus antibodies. Similar proportions of subjects in both groups also achieved antibody concentrations of approximately 10 times the seroprotective of antibody for both anti-diphtheria and anti-tetanus antibodies. With respect to antibody GMCs, both groups had similar post-vaccination levels of anti-diphtheria. Post-vaccination anti-tetanus GMCs were higher in the Td group than in the Boostrix[®] group, so subjects who received both Boostrix[®] and Td achieved similarly high anti-tetanus seroprotection rates, with no appreciable differences between the groups. The difference in anti-tetanus GMCs is unlikely to be clinically relevant. Regarding the antibody GMCs for the three pertussis antigens contained in Boostrix[®] before and after vaccination, robust increases were observed in GMCs for anti-pertussis toxoid, filamentous hemagglutinin, and pertactin in the Boostrix[®] group. As expected, there were no pertussis responses in the Td group.

There was no pertussis comparator in Study 11, given that there is no pertussis vaccine licensed in the US for us in this age group. In agreement with the FDA prior to the conduct of this study, criteria for licensure in adults 65 years of age and older included an immunobridge; that is, a comparison of post-vaccination antibody levels in subjects 65 and older to those observed in a previous pertussis vaccine efficacy study (APV-039) conducted in Germany of a 3-dose DTaP series given with Infanrix[®] at 2, 4, and 6 months. In this household contact study (APV-039), the efficacy of Infanrix[®] in preventing pertussis was shown to be 89% (anti-PT: 45.7; anti-FHA: 83.6; anti-PRN: 112.3). The same immunobridge approach was part of the basis of licensure for Boostrix[®] in adolescents 10 through 18 years of age and adults 19 through 64

years of age. Pertussis antibody GMCs (EL.U/mL) in Study 11 were comparable to those in APV-039 for infants and adults aged 65 and older (anti-PT: 48.9; anti-PRN: 104.7), while the anti-FHA GMCs are much higher in 65 and older population (689.1).

For the non-inferiority comparisons done for the study, Boostrix[®] was compared to Td vaccine with respect to percentages of subjects with defined anti-diphtheria and anti-tetanus levels. Boostrix[®] was also compared to the 3-dose Infanrix[®] series with respect to pertussis antibody GMCs. The criteria for non-inferiority were satisfied for all study comparisons as reflected in the following table:

Endpoint	Measure	Value	95% CI (LL, UL)	Non-inferior?
% Anti-D \geq 0.1	LL of 95%CI for difference (Boostrix-Td) \geq -10%	-1.71%	(-5.59, 2.48)	Yes
%Anti-D \geq 1.0	Not defined	0.88	(-4.88, 6.65)	ND
%Anti-T \geq 0.1	LL of 95%CI for difference (Boostrix-Td) \geq -10%	-0.74	(-2.54, 1.41)	Yes
%Anti-T \geq 1.0	LL of 95%CI for difference (Boostrix-Td) \geq -10%	-1.20	(-4.59, 2.50)	Yes
Anti-PT GMC	LL of 95%CI for ratio (Boostrix/Infanrix) \geq 0.67	1.07	(1.00, 1.15)	Yes
Anti-FHA GMC	LL of 95%CI for ratio (Boostrix/Infanrix) \geq 0.67	8.24	(7.45, 9.12)	Yes
Anti-PRN GMC	LL of 95%CI for ratio (Boostrix/Infanrix) \geq 0.67	0.93	(0.79, 1.10)	Yes

Regarding vaccine safety, solicited local symptoms included injection site pain, redness, and swelling within 4 days of study vaccination. Boostrix[®] appears to be similar to Td vaccine with respect to local reactogenicity. For both vaccines, Grade 3 symptoms are reported at low frequency and are similar between the two vaccine groups. Solicited general symptoms reported within 4 days of vaccination included fatigue, fever, gastrointestinal symptoms, and headache. Again, Boostrix[®] is comparable to Td vaccine with respect to reporting of these solicited general symptoms. Grade 3 intensity symptoms were again reported with low frequency and were similar between the two vaccines.

For Study 011, unsolicited adverse events within 31 days of vaccination were reported by 152 Boostrix recipients (17.1%) and 64 Td recipients (14.4%). Grade 3 adverse events were reported by 13 Boostrix[®] recipients (1.5%) and 11 Td recipients (2.5%). Severe adverse events within 31 days of vaccination were reported by 6 Boostrix[®] recipients (0.7%) and 4 Td recipients (0.9%). Severe adverse events over entire study period (6 months) were reported by 37 Boostrix[®] recipients (4.2%) and 10 Td recipients (2.2%). There were 5 fatalities, of which 4 occurred in the Boostrix[®] group (2 CVA, 2 MI) and 1 occurred in the Td group (non-small cell lung cancer). No serious adverse events were considered by study investigators to be related to vaccination.

Dr. Weston briefly discussed Study 008 in which Boostrix[®] was co-administered with influenza vaccine in a subset of subjects 65 years of age and older. This was a randomized, open label study of Boostrix[®] co-administered with influenza vaccine in a primary cohort of subjects 19 years of age and older. This study included a cohort of 221 subjects 65 years of age and older to provide proof of concept data for this age group. Subjects received Boostrix[®] co-administered with Fluarix[®] (n=112) or Boostrix[®] given 1 month after Fluarix[®] (n=105). In both groups, Boostrix[®] vaccination led to increases in antibody GMCs for all vaccine antigens, and increases in percentages of subjects with seroprotective levels of D and T antibodies. Local and general reactogenicity were similar between groups.

In conclusion, studies have concluded that Boostrix[®] is immunogenic in adults 65 years of age and older. Immune responses to D and T antigens are non-inferior to those produced by Td vaccine. Immune responses to acellular pertussis antigens are non-inferior to those observed following a 3-dose primary pertussis vaccination series, in a study where vaccine efficacy was demonstrated. No increase was observed in local and general reactogenicity compared to Td vaccine, despite additional antigen components. The overall safety profile in this age group was found to be comparable between Boostrix[®] and Td vaccine.

Discussion Points

For Boostrix[®] co-administered with influenza vaccine, Dr. Duchin asked whether the levels of pertussis-related antibodies comparable to administration without influenza vaccine.

Though he did not have this data with him, Dr. Weston recalled that the levels were comparable between the two vaccine groups regardless of whether they received influenza vaccine.

Dr. Whitley-Williams (NMA) requested that Dr. Decker comment on the diversity of the study population, particularly as it relates to the diversity within the US population.

Dr. Decker replied that he did not have this information readily available.

Dr. Keitel inquired as to whether influenza vaccine responses were assessed, and whether anyone had antibody persistence data.

Dr. Westin responded that they did assess influenza vaccine responses, which were found to be comparable regardless of whether Boostrix[®] was co-administered. Regarding antibody persistence data, they only have the antibody levels one month after vaccine.

Dr. Decker indicated that they also had only antibody levels one month following vaccine.

Dr. Baylor (FDA) asked whether there additional data on immunobridging and the endpoints in any of the studies discussed. Even though they were not discussing licensure, the criteria for licensure would be a link to the infant data.

Dr. Decker replied that the only data he had with him were those that he showed. There are multiple criteria for licensure, including the conduct of an endpoint clinical trial. With respect to bridging back to the infant study, as he recalled the data, some of the antibody levels were higher and some lower than following a full infant primary series.

Dr. Baylor indicated that it would be useful for the ACIP members to see those data.

Dr. Clark (SME) reported that the work group did review these data, and that Dr. Liang would be reporting their interpretation of the conclusions of the bridging study.

Dr. Cieslak inquired as to whether there were any data on co-administration with pneumococcal or zoster vaccine.

Drs. Decker and Weston indicated that they did not have any data on co-administration with these vaccines.

In relation to the antibody data, Dr. Plotkin (Consultant, sanofi pasteur) emphasized that although it is often said that there are no correlates of protection, he believes this to be incorrect. There are good correlates of protection, it's just that they are multiple. Not only do the Storsaeter et al data show this, but also Jim Cherry's household efficacy studies show this. As long as certain levels are reached, one can expect efficacy regardless of the age group involved.

Use of Tdap in Adults Ages 65 Years and Older

Dr. Jennifer L. Liang
ACIP Pertussis Vaccine Working Group
CDC / NCIRD

Dr. Liang presented an overview of the key topics discussed by the working group and the proposed recommendation on the use of Tdap in adults ages 65 years and older. She reminded everyone that infants have substantially higher rates of disease and the largest burden of death compared to other age groups. Many cannot be vaccinated and require other strategies for prevention of pertussis, such as cocooning. The low incidence in all adults is likely due to under-recognition and under-reporting of disease. The incidence of pertussis is somewhat lower in adults 65 years and older than adults aged 20 through 64 years. In several states (e.g., Arizona, Michigan, Minnesota and Wisconsin) the incidence of pertussis in adults 65 years and older is similar to or greater than (0.75 per 100,000 (Range: 0.2 – 1.6)) incidence among adults 20 through 64 years of age (2.1 per 100,000 (Range: 0.9-4.2)) and are significantly reduced compared to the overall US average incidence of 4.89 per 100,000 (Range: 2.6 – 8.8). In 2009, there were.

Of reported cases of pertussis in adults aged 65 years and older with known clinical symptoms, 96% coughed at least 14 days, 90% reported positively for paroxysms, 33% reported having "whoop," 27% experienced post-tussive vomiting, and 13% were hospitalized during their illness. Of those, 60% were hospitalized no more than 1 week, 3% were hospitalized greater than a month, and 6 (0.2%) cases died due to pertussis between 2000 and 2009. A review of the literature is consistent with these data [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System].

Outbreaks in this age group do occur, but few are reported due to under-recognition of disease in this age group. Prevention and control measures for this age group are limited to the use of antibiotics. The current Tdap recommendations limit the ability for use of vaccine in this age group and in settings such as an outbreak.

Several studies have provided evidence that household members were primarily responsible for transmission of pertussis to infants (75%–83%). Grandparents have been identified as a source as well. Sources of pertussis transmission to infants included: Parents (55%), Siblings (16%–20%), Aunts / Uncles (10%), Grandparents (6%–8%), and Caretakers (2%) [Wendelboe AM, et al. Transmission of *Bordetella pertussis* to Young Infants. *Pediatr Infect Dis J* 2007;26: 293–299; Bisgard KM et al. Infant pertussis: who was the source? *Pediatr Infect Dis J* 2004; 23(11):985–989]. Grandparents are increasingly becoming primary caregivers to their grandchildren. Up to 30% of working mothers have a grandparent provide childcare to children less than 5 years of age, and 35% of children between 0 to 3 years have received grandparent care during at least one 3-month period [Laughlin L. 2010. Who's Minding the Kids? *Child Care Arrangements* : Spring 2005 and Summer 2006. *Current Population Reports*, P70-121. U.S. Census Bureau, Washington DC, 2005; Vandell, DL, et al. 2004. Variations in Child Care by Grandparents During the First Three Years. *J Marriage and Family*. 66].

The following is the current Tdap recommendation for adults ages 65 years and older. Current language does not allow for permissive use of Tdap in this age group:

“Tdap is not licensed for use among adults aged >65 years. The safety and immunogenicity of Tdap among adults aged ≥65 years were not studied during U.S. pre-licensure trials. Adults aged ≥65 years should receive a dose of Td every 10 years for protection against tetanus and diphtheria and as indicated for wound management. Research on the immunogenicity and safety of Tdap among adults aged ≥65 years is needed. Recommendations for use of Tdap in adults aged ≥65 years will be updated as new data become available.”

During 2005 through 2010, there were 243 reports in adults 65 years of age and older given Tdap vaccine. Of these, 95.5% were non-serious reports. The most frequent adverse events after Tdap were local reactions. There were 11 serious reports, included 2 deaths among individuals with multiple underlying conditions. VAERS cannot assess causality, but it is unlikely both deaths could be related to the vaccine. Data suggest that the safety profile of Tdap vaccine in adults 65 years of age and older was as safe as Td vaccine. For Td vaccine, there were 28 serious reports (includes 3 deaths) of a total 404 for the same time period.

In summary of the immunogenicity data presented earlier by sanofi pasteur and GSK, diphtheria and tetanus antigens resulted in a non-inferior immune response to those produced by Td. In terms of pertussis antigens, Boostrix[®] (GSK) administration resulted in immune responses to pertussis antigens (PT, FHA, PRN) and were non-inferior to those observed following 3-dose primary pertussis vaccination series. For Adacel[®] (sanofi pasteur), immune responses were observed in all pertussis antigens (PT, FHA, PRN, FIM), but immune response to PRN was inferior to 3-dose primary pertussis vaccination series.

The working group interpretation of the safety and immunogenicity data was that post-marketing VAERS data support acceptable safety profile of Tdap vaccine. It is reassuring that there was no demonstrated increased risk of severe local or systemic adverse events, and that Tdap would provide pertussis protection to this age group. The working group recognizes that the burden of disease in adults ages 65 and older is under-recognized, but that grandparents and healthcare practitioners are potential sources of pertussis transmission to infants. Overall, the safety profile of Tdap is similar to that of Td for this age group. However, in the absence of data, the working group also discussed how the safety of Tdap may be impacted by the health of an older adult. The spectrum of health in this age group ranges from healthy individuals to

those with poor health. Working group members also raised the question about the cost-effectiveness of Tdap in this age group, and felt strongly that an economic analysis should be done in advance if Tdap is licensed for use in individuals aged 65 years and older. The working group unanimously supported a change to the Tdap recommendation and agreed that at this time, the goal of vaccinating this age group is cocooning.

Based on data presented to the working group, there was no demonstrated increased risk of severe local reactions or serious adverse events in adults ages 65 years and older. Given this, the working group felt that there should be some recommendations for Tdap in those aged 65 and older. However, because Tdap vaccine is not licensed for use in this age group, there was a range of opinions about how aggressive a recommendation for Tdap should be. Working group members came to a consensus on an overall permissive recommendation with a more directive statement in regard to individuals who are in direct contact with infants (e.g., cocooning). It was also agreed that if one of the Tdap products is licensed for use in individuals aged 65 years and older, the recommendations would be re-considered. Despite some differences in immunogenicity, the working group felt strongly not to express preference for a specific Tdap product, but that licensure would change this. The working group also consulted with Kenneth Schmader, the ACIP American Geriatric Society representative who provided valuable input and support for the proposed recommendation.

The working group unanimously supported the proposed recommendation and requested that ACIP consider the following proposed language. There are two parts to the proposed recommendation for use of Tdap in adults aged 65 years and older:

- For adults ages 65 years and older, a single dose of Tdap vaccine may be given in place of a tetanus and diphtheria toxoids (Td) vaccine, in persons who have not previously received Tdap.
- Adults ages 65 years and older who have or who anticipate having close contact with an infant ages less than 12 months (e.g., grandparents, child-care providers, and HCP) should receive a single dose of Tdap to protect against pertussis and reduce the likelihood of transmission of pertussis to infants ages less than 12 months.

Discussion Points

Regarding the immunogenicity of the two products, Dr. Duchin noted that they saw the data on Boostrix[®], which is comparable for the primary series. Though they did not see the data, it was reported that the Adacel[®] response was inferior to the primary series. However, no preference was stated in the recommendation for either antigen.

Dr. Baker clarified that the Adacel[®] response was inferior to the primary series for only one antigen.

Dr. Liang confirmed that only one antigen, pertactin, did not meet the criteria.

Ms. Rosenbaum thought there was an argument to be made that because infants cannot be immunized and because it is a direct caregiving situation, a vaccine given for cocooning should be VFC reimbursable and ought to be part of a child's immunization entitlement. There have been some cases under Medicaid in which services for parents are recognized as a service to the child. She urged, in the strongest terms, collaboration between CDC and CMS to disseminate clarification information to states about situations in which either regular Medicaid

reimbursable rates or 100% VFC financing can be obtained. She said she was very concerned that there was a very important issue that could only be addressed by care for parents or grandparents, and she would like to see the loop closed on this.

Dr. Baker responded that while she loved this suggestion, it was not within ACIP's purview. However, CDC and CMS representatives were in the room who heard the suggestion.

Dr. Baylor cautioned everyone to be very careful when parsing out antigens on pertussis vaccines because these vaccines are evaluated as a whole. To say that non-inferiority was not met for one of the antigens cannot be trivialized because it is an important component. Regarding off label use, while he understood the intent, the manufacturers need to state their intents in terms of licensing these vaccines for those over 65 years of age.

Dr. Decker responded that sanofi pasteur fully intend to seek licensure for those over 65 years of age, and are actively engaged in that process.

Dr. Westin reported that GSK recently submitted a supplemental biologics license application (sBLA) for licensure in this age group.

Mr. Foster (APhA) pointed out that one issue which may arise in those over 65 years of age is that Medicare Part D plan will be approved for this as a pharmacy-based immunization. Td is not currently covered by Part B or D currently.

Dr. Turner (ACHA) noted that there will be a small cohort of individuals between the ages of 60 to 64 who have received Tdap who then turn 65. This recommendation needs to clarify that if someone has been previously immunized with Tdap, it is not necessary to receive it again after age 65. The second bullet of the recommendation does not refer to having received the vaccine previously.

Dr. Sawyer responded that it was the intent of the work group for that to be included, so the language from the first bullet that states "for persons who have not previously received Tdap" should be included in the second bullet.

Dr. Tan (AMA) noted that the first bullet sounded permissive because it states "may be given." He wondered whether that meant that Medicare Part D would not cover it.

Dr. Murphy (CMS) responded that she represents Medicaid not Medicare. She requested that someone email her with this question so that she could forward it to the appropriate person at the office.

Dr. Baker pointed out that if they vote affirmatively on this, they would be recommending that grandparents or great grandparents should be immunized if they care for a young infant.

Ms. Stinchfield (NAPNAP) liked the use of "close contacts" and not just grandparents. In the settings like the one in which she works, Children's Hospital of Minnesota, there are a number of elderly ladies in pink jackets who might be on a medical surgical floor rocking a baby with pertussis, and the next day will do the same in NICU.

Dr. Iskander offered a note of caution as a caveat to the VAERS data presented. During this whole period, there was not an age indication for those aged 65 and over to receive Tdap. Although he was not privy to this particular dataset, he thought it was likely that a large percentage of these are people who are intending to report medical errors. That likely

contributes to the interpretation of a very low percentage of adverse events reports. He could not think of a biological reason in which this would be less safe, but he wanted everyone to think as clearly as possible about what that data means and does not mean.

Dr. Cieslak liked the second paragraph for people with close contact. Given that the strategy is cocooning, and given that the rates of illness among persons over 65 are fractions of a case per hundred thousand, he wondered why the permissive recommendation. In general, he preferred to avoid permissive recommendations when possible.

Dr. Sawyer replied that one concern was that even seniors who do not have grandchildren themselves contact infants in community settings and other such places. If such a person were to seek a vaccine, they work group wanted to let the provider make the determination with that person about the risks and benefits of doing so.

Dr. Clark (SME) added that they did not want to preclude the opportunity to use Tdap in a nursing home outbreak, for example.

Dr. Baker inquired as to whether there are plans to conduct active surveillance in elders, who are significantly under-diagnosed in terms of this disease.

Dr. Clark (SME) replied that enhanced surveillance is in place. Some of the sites are included in the states in which the incidence is higher. The focus is on surveillance and diagnostics.

Dr. Campos-Outcalt asked whether there had been consideration for a local health department to vaccinate this age group if it is believed to be helpful to stop the outbreak, and who would pay for this in such a situation. It seemed that the payment issue may be a major hindrance in terms of controlling a local outbreak. There may also be situations in which there is a school case or a household with an older person in the home, such that there may be post-exposure considerations and preventive measures that need to be taken. This would place the recommendation into a higher category than "may."

Dr. Sawyer replied that in California, that is certainly what occurred. CDPH has recommended broad immunization in this age group. That was part of the reason to make the recommendation permissive. He did not know who was paying for it.

Dr. Schuchat added that CDC made additional resources available to supplement California's 317 dollars. Some of the funding was from the ARRA one-time only funds, and some of it was from the 317 discretionary dollars. Outbreak response can often be covered by discretionary dollars.

Ms. Rosenbaum pointed out that the issue of permissive language was going to arise during the next discussion as well. As she understood it, they were talking about clinical discretionary judgment versus discretion in coverage design. This will repeatedly arise if they do not refine the terminology to clarify clinical judgment and payer conforming to clinical judgment.

Dr. Baker responded that the discretionary terminology gives the physician and patient some options; however, the insurance is quite variable in terms of private insurance.

Dr. Schuchat pointed out that there were different degrees of permissive recommendations. One factor that Dr. Liang mentioned was that this vaccine is not yet licensed for this age group. Although a path is being followed for potential future licensure, cost-effectiveness data have not yet been presented for any sort of routine recommendation upon licensure. The discussion

during this session was in the backdrop of these outbreaks in terms of whether there should be direction from ACIP and cocooning in that age group prior to licensure.

Dr. Sawyer reported that there was version of the first bullet language that included the example of an outbreak. He asked whether Dr. Rosenbaum thought including this would be beneficial.

Ms. Rosenbaum responded that there were now three levels of discretion: 1) discretionary practice due to unapproved use of vaccine, 2) discretionary practice due to clinical judgment, and 3) discretionary judgment in coverage design. She thought they needed to work on the terminology to ensure that all three of these are clear, and that the payer does not interpret this as coverage being discretionary. The recommendation binds the payer and they should not have to be concerned about whether 317 funding is available. As she read PPACA, payer design is supposed to conform to public health practice.

Dr. Tan (AMA) thought this begged the question, "What is ACIP's will on this?" If the desire was to make the vaccine available to physicians to administer to those over the age of 65 for whatever reason, he would keep the recommendation as written and would not specify with examples. That will allow coverage flexibility. However, if the desire was about an outbreak control situation and that was the only time it should be used, they should specify that. As written, he was not convinced that some payers would pay based on the first bullet.

Dr. Duchin commented that the primary rationale for this recommendation was a cocooning strategy to prevent transmission to infants from those over the age of 65. With that in mind, he suggested leading with and emphasizing that recommendation. He also suggested that they remind people that routine vaccination of adults over the age of 65 is not recommended and that they could use examples such as flexibility during outbreak control. Just about everyone they would want to vaccinate falls within the second bullet. He was concerned that this would be taken as an implicit routine recommendation for those over 65 years of age. However, they are not a major player in pertussis transmission in the community setting.

Dr. Baker agreed that if they reversed the first and second bullets, it would send a stronger message about the important cocooning group.

Dr. Englund agreed but did not want more specification in second bullet which would become the first bullet. There are outbreaks in various settings, and with transplant patients, she needs the freedom to make larger level cocooning decision about outbreaks outside of just an individual's immediate setting.

To further clarify the payment issues under PPACA, Dr. Judson pointed out that requiring coverage for ACIP recommendations takes effect immediately. He wondered whether the act would distinguish between permissive recommendations and consider recommendations for which the vaccine is not licensed. He also wondered how many instances of infant pertussis cases were traceable to someone over the age of 65.

Dr. Baker responded that this question was the question that would be submitted to CMS.

Regarding the link to infant pertussis cases and those over the age of 65, Dr. Liang replied that based on the two studies reviewed, grandparents were identified as a source 6% to 8% of the time.

Katie Brewer (ANA) felt that the second bullet was very important to the discussion of cocooning, but it was not clear to her that it was inclusive enough (e.g., that all people with close contact with an infant should acquire Tdap vaccine).

Dr. Baker responded that the 2006 recommendation already mentions everyone in contact with infants. It specifically mentions household contacts, and this would be an addition to that. This is very comparable to what has already been said about those under 65 years of age who have contact with infants.

Dr. Marcy emphasized that at some point, consideration would need to be given to a Tdap booster.

Dr. Baker responded that information would be forthcoming on this issue, which would be revisited at that time.

Motion: Use of Tdap in Adults Ages 65 Years and Older

Ms. Rosenbaum made a motion to accept the language as proposed, but with the reversal of the first and second bullets. Dr. Cieslak seconded the motion. The motion carried with 12 affirmative votes, 0 negative votes, and 1 abstention.

Use of Tdap in Under-Vaccinated Children Ages 7 through 10 Years

Dr. Jennifer L. Liang
ACIP Pertussis Vaccine Working Group
CDC / NCIRD

Dr. Liang explained that the objective for the proposed recommendation for the use of Tdap in under-vaccinated children ages 7 through 10 years of age is to provide protection from pertussis to these children with incomplete or unknown pertussis vaccine history. The Pertussis Working Group's primary concern was a review of Tdap safety data in this age group. With limited immunogenicity data, it is difficult to extrapolate immunogenicity in this age group because of the differing prior vaccine histories. In the current pertussis vaccine schedule, the last childhood booster is for pre-school age at 4 through 6 years, then the adolescent booster at 11 years. This leaves a gap for under-vaccinated 7 through 10 year olds who are currently not recommended to receive a Tdap booster in a catch-up schedule.

The current language in the Tdap statement for incomplete pediatric DTP / DTaP vaccination history states that"

- Neither Tdap vaccine is licensed for use in children aged <10 years.
- Children aged 7–10 years who never received a pediatric DTP / DTaP / DT dose or a Td dose generally should receive 3 doses of Td.
- When these children become adolescents (aged 11–18 years), they should receive Tdap according to the routine recommendations and interval guidance used for adolescents who completed the childhood DTP / DTaP series.

Coverage of DTaP at school entry is 97.3% (range 74%-100%) for children who are up-to-date on the complete series. This means that for some states, up to 26% of children would be eligible for Tdap in a catch-up schedule [CDC. School Vaccination Coverage Assessment Kindergarten Report Results for all Grantees - School Year 2009-10]. Several studies have provided evidence that household members were primarily responsible for transmission of pertussis to infants. Siblings have been identified as a source of pertussis transmission to infants, which is another reason why under-vaccinated children should receive a Tdap vaccine.

In the interest of time, GSK permitted Dr. Liang to present on their behalf. Study 711866/001 was a comparison of Tdap-IPV to Tdap in children 4 through 8 years of age who had received 4 previous doses of infant formulation acellular pertussis containing vaccine. The comparison between children 4 through 6 and 7 through 8 was not a defined comparison for this study but a post-hoc assessment done for the purposes of this discussion. Subjects received either Tdap-IPV (N=822) or separate Tdap and IPV vaccines (N=136). 118 Tdap-IPV recipients were 7-8 years of age.

With regard to the incidence of solicited local symptoms (e.g., pain, redness or swelling at the injection sites) observed within 48 hours of vaccination, the incidence of local symptoms of any intensity was similar between children 4 through 6 and 7 through 8 years of age receiving Tdap as a 5th dose of acellular pertussis vaccine. The incidence of Grade 3 pain (e.g., pain which prevented normal activities), redness ≥ 50 mm in diameter, or swelling ≥ 50 mm in diameter, was low overall and similar between the age groups. For all general symptoms within 48 hours of receiving Tdap-IPV vaccine in children 4 through 6 and 7 through 8 years of age, the incidence appeared to be similar between younger and older children. For some symptoms, incidence appears less in 7 through 8 year olds than in 4 through 6 year olds, but with wide confidence intervals around the incidences data must be viewed with caution. Incidence of Grade 3 symptoms (e.g., preventing normal daily activities, or in the case of loss of appetite, not eating at all) or fever $>39^{\circ}\text{C}$, was low overall and did not appear to differ between the age groups. Unsolicited adverse events were reported by 35.7% of Tdap-IPV recipients 4 through 6 years of age, and 24.6% of recipients 7 through 8 years of age. There were no apparent differences between the age groups in the nature of unsolicited symptoms reported, and no serious adverse events were reported by Tdap-IPV recipients 7 through 8 years of age.

Immune responses to vaccine were measured 1 month after vaccination. In both age categories, all subjects were found to have seroprotective levels ($>0.1\text{IU/mL}$) of anti-diphtheria toxoid antibody, and all but 1 subject in the 4 through 6 year old category had seroprotective levels of anti-tetanus. Post-vaccination GMCs for antibodies to pertussis antigens were comparable between age groups, and in both age groups were greater than those observed in a clinical study demonstrating protective efficacy of a 3-dose Infanrix[®] series.

The conclusions from this study were that there were no apparent differences in reporting of solicited or unsolicited adverse events between children 4 through 6 years of age and 7 through 8 years of age who received Tdap-IPV as a 5th dose of acellular pertussis vaccine. The available data indicates that Tdap vaccines should be well tolerated in children 7 through 9 years of age. Pertussis antibody levels post-vaccination were as high or higher than observed in the pivotal infant efficacy trial.

In addition to the data provided by GSK, the Working Group reviewed four published studies which were relevant, although in each case the studies replaced the 5th DTaP dose with Tdap in 4 through 6 year olds. There are subtle differences in the infant schedules. For this age group, the most commonly reported adverse events 14 to 15 days after receipt of Tdap were pain, redness, and swelling. Other reported adverse events included fever, sleep interference, and loss of appetite. Fewer adverse events were observed in Tdap recipients compared to those who received DTaP-IPV. Serious adverse events were reported, but only one was vaccine-related [Sänger R et. al. Booster vaccination and 1-year follow-up of 4-8-year-old children with a reduced-antigen-content dTpa-IPV vaccine. *Eur J Pediatr.* 2007 Dec;166(12):1229-36]. There was no demonstrated increased risk of severe local or systemic adverse events. The conclusion by the working group was that the reassuring Tdap safety profile for children fully vaccinated would likely not be different for under-vaccinated children ages 7 through 10 years. Again, limited immunogenicity data showed an immune response to receipt of Tdap [Langley et al; Meyer et al].

The working group discussed several points when considering the use of Tdap in 7 through 10 year olds. It is important to provide pertussis protection in under-vaccinated children despite the lack of a licensed Tdap product in this age group. Tdap is preferred over DTaP due to the reactogenicity profile. The recommendation would also be in line with the current recommendation for under-vaccinated adolescents and adults. A single dose of Tdap is preferred rather than multiple doses of Tdap. Use of Tdap would likely boost a child who is incompletely vaccinated or who has an unknown vaccine history, but likely has been exposed to pertussis. Currently, only a single dose of Tdap is recommended for adolescents and adults, but the need for revaccination will be addressed in the future. The working group considered that in the absence of data, children 7 through 10 year olds need not be re-immunized with Tdap at 11 through 12 year old visit. If revaccination is necessary, future recommendations for additional dose of Tdap will be forthcoming.

The Working Group unanimously agreed to the following proposed language:

“Children ages 7 through 10 years who are not fully immunized against pertussis* and for whom no contraindication to pertussis vaccine exists should receive a single dose of Tdap to provide protection against pertussis. If additional doses of tetanus and diphtheria toxoid-containing vaccines are needed, then children ages 7 through 10 years should be vaccinated according to catch-up guidance.”

Footnote:

*Children who have not received 5 doses of DTP / DTaP or 4 doses of DTP / DTaP if the fourth dose was administered at age 4 years or older. Children with unknown vaccine history should be considered not immunized.

“Children ages 7 through 10 years who have never been vaccinated against tetanus, diphtheria, or pertussis or who have unknown vaccination status should receive a series of three vaccinations containing tetanus and diphtheria toxoids. The preferred schedule is a single dose of Tdap, followed by a dose of Td >4 weeks after Tdap and another dose of Td 6–12 months later. If not administered as the first dose, Tdap can be substituted for any of the other Td doses in the series.”

Discussion Points

Dr. Keitel requested clarification regarding whether a child who received a dose of Tdap between the ages of 7 and 10 would still be eligible for a booster dose at age 11.

Dr. Liang responded that the working group does not recommend that at this point. A child who received Tdap at 7 to 10 years of age would not be revaccinated for the adolescent dose.

Dr. Sawyer clarified that the working group did not intend to be silent on this. The intent was to specifically state that these children should not be revaccinated, and that a recommendation regarding how to proceed with these children would be forthcoming along with recommendations for second doses in any other population.

Dr. Pickering noted that one of the adverse events that occurs with DTaP that occurs with Doses 4 and 5 is total limb swelling, which is very frightening to parents. In the GSK data pertaining to solicited local symptoms within 48 hours of vaccination, he inquired as to whether any of the cases with redness and swelling ≥ 50 mm in diameter had total limb swelling. With that in mind, he wondered whether language should be included to indicate that Tdap is not a contraindication or even a precaution for children who have had total limb swelling following the 4th or 5th dose of DTaP, and to offer assurance that if this does occur it is benign and will resolve with no residual after 24 hours.

Dr. Weston replied that with regard to limb swelling, there was a low incidence ≥ 50 mm in diameter; however, he did not recall observing any large or total limb swelling in that study.

Dr. Duchin was curious about why only one dose of Tdap would be recommended for children who are totally un-immunized between 7 to 10, and what the level of protection could be expected after only one dose in that age range.

Dr. Liang replied that the working group raised that question as well. Because of the current licensure and not wanting to recommend multiple doses, the working group felt that one dose of Tdap children of unknown vaccine history would likely have already been exposed to pertussis and that a single dose of Tdap would boost their immune system.

Regarding arm swelling, Dr. Sawyer pointed out that this particular regimen would not be recommended for a child who had received 5 doses already. It would be for those who had received 4 or less doses because they were under-immunized. In California, there was a lot of confusion about the intent of a recommendation in this age group. It is only for children who are not current on immunization.

Dr. Middleman (SAM) suggested that rather than saying not to give the vaccine at 11 to 12, it would be preferable to instruct people to wait for further guidance.

Dr. Keitel said the problem was that if one dose was given at age 10, that would be one year later.

Dr. Clark (SME) clarified that the intent was for those vaccinated with Tdap at 7 through 10 not to receive a second dose at 11 through 12 at this time, and to state that further guidance will be forthcoming.

Dr. Marcy expressed confusion about what they would be voting on. He requested that they defer the vote until the language was further clarified.

Dr. Englund emphasized that it would be important to include actual language because many states have 11 to 12 year old school recommendations.

Dr. Cieslak found the footnote wording to be mildly confusing. He did not believe it needed to be part of the official statement and requested that CDC work on this to perhaps break it into a couple of clauses.

Dr. Chilton made a motion to accept the revised language, and Dr. Meissner seconded. However, further discussion ensued with respect to revising the language.

Dr. Liang read the revised language into the record, which was as follows:

Children ages 7 through 10 years who are not fully immunized against pertussis and for whom no contraindications for pertussis vaccine exist should receive a single dose of Tdap to provide protection against pertussis. If additional doses of tetanus and diphtheria toxoid containing vaccines are needed, then children ages 7 through 10 years should be vaccinated according to catch-up guidance. Further guidance will be forthcoming on timing of revaccination in persons who have received Tdap prior to age 11 years.

Children ages 7 through 10 years who have never been vaccinated against tetanus, diphtheria, or pertussis or who have unknown vaccination status should receive a series of 3 vaccinations containing tetanus and diphtheria toxoid. The preferred schedule is a single dose of Tdap followed by a dose of Td more than 4 weeks after Tdap and another dose of Td 6 to 12 months later. If not administered as a first dose, Tdap can be substituted for any of the other Td doses in the series. Further guidance will be forthcoming on timing of revaccination in persons who have received Tdap prior to age 11 years.

Given that the footnote was confusing, the recommendation will refer to the current recommendations on the definition.

Dr. Keitel commented that she thought they had identified a research need to understand whether a single dose of pertussis containing vaccine is adequate for children who have not been immunized.

Dr. Middleman (ACP) suggested that the last sentence of first bullet regarding further guidance should also be the last sentence of the second bullet.

Dr. Liang indicated that they could add this to the second bullet as well.

Dr. Brewer (ANA) inquired as to whether the recommendation should read "children 7 through 9 years" because Boostrix[®] could be given at 10. There will be children who are entering 6th grade who are 10 who receive Boostrix[®] to get into school. This will muddle some of the considerations for who is compliant based on school mandates.

Dr. Liang responded that the working group considered this language, but given that the current Tdap is 11, they wanted to be more inclusive and say 7 through 10 years.

Dr. Clark (SME) noted that in general, guidance on revaccination of everyone will be forthcoming, not just these groups.

Dr. Sawyer pointed out that the intent of the revised language is to state that a child who receives Tdap between 7 through 10 years of age should be considered up to date for a school entry requirement. The follow-up sentence states that further guidance will be forthcoming.

Dr. Baker added that another issue is that one vaccine is licensed for 10 and above and another is licensed for 11 and above.

Dr. Hasbach (sanofi pasteur) thought clarity should be provided to schools and states. He did not think the indication of age 10 versus 11 was the issue. It was the actual wording of recommendation that the states have. Some say 6th grade and some say 6th grade and 11 years of age. He deferred to NACCHO, ASTHO, and school administrators' guidance on this.

Dr. Duchin agreed that comment clarity should be improved to define what constitutes "up to date" in this age range. He thought the sentence on further guidance should also be clarified.

Dr. Judson envisioned this getting completely out of control in terms of referring people to recommendations for 11 to 12 and then 13 to 14. Given the data, he wondered how far they could go with this such as 7 to 15.

Dr. Baker pointed out that there is already a routine recommendation at 11 and above.

Dr. Judson suggested consolidating these.

Dr. Liang stressed that this recommendation would be in line with the current adolescent catch-up schedule. It is basically the same language, but because the previous recommendation stated that 7 through 10 year olds were not recommended to receive Tdap.

Dr. Englund suggested that a comment be added to the note in the *MMWR* that these children will be considered caught up for the purpose of school immunization.

Dr. Plotkin pointed out that they were recommending one dose of acellular pertussis for a child who has never received pertussis antigen. This differs from those who received pertussis as infants. He thought this was asking a lot of essentially a sub-unit vaccine to have a response after a single dose. He suggested that this really needed to be studied if they were going to make such a recommendation.

Dr. Jane Zucker (New York City Department of Health) did not think they should make a statement that said "should be considered acceptable for school requirements." Every state defines that differently with a different number of tetanus and diphtheria containing doses. She thought they should be cautious about ACIP recommendations versus state requirements for school admission.

Dr. Baker though one could defer to the idea that if there is state requirement and a child received this schedule, that should be acceptable rather than making them receive another dose. She agreed with Dr. Englund's suggestion to put this in the language of the Notice to Readers.

Motion: Use of Tdap in Under-Vaccinated Children Ages 7 through 10 Years

Ms. Ehresmann made a motion to accept the revised language, which states the following:

Children ages 7 through 10 years who are not fully immunized against pertussis and for whom no contraindications for pertussis vaccine exist should receive a single dose of Tdap to provide protection against pertussis. If additional doses of tetanus and diphtheria toxoid containing vaccines are needed, then children ages 7 through 10 years should be vaccinated according to catch-up guidance. Further guidance will be forthcoming on timing of revaccination in persons who have received Tdap prior to age 11 years.

Children ages 7 through 10 years who have never been vaccinated against tetanus, diphtheria, or pertussis or who have unknown vaccination status should receive a series of 3 vaccinations containing tetanus and diphtheria toxoid. The preferred schedule is a single dose of Tdap followed by a dose of Td more than 4 weeks after Tdap and another dose of Td 6 to 12 months later. If not administered as a first dose, Tdap can be substituted for any of the other Td doses in the series. Further guidance will be forthcoming on timing of revaccination in persons who have received Tdap prior to age 11 years.

Given that the footnote was confusing, the recommendation will refer to the current recommendations on the definition.

Dr. Cieslak seconded the motion. The motion carried with 12 affirmative votes, 0 negative votes, and 1 abstention.

VFC Resolution Update: Vaccines to Prevent Diphtheria, Tetanus, and Pertussis

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

Dr. Rodewald explained that the purpose of this resolution is to revise the previous resolution to incorporate new recommendations regarding the interval between Tdap and last dose of Td for children aged 11 through 18 years of age, and to update recommendations for certain children between the ages of 7 and 10 years and to streamline the recommendation through the use of links to published documents. There are no differences in eligible groups, which include children and adolescents aged 6 weeks through 18 years.

Recommended Schedule, Intervals (1) is unchanged:

Recommended Schedule, Intervals (1)

Dose	Age
Primary 1	2 months
Primary 2	4 months
Primary 3	6 months
First Booster (1)	15-18 months
Second Booster (2)	4-6 years
Tdap or Td Booster (3)	11-12 years

(1) The first booster dose may be administered as early as age 12 months, provided 6 months have elapsed since the third dose.
(2) The second booster is not necessary before entering kindergarten or elementary school if fourth dose is administered on or after the fourth birthday.
(3) Tdap is preferred over Td. Tdap is preferred over Td as adolescents are susceptible to pertussis due to waning immunity. A Tdap or Td booster is recommended at any age from 11 through 18 years if they have completed the recommended childhood DTP/DTaP vaccination series and have not received a Td dose. In some special situations, Td, rather than Tdap may be indicated (more information is available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/r5503a1.htm?&_cid=r5503a1_e).

Recommended Schedule, Intervals (2) language also remains unchanged:

DTaP, DT, Tdap, and Td vaccine formulations

There are currently two licensed formulations of Tdap for adolescents, BOOSTRIX® and ADACEL®. BOOSTRIX® (Tdap) vaccine is indicated for active immunization of persons 10-18 years of age. ADACEL™ (Tdap) is indicated for active immunization of persons aged 11 years and older. Td vaccine is indicated for active immunization of persons 7 years of age or older for prevention of tetanus and diphtheria. For immunization of infants and children younger than 7 years of age against pertussis, tetanus and diphtheria, refer to the manufacturers' package inserts for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) or combination vaccines containing DTaP and for Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT). Use diphtheria and tetanus toxoids, adsorbed (DT or Td) if encephalopathy has occurred after administration of a previous dose of pertussis-containing vaccine. The use of brand names is not meant to preclude the use of other comparable licensed vaccines.

Changes in the Recommended Schedule, Intervals (3) are shown in blue for dosage intervals and minimum age. The footnote that the first one, Tdap / Td (6), refers to is modified and the previous resolution just referred to Td:

Recommended Schedule, Intervals (3)

Dosage Intervals	Minimum Age	Minimum interval between doses		
		Dose 2 to 3	Dose 3 to 4	Dose 4 to 5
DTaP	6 weeks	4 weeks	4 weeks	6 months
DTaP-HepB-IPV(2)	6 weeks	4 weeks	4 weeks	
DTaP-Hib-IPV(3)	6 weeks	4 weeks	4 weeks	6 months
DT	6 weeks	4 weeks	4 weeks	6 months
DTaP-Hib(4)	15-18 months			6 months
DTaP-IPV(5)	4 years			
Tdap/Td(6)	11 years			
Tdap/Td Catch-up schedule(7)	7 years	4 weeks	6 months	5 years

Table notes differ in that items 6 and 7 have been added:

Table Notes

Note: DT containing vaccines are not indicated for children > 6 years of age.

- (1) The fifth dose is not necessary if the fourth dose was given after the fourth birthday.
- (2) The combined DTaP-HepB-IPV vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. The combined DTaP-HepB-IPV vaccine is approved for the primary series only (Doses 1-3). For adequate immune response, the last dose of hepatitis B vaccine should be given at ≥ 24 weeks of age and therefore this combination vaccine should not be administered as a complete primary series on an accelerated schedule at 4 week intervals for prevention of pertussis.
- (3) The combined DTaP-Hib-IPV vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. The combined DTaP-Hib-IPV vaccine is approved for the primary series and first booster dose (Doses 1-4). The combined DTaP-Hib-IPV vaccine is not indicated for children 5 years of age and older.
- (4) The combined DTaP/Haemophilus influenzae type b (Hib) vaccine is only indicated for the fourth dose at age 15-18 months.
- (5) The combined DTaP-IPV vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. The combined DTaP-IPV vaccine is approved for the booster dose at age 4-6 years.
- (6) Tdap is indicated for a single booster dose at age 11 or 12 years if the childhood DTP/DTaP vaccination series has been completed. Tdap is preferred over Td as adolescents are susceptible to pertussis due to waning immunity, though Td may be indicated rather than Tdap in special situations (more information is available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5503a1.htm?s_cid=rr5503a1_e). Adolescents who did not receive Tdap at age 11 or 12 should receive a single dose of Tdap in place of a single Td booster dose. Tdap can be administered regardless of interval since last Td.
- (7) Tdap should be given to children 7 through 18 years of age who have received tetanus and diphtheria containing vaccines (DT or Td) instead of DTP/DTaP for some or all doses of the childhood series; have received fewer than 5 doses of DTP/DTaP or 4 doses if the fourth dose was administered at age 4 years or older; or have never been vaccinated against tetanus, diphtheria, or pertussis (no doses of pediatric DTP/DTaP/DT or Td). The preferred schedule is a single Tdap dose, followed by a dose of Td four weeks after the first dose and a second dose of Td 6-12 months later. If not administered as the first dose, Tdap can be substituted for any of the other Td doses in the series. More information about the catch-up is available in Appendix D at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5503a1.htm?s_cid=rr5503a1_e.

Of note, this appendix which was designed to provide catch up guidance for children aged 11 through 18 years, now applies to children aged 7 through 18 years. Tdap is preferred over Td as adolescents are susceptible to pertussis due to waning immunity, though Td may be indicated rather than Tdap in special situations (more information is available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5503a1.htm?s_cid=rr5503a1_e).

The resolution will be modified to match the language voted upon by ACIP, and recommended dosage and contraindications / precaution will be included, as will a statement regarding updates based on published documents:

Recommended dosage and Contraindications/Precautions

Recommended dosage

- Refer to product package inserts.

Contraindications and Precautions

- Contraindications and precautions can be found at:
- <http://www.cdc.gov/mmwr/preview/mmwrhtml/00041645.htm>
- http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5503a1.htm?s_cid=rr5503a1_e

Statement Regarding Update Based on Published Documents

[If an ACIP recommendation regarding vaccination against diphtheria, tetanus, and pertussis 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

Dr. Sawyer made a motion to accept the VFC recommendation as proposed. Dr. Chilton seconded the motion. The motion carried with 12 affirmative votes, 0 negative votes, and 1 abstention.

Evidence-Based Recommendations Work Group

Introduction

Jon Temte, MD, PhD, Chair

Evidence-Based Recommendations Work Group

Dr. Temte reminded everyone that the terms of reference for the Evidence-Based Recommendations Work Group (EBRWG) was to develop a uniform approach to making explicit the evidence base for ACIP recommendations. The EBRWG was reactivated in November 2007 and began monthly conference calls starting in January 2008. Since that time, the group has developed guiding principles and reviewed several evidence-based systems for developing guidelines. The guiding principles have focused on transparency; use of evidence of varying strengths; considering of individual and community health; and adopting or adapting an existing

system rather than re-creating something that may already exist. The approach has been to strive for continuous quality improvement of the process, and to apply the proposed process to new recommendations and changes to existing recommendations versus applying the process to all previous recommendations.

The key elements for consideration in terms of the components of evidence-based vaccine recommendations include safety, efficacy, and burden of illness. This aligns with the ACIP charter in terms of what this body should be considering when making recommendations. The working group is proposing an assessment method for use of existing evidence, a form that the recommendations should take, and the format for reporting the elements and evidence. The EBRWG has been reliant upon input and expertise from professional organizations (e.g., AAFP, AAP, ACP, AMA, AIM, NFID, and VA); methodological experts (GRADE and USPSTF); and vaccine advisory groups (NACI, and WHO-SAGE discussion group on EBR).

A number of EBRWG presentations had been delivered previously to ACIP. In February 2010, there was a review of methodological standards for clinical practice guidelines, guidelines for grading the quality of evidence were reviewed, and the proposed recommendations were synthesized and presented. In June 2010, organizational perspectives and endorsements were offered by AAFP, AAP, and ACP. A detailed reviewed review of the GRADE methodology was presented, and input was offered from WHO's Strategic Advisory Group of Experts (SAGE) regarding their approach and experience with evidence-based recommendations. There was also a presentation of a pilot approach to grading evidence as applied to some recent existing recommendation (e.g., rotavirus and MMRV).

The proposed ACIP evidence evaluation system consists of the adoption of the Grades of Recommendation Assessment, Development and Evaluation (GRADE) framework; use of proposed evidence grades of A, B, C, and D to express the confidence in the estimated effect on health outcomes based on the existing body of evidence; and use of two proposed recommendation categories: Category I (recommendation for, or against); and Category II (recommendation for individual clinical decision making).

Issues raised during the June 2010 ACIP meeting included the following:

- What are the ramifications of the terminology used?
- When would evidence grading be used?
- Why have four evidence levels?
- What if it is not possible to conduct randomized trials in subpopulations?
- Does GRADE take into account biologic information?
- Will cost-effectiveness studies be graded?
- Can GRADE assist in evaluating observational studies assessing risk factors?
- What support will be needed to implement GRADE?
- How will the GRADE approach be translated for the public?

Dr. Temte emphasized that what the working group desired in terms of a vote was to adopt the explicit evidence-based framework based on the GRADE framework. The terminology would not be voted upon as it would evolve over time, and enhancements will be made to the framework in the future. The framework and guidelines for cost analyses have been implicitly been accepted, and ACIP and all of its working groups are now reliant and dependent upon this framework in their discussions. The GRADE framework should be viewed as a similar approach to address the evidence used to make recommendations based on safety, efficacy, and other considerations.

Explicit Evidence-Based Framework Based on GRADE

Faruque Ahmed, PhD
National Center for Infectious and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Ahmed reiterated that the key elements for any ACIP recommendation include vaccine safety, efficacy, and burden of illness. Evidence subjected to the GRADE methodology would be applied to data on vaccine safety and efficacy. Indirect evidence assessment of burden of illness is used for estimates of number needed to treat (NNT) or number needed to harm (NNH).

The evidence-based framework has two components: 1) Proposed evidence grades for safety and efficacy (A, B, C, D); and 2) Proposed recommendation categories (Category I, Category II). Evidence grade is only one factor in developing a recommendation. Other factors include balance of benefits and harms, values, and economic data. As noted by Dr. Temte, economic studies will not be graded. The definitions of the evidence grades are as follows:

- A Further research is unlikely to change the estimated effect on health outcomes
- B Further research may change the estimated effect on health outcomes
- C Further research is likely to change the estimated effect on health outcomes
- D Available data are insufficient to provide a reliable estimate of the effect on health outcomes

A and B are often considered to be good levels of evidence. Further research may not always be possible. The grading of evidence begins with the study design. Randomized controlled trials (RCTs) are initially rated as Grade A and observational studies as Grade C. Five factors can lower the grade: study limitations (e.g., lack of blinding), inconsistency, indirectness (e.g., use of immunogenicity as a surrogate for disease outcomes), imprecision (e.g., wide confidence intervals due to small sample sizes), and publication bias. Three factors can increase the grade: strength of association, dose-response, and direction of plausible residual confounding.

A recommendation may be upgraded by one level if there is a strong association such as a relative risk > 2 or vaccine efficacy of > 50% from at least two observational studies with no plausible confounders. A grade may be upgraded by two levels if there is a very strong association such as a relative risk > 5 or vaccine efficacy of > 80% based on direct evidence. A hypothetical example of upgrading based on the direction of all plausible residual confounding or bias would be that vaccine X is suspected of being associated with adverse event Y. Publicity about the potential adverse event may result in an increased spontaneous reporting of adverse event Y in vaccinated persons compared to that in unvaccinated persons. The epidemiological studies find no association. The initial grade of C can be upgraded to B because no association is found despite the bias associated with differential reporting due to publicity.

Examples of application of the grading post-licensure vaccine safety studies include Rhesus-based tetravalent rotavirus vaccine (Rotashield) and combination Measles, Mumps, Rubella, and Varicella vaccine (MMRV).

The Rotashield vaccine was withdrawn from the US market in 1999 due to a reported association with intussusception. The grade of evidence for intussusception associated with Rotashield vaccine was based on 2 cohort and case-control studies available at the time the ACIP withdrew its recommendation for use of this vaccine. Ecological studies were excluded. There were no serious study limitations, inconsistencies, indirectness, or imprecisions. The initial Grade of C was upgraded by two levels because relative risk of intussusception for vaccinated compared to unvaccinated infants is > 5 . This upgrade was based on the strength of association criterion.

Another example is evidence grades for MMRV vaccination associated with febrile seizure following Dose 1 compared with separate injections of MMR and V vaccines for the 5- to 12-day and 13- to 30-day windows for children ages 12 through 23 months. Two observational studies, one sponsored by Merck and the other by CDC, showed an increased risk of febrile seizure 5 to 12 days following the Dose 1 of MMRV vaccine. The initial evidence grade of C for the 5- to 12-day window was upgraded one level to Grade B because the relative risk was approximately 2 based on consistent evidence from two studies for which there were no serious study limitations, inconsistencies, indirectness, or imprecisions (*strength of association*). The initial evidence grade of C for the 13- to 30-day window was downgraded by one level to D because of imprecision. One study indicated a decrease but not significant, and one study found no association.

The key considerations for formulating recommendations include evidence grades for safety and efficacy, the balance of benefits and harms, and the values attributed to benefits and harms by persons making recommendations. Modifications can be made, if warranted, by consideration of economic analyses (e.g., cost-effectiveness). In general, the higher the burden of disease, the higher the net benefit of vaccination.

The proposed ACIP recommendation categories include:

- Category I (recommendation for, or recommendation against)
 - Universal recommendation
 - Risk-based recommendation
- Category II (recommendation for individual clinical decision making; similar to what is currently referred to as a permissive recommendation)
- No recommendation / unresolved issue

Considerations that may result in a Category II recommendation include smaller net benefit, lower evidence grade, variability in values attributed to benefits and harms, and uncertainty about whether the net benefits are worth the costs (e.g., cost-effectiveness). For Category I recommendations, the working group proposed using words such as “recommend,” “recommend against,” “should,” “should not.” For Category II, the working group proposed using words like “may.” The proposed format for presenting ACIP recommendations would be as follows:

- ❑ Recommendation
 - ACIP recommends/does not recommend . . . (Recommendation category, Evidence level)
- ❑ Remarks
 - Explicit consideration of benefits, harms, evidence grade, cost-effectiveness, and values for making a recommendation should be described here
 - For recommendations based on lower evidence grades, the reasoning should be highlighted here

Proposed evidence tables would include benefits, harms, and evidence grades and would look like the following samples:

Outcome	No. of subjects (# studies)	Incidence in controls	Incidence in vaccinated	Vaccine efficacy (Relative risk)	Absolute risk	Number Needed to Treat (Harm)
Outcome 1						
Outcome 2						
Outcome 3						

Outcome	Design (# studies)	Study limitations	Inconsistency	Indirectness	Imprecision	Other considerations*	Evidence grade
Outcome 1							
Outcome 2							
Outcome 3							

*Strength of association, dose-response, plausible residual confounding, publication bias

Due to lack of space, some factors are included in the Evidence Grades table column titled “Other Considerations.”

The working group conducted a pilot by applying the GRADE framework to human-bovine reassortant pentavalent rotavirus vaccine (RotaTeq), as an example of using the framework with a new vaccine. Studies were used that were available at the time of the 2006 ACIP recommendation. Phase 3 studies of the pentavalent vaccine were included, Phase 1 and 2 studies that used a different vaccine formulation were excluded, and studies of rotavirus vaccines using other rotavirus strains (e.g., human-rhesus, human, lamb, bovine) were excluded. The benefits and safety tables would appear as follows:

Outcome	No. of subjects (# studies)	Incidence in controls	Incidence in vaccinated	Vaccine efficacy (95% CI)	Absolute risk per 1000 (95% CI)	Number Needed to Treat (Vaccinate)
Rotavirus diarrhea (RV)	5,627 (2 RCTs)	12.9%	3.5%	73% (66, 78)	-94 (-85, -100)	11
Severe RV diarrhea	5,627 (2 RCTs)	2.0%	0.1%	97% (86, 99)	-19 (-17, -20)	52
Hospitalization for RV diarrhea	57,134 (1 RCT)	0.5%	0.02%	96% (91, 98)	-5 (-5, -5)	205

*Incidence over one full rotavirus season after vaccination.
RCT: Randomized controlled trial.

Outcome	No. of subjects (# studies)	Incidence in controls	Incidence in vaccinated	Relative Risk (95% CI)	Absolute risk per 1000 (95% CI)	Number Needed to Harm
Intussusception	70,139 (3 RCTs)	1.4 per 10,000	1.7 per 10,000	1.20 (0.37–3.93)	0.03 (-0.1, 0.4)	-
Other serious adverse events	70,139 (3 RCTs)	2.3%	2.2%	0.96 (0.87–1.06)	-1 (-3, 1)	-
Fever	10,915 (3 RCTs)	38.9%	37.7%	0.97 (0.92–1.01)	-12 (-31, 4)	-

For the outcome rotavirus diarrhea, the initial grade for the body of evidence was A based on the study design. There were no serious study limitations, indirectness, or imprecision. The final evidence grade was A for this and the other outcomes. In terms of formulating a recommendation, benefits were found to be large compared to the potential harms. With respect to values, parents are likely to place high value on preventing severe rotavirus diarrhea. Regarding cost-effectiveness, the vaccine price was not known at the time ACIP was making the recommendation. An analysis was done that showed that the vaccine was likely to be cost-saving from the societal perspective at a cost of \$42 per dose.

Using the proposed format, the ACIP recommendation for the use of rotavirus vaccine (RotaTeq) would appear as follows:

Recommendation: ACIP recommends vaccination of U.S. infants with three doses of rotavirus vaccine administered orally at ages 2, 4, and 6 months (recommendation category: I, evidence grade: A).

Remarks: Nearly every child in the U.S. is infected with rotavirus by age 5 years, resulting in approximately 410,000 physician visits, 205,000–272,000 emergency department visits, and 55,000–70,000 hospitalizations each year. Benefits of vaccination are large compared to potential harms.

An example of a risk-based recommendation would be as follows:

Recommendation: Pneumococcal polysaccharide vaccine should be administered to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant.
(recommendation category: I, evidence grade: ...).

Remarks: ...

An example of a Category II recommendation would be as follows:

Recommendation: The 3-dose series of quadrivalent human papillomavirus vaccine (HPV4) may be given to males aged 9 through 26 years
(recommendation category: II, evidence grade: ...).

Remarks: ...

An example of a recommendation against would be as follows:

Recommendation: ACIP recommends that the 2010-11 Afluria vaccine should not be administered to children aged 6 months through 8 years. (recommendation category: I, evidence grade: ...).

Remarks: ...

Dr. Ahmed reminded everyone of the issues raised during the June 2010 ACIP meeting, and responded to each of these.

What are the ramifications of the terminology used?

With regard to the concern about how recommendations based on evidence grades C or D may be perceived, it will be important to explain the rationale clearly. The grades reflect the confidence in a vaccine's estimated effect on health outcomes:

- A: Estimated effect unlikely to change
- B: Estimated effect may change
- C: Estimated effect likely to change
- D: Not possible to provide a reliable estimate of the effect

Stating that a recommendation is based on C or D level evidence can drive the research agenda, which is very valuable.

When would evidence grading be used?

Evidence grading would be used for new recommendations, and for updates to existing recommendations. Key recommendations should be graded, and current ACIP recommendations are to be grandfathered in.

Why have four evidence levels?

The rationale for having four evidence levels is for uniformity with other organizations that have adopted the GRADE approach. Unsystematic observations would have the lowest level of D (e.g., case reports, case series). Observational studies are initially graded as C, which may be upgraded or downgraded.

What if it is not possible to conduct randomized trials in sub-populations?

GRADE's indirectness criterion can be used to assign evidence grade for sub-populations not included in trials. Experts judge applicability of the evidence for the general population to sub-populations. One example is rotavirus vaccine. The evidence grade for vaccine efficacy in healthy infants is an A. Efficacy data are not available for infants with chronic gastrointestinal tract diseases. Based on experts' judgment of the applicability of the evidence, the evidence grade may be assigned as B or C using GRADE's indirectness criterion.

Does GRADE take into account biologic information?

Biologic information may be taken into account when assessing applicability of indirect evidence. Examples include applicability of evidence for the general population to subpopulations, applicability of evidence for an old vaccine to a new formulation of the vaccine, and applicability of evidence for surrogate outcomes to long-term outcomes (e.g., precancerous lesions vs. cancers).

Will cost-effectiveness studies be graded?

Evidence on safety and efficacy will be graded, but not cost-effectiveness studies. Cost-effectiveness is an important factor that informs judgments in formulating recommendations. Further work may improve the methods to assess and integrate economic data in developing recommendations.

Can GRADE assist in evaluating observational studies assessing risk factors?

The criteria for assessing “study limitations” can be applied. Example of criteria for cohort studies include representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that the outcome was not present at start of study, comparability of cohorts, assessment of an outcome, adequate duration of follow-up for outcomes to occur, and loss to follow-up.

What support will be needed to implement GRADE?

Staff with experience in health research methodology and training in the application of the GRADE method and grading of evidence would be needed to assist ACIP work groups.

How will the GRADE approach be translated for the public?

CDC communications staff can help translate for the public.

Dr. Ahmed reminded everyone that the ACIP vote would be to adopt an explicit evidence-based framework based on GRADE, that the terminology was not being voted on as it would evolve over time, and that enhancements may be made to the framework in the future.

Discussion Points

Dr. Baker pointed out that there were some strong emotions about cocooning adults and adolescent in the home and other contacts (e.g., healthcare settings, childcare settings, grandparents, et cetera). Infants under six months of age are not protected until after their 3-dose primary series. If the series is administered in a timely manner, they are protected by 6.5 to 7 months of age. There are no data and no RCTs to show that this works. However, based on the kind of disease, attack rate, and death rate, ACIP feels strongly as a policy committee that these infants should be protected by this method. With that in mind, she requested that Dr. Ahmed grade that strategy.

Dr. Ahmed responded that the first task would be to determine whether there is any indirect evidence from other diseases that might be applicable to this situation. This is why ACIP is needed to make judgments. If not, the recommendation would be built on expert opinion, which would be a Grade D—the lowest level.

Given that most people in the US are familiar with the A, B, C, D, F grading system in school, Dr. Baker thought this method of grading evidence would pose a major communication challenge to the public.

Dr. Temte responded with a hypothetical situation similar to what Dr. Baker proposed in which a recommendation is made based on absolutely no evidence, but about which ACIP feels strongly. The only difference between that and the GRADE approach is the openness, transparency, and honesty. He agreed that it would be imperative to have good communication with the public. It would be a difficulty and probably unethical study to randomize infants to no cocooning versus cocooning protocol. Sometimes ACIP is left with only expert opinion. The important component is being straightforward about this. In addition, within a recommendation, there is an area for remarks. That is where it will be highly important to be clear about how they reached the recommendation, including making a statement that conducting appropriate testing is neither feasible nor ethical.

Dr. Baker emphasized that every ACIP meeting is public and every word is transcribed, so the process is transparent.

Dr. Schuchat thought that one of the nice features of the effort of the working group was articulating grades of evidence for different outcomes. There was very explicit information for influenza about the strength of the evidence for the direct benefit, as well as the strength or weakness of the evidence that was available for indirect benefit. ACIP explicitly voted on the routine childhood vaccination for the direct benefit of the child hoping that the preliminary evidence of the indirect effect would come about as additional studies were conducted. At the time, the rationale was for direct benefit. Regarding Tdap, there is an evidence base for each tetanus, diphtheria, and pertussis and they all probably have limits. However, there is presumably some direct information that would be outcomes as well as the indirect cocooning benefit, which would not have evidence. While ACIP's deliberations are transparent, organizing it in this way is actually an advance for the public, critics, and those who feel that there are undue influences on the decision-making.

Dr. Duchin applauded the working group. He thought the description of evidence would be very valuable in communicating to stakeholders how / why ACIP decisions are made, and in highlighting gaps in data. He also emphasized that this grading system does not grade the recommendation. It grades the evidence on which the recommendation is based, which is probably a communication point.

Dr. Chilton thought Categories I and II graded the recommendation and the A, B, C, and D graded the evidence. He recently reviewed a long document regarding community-acquired pneumonia that the Infectious Disease Society of American (IDSA) published. He believes IDSA is using the GRADE system, but is using it in a slightly different way in which they say strong recommendation / high grade evidence; weak recommendation / very low quality evidence. He thought that was even more transparent than using a Roman numeral and a letter, and it might result in less problems with translation.

Dr. Judson felt that the working group had made significant progress, that the system was becoming clearer, and that they were getting closer to the details and weighting. Medicine and science have always had to deal with inadequate evidence. Terms such as "clinical judgment" are used, which could be defined as "an excuse for making decisions based on insufficient information." The same is true for "epidemiologic judgment." Reasoning can be deductive and inductive. A lot of the reasoning ACIP will be using to judge the strength of the reasoning can be indirect or deductive. He thought that cost-effectiveness should be a key element for consideration. PPACA has a section regarding comparative-effectiveness / cost-effectiveness. In terms of grading the evidence grading, he felt that some items were included in the tables

that were not helpful. Under “Strength of Association” they should avoid anything that was completely arbitrary. Upgrading by one level if there is strong association of a relative risk of > 2 does not say much about the strength of the association, and a vaccine efficacy of > 50% is a fairly low bar and does not mean much. He thought this was pretty arbitrary upgrading or downgrading of evidence that would not fit very many situations realistically.

Dr. Ahmed replied that they could take such issues to the GRADE Working Group to discuss potential modification.

Dr. Keitel said that her understanding was that using the GRADE system, only direct evidence is graded. With cocooning, if there is no evidence, there would be nothing to grade.

Dr. Ahmed replied that this is where expert opinion comes in. The definition of Grade D is “Available data are insufficient to provide a reliable estimate of the effect on health outcomes.” This describes expert opinion.

Dr. Cieslak said he appreciated that the current proposed framework reflected considerable improvement and more consciously incorporated some of the Bradford Hill criteria mentioned during the last ACIP meeting. Nevertheless, the problem it would solve remained unclear. ACIP is probably more transparent than most agencies making guidelines, and he felt that they were trying to “shoe horn” something into this framework that it was not really made for. It was developed for clinical decision-making; whereas, ACIP is making national policy. He did not think it was the best fit and he feared that because the framework would entail considerable labor, its use would slow down the process and the richness of the deliberations would not be captured in the end product.

Ms. Rosenbaum expressed appreciation for all of the work that had gone into this, and said that she was very mindful of the fact that their weakest recommendation, meaning a D or below, would have far more integrity than an arbitrary coverage exclusion, which is typically based on no evidence other than actuarial estimate. She was very worried that ACIP / CDC had not thought through the effect of this given the new statutory obligations of the ACIP and the tensions it will create—never mind the parents who do not understand when ACIP makes a recommendation based on D data or worse. The world of insurer stakeholders will complain loud and long that recommendations are being made on what is being called poor quality data. She would have no problem saying that their poorest quality data are a thousand times better than an arbitrary exclusion (e.g., Show me the data that we *shouldn't* try cocooning). As a layperson, she would say that the best clinical judgment is based on what is known about herd immunity. So there actually is some evidence for what is recommended about cocooning. She shared Dr. Cieslak’s observation that it was not clear what problem they were trying to solve, or that at this most pivotal time in life of ACIP and its relationship to coverage that it was a great time to introduce a new overlay on its evidentiary recommendations. They should be very clear about the evidence on which they are relying rather than giving a qualitative grade. If they are relying on expert opinion, they should simply say that. Ms. Rosenbaum remained unsettled about what this new system meant without a much broader discussion with payers about what messages they receive when they hear “D” evidence.

Dr. Temte explained that the benefit of the GRADE system is the clear separation between the strength of the recommendation and the level of evidence. There are situations, for example, where there is a rapidly evolving situation in which they may make a strong recommendation (Category I) based on insufficient evidence. Being tied into the category of recommendation with the strength of evidence can be a problematic situation. They are just proposing adoption of a system that has been adopted by a number of organizations. Regarding the arbitrariness of certain relatively risks, et cetera, the working group's interaction with the SAGE group indicated that these were definitely works in progress. What is being proposed is not the end. It must evolve over time. The group was not proposing a final solution to the process, but rather was proposing a way to get there. In terms of the amount of labor required, the working groups are not currently asked to do their cost analyses at this point. However, ACIP has become quite reliant on that. There is a crew of economists at CDC who do a superb job of doing that. Similarly, there could be a couple of resource people who are well-trained in conducting evidence reviews and fairly quickly providing the amount of information needed by the working group. The AAFP recently submitted a letter to CDC strongly requesting that recommendations by CDC be put in an evidence-based framework, and ACP has had some reservations in terms of adopting vaccine recommendations because they are not evidence-based. ACIP is there for a much larger stakeholder group (e.g., vaccine providers, implementation programs, et cetera). Despite the fact that ACIP is very open and is on the web, most physicians in the clinic who want to know what to do see only the recommendations and most likely stop at the first line.

Dr. Campos-Outcalt (AAFP) reiterated that it is very important for their members. AAFP now has a process of reviewing recommendations from an array of groups, and their members have come to expect evidence grading and recommendation levels. If it is not there, they ask why. AAFP as a whole typically does not endorse recommendations if they do not include evidence grading. They have been making an exception for ACIP for the past five years or so because this process has been playing out, but the younger members of AAFP in particular want to know a level of evidence. This does not mean they will not do something that is a D level. It just puts it in perspective for them.

Dr. Brady (AAP) thought the definition for C sounded as though they were saying they believed current information was wrong and that future research would actually come up with the right evidence. He suggested changing the wording to be clearer about what they meant. He was also concerned about the A, B, C, D system in that each is of lower value. Perhaps D could be changed to suggest that they are not grading the evidence because there is no evidence.

Dr. Baker clarified that she had no problem with the evidence system for communicating with physicians, especially young physicians. She remained concerned about the non-physician public.

Dr. Fryhofer (ACP) indicated that the ACP is on record as being a strong proponent of evidence-based guidelines and a systematic way of organizing and evaluating the level of evidence. It is a different direction than what ACIP has done in the past. It was a big deal for the ACP Adult Immunization Advisory Board to convince the Board of Regents to endorse the ACIP adult immunization guidelines because they were not evidence-based.

Dr. Netoskie (AHIP) concurred with Dr. Brady about the D recommendation as being very difficult to sell, especially to employer groups. Almost all medical policy in the private insurance base starts in the clinical workgroups within those organizations, so they spend a lot of time trying to pour through the evidence and understand recommendations. They will read the additional data that is necessary to make a good decision. However, he thought the increased transparency would be beneficial and he applauded the effort.

Dr. Iskander commended the work of Drs. Temte and Ahmed and their colleagues on this work group. He serves as a Senior Policy Reviewer, and that includes all of the ACIP statements. The most frequent question that his office sends back to authors regards clarification of the link between evidence provided and how that translates into recommendations. While he thought it would take some time to develop the support infrastructure needed, ultimately authors are required to do this anyway. He appreciated that ACIP was very sensitive to trying to publish its recommendations in the *MMWR* in a timely manner, and he thought they could think of it as an investment toward longer-term efficiency, clarity, and transparency of ACIP recommendations.

Dr. Ward said it was clear that the actions of this committee could not be reduced to an algorithm or a logic sequence. So many of the decisions he has observed over 30 years by this committee, including some during that day, could not follow an algorithm. Some pieces of evidence are very powerful and would not meet the criteria. Thus, he was concerned about the algorithm approach and the grading scale. He liked Dr. Baker's suggestion that the reason for doing this was to communicate with the public. He thought the grading scheme, based on the strength of evidence, should be firm or strong evidence (A); evidence that is middle grade, controversial, or not definitive (B); or limited evidence (C). The key point to get out to the public is whether an individual will receive direct benefit and / or there will be a public health benefit.

Dr. Salisbury (DOH, UK) said that as the out-going chair of SAGE, he had been through this process with the committee increasingly being obliged to grade the evidence. This is extraordinarily time-consuming according to the quantity of evidence. It is not trivial as an undertaking. When doing this for SAGE, they found that some studies and some decisions are much better suited than others. Pre-licensure studies very easily conform to an A level of evidence because that is how the study was set up. However, the many realistic problems in immunization programs after licensure simply do not stack up to the same quality of evidence and automatically are pitched into at best C and at worst D. Some of the most difficult decisions they make and the recommendations that they then have to follow through are based on what appears to be the weakest of evidence, Category D. It makes the whole justification of decision-making look as if it is being done on poor quality evidence. The UK Joint Committee on Vaccination / Immunization does not use the GRADE system at this time, but for each recommendation they do publish the synthesis of the evidence and make clear what the strength of the evidence was. They do not have a problem in saying that a recommendation is based on clinical judgment. For many recommendations that they all have to make on sub-groups, there is no direct evidence and they have to work on the basis of clinical judgment. That is an acceptable position to be in, but seeing it listed as D does not make it look very good.

Dr. Zimmerman (University of Pittsburgh) agreed that this process could be time-consuming. Nevertheless, he thought there was value in the transparency as an increasing number of younger physicians are moving to understanding explicit evidence-based criteria and to using an explicit coding system that is well-recognized. He was glad to see this move by ACIP and supported it.

Dr. Decker (sanofi pasteur) said that note had already been taken of the potential adverse impact of using A, B, C, D, but he thought they increased that risk when they combined that with the word “grade.” Everyone in the country knows what it means to come home with a grade of D. He suggested using the word “category” if they planned to use A, B, C, D.

Dr. Schuchat said she thought the pre-licensure, new vaccine quality of data is often very strong and the vast majority of “big ticket” recommendations that ACIP makes are in that category. CDC is extremely committed to very strong, high quality evaluation of its policy to strengthen the evidence base in support of policies post-licensure. Duration of protection and safety issues, for example, do not emerge pre-licensure. A lot of the ARRA resources have been used to improve the ability to evaluate the impact of recent recommendations. She believes this will be important going forward.

[Note: Given the late hour and the potential for overlapping with a planned fire drill in the facility, a decision was made to defer the discussion and vote until the following morning].

Dr. Baker welcomed everyone to the second day of the October 2010 ACIP meeting, reminding them that the previous day the evidence-based vote was tabled.

Dr. Schuchat said she was glad that this vote was delayed until the second day because the first day of the meeting had been very long and challenging. From the institutional perspective, the use of evidence to inform policy is an extremely high priority for CDC and Dr. Frieden, CDC’s director. Dr. Frieden has instituted five priorities, one of which is related to policy and one of which is related to strengthening the epidemiology, laboratory, informatics, and science that the agency conducts and / or supports. They also heard the first day from CDC’s valued partners, healthcare professional organizations, and the healthcare professional community that they expect evidence to be systematically reviewed and for the process to be transparent. CDC is committed to continuous quality improvement of the ACIP process, and the agency has heard over the years about how staff can better support the committee and the community. The doors of the meeting have been opened even further with the use of webcasts, so she personally views the evidence-based discussions they have been having as a part of the quality improvement process. She expressed her hope that as they deliberated about the right thing to do, they would keep that context in mind.

Explicit Evidence-Based Framework Based on GRADE

Jon Temte, MD, PhD, Chair Evidence-Based Recommendations Work Group

Dr. Temte reviewed the options for the vote, which were as follows:

Option 1: As Presented

- Proposed recommendation categories
 - Category I, Category II
- Proposed evidence grades for safety and efficacy
 - A, B, C, D

Proposed ACIP Recommendation Categories

- Category I (recommendation for, or recommendation against)
 - Universal recommendation
 - Risk-based recommendation
- Category II (recommendation for individual clinical decision making)
- No recommendation/unresolved issue

Description of Evidence Grades

- A: Further research is unlikely to change the confidence in the estimated effect on health outcomes
- B: Further research may change the confidence in the estimated effect on health outcomes
- C: Further research is likely to change the confidence in the estimated effect on health outcomes
- D: Available data are insufficient to provide a reliable estimate of the effect on health outcomes

Proposed Format for ACIP Recommendations

- Recommendation
 - ACIP recommends/does not recommend ... (Recommendation category, Evidence grade)
- Remarks
 - Explicit consideration of benefits, harms, evidence grade, cost-effectiveness, and values for making a recommendation should be described here
 - For recommendations based on lower evidence grades, the reasoning should be highlighted here

Example of Recommendation

Recommendation: ACIP recommends that ...
(recommendation category: I. evidence grade: A).

Remarks: ...

The advantages of Option 1 are that it is the result of extensive working group discussion with previous feedback from ACIP members, and it is directly comparable with GRADE. The disadvantage is the negative connotation of “grading,” especially with expert opinion.

Option 2: Modified Descriptors

- Proposed recommendation categories
 - Category A, Category B
- Proposed evidence levels for safety and efficacy
 - 1, 2, 3, 4

Proposed ACIP Recommendation Categories

- Category A (recommendation for, or recommendation against)
 - Universal recommendation
 - Risk-based recommendation
- Category B (recommendation for individual clinical decision making)
- No recommendation/unresolved issue

Description of Evidence Grades

- 1: Further research is unlikely to change the confidence in the estimated effect on health outcomes
- 2: Further research may change the confidence in the estimated effect on health outcomes
- 3: Further research is likely to change the confidence in the estimated effect on health outcomes
- 4: Available data are insufficient to provide a reliable estimate of the effect on health outcomes

Proposed Format for ACIP Recommendations

- Recommendation
 - ACIP recommends/does not recommend ... (Recommendation category, Evidence level)
- Remarks
 - Explicit consideration of benefits, harms, evidence grade, cost-effectiveness, and values for making a recommendation should be described here

Example of Recommendation

Recommendation: ACIP recommends that ...
(recommendation category: A. evidence level: 1).

Remarks: ...

The advantages of Option 2 are that it is similar to Option 1, but removes the obvious “grade” with the less pejorative “level,” and it remains directly comparable with GRADE. The disadvantage is that it could still connote the negativity of “grading,” especially with expert opinion.

Option 3: Evidence Narrative

- Proposed recommendation categories
 - Category I, Category II
- Replace evidence level with synthesis:
 - Based on evidence from randomized controlled trials with no important limitations, or from well-conducted observational studies with very strong effects
 - Based on evidence from randomized trials with important limitations or from observational studies with special strength
 - Based on evidence from observational studies, or from randomized trials with very serious limitations
 - Based on expert clinical opinion

Proposed ACIP Recommendation Categories

- Category I (or A) (recommendation for, or recommendation against)
 - Universal recommendation
 - Risk-based recommendation
- Category II (or B) (recommendation for individual clinical decision making)
- No recommendation/unresolved issue

Proposed Format for ACIP Recommendations

- Recommendation
 - ACIP recommends/does not recommend ...
(Recommendation category, Evidence narrative)
- Remarks
 - Explicit consideration of benefits, harms, evidence grade, cost-effectiveness, and values for making a recommendation should be described here

Example of Recommendation

Recommendation: ACIP recommends that ...
(recommendation category: I, based on expert clinical opinion.)

Remarks: ...

The advantages of Option 3 are that it directly describes the evidence used, removes “grading” of evidence, and is indirectly comparable with GRADE. The disadvantage is that it is more complicated, especially when there are multiple / complex sources of evidence synthesized. Here they could use Category I or II or Category A and B, but this option is more explicit and transparent rather than utilizing a level or grade.

Discussion Points

Ms. Rosenbaum said she loved Option 3, and thought that if they could get all evidence-based decision making to this model, they would have done a great service to American society because it really says explicitly what they are doing, and does not disparage any source of evidence. Her greatest concern with the other models (whether they called them 1, 2, 3, 4 or A, B, C, D was that D or 4 said “no data.” Even if there were not data, there may be evidence of some sort, so it would be a misnomer to leave people with a sense that there is no evidence. Option 3 meets CDC’s goals of transparency, is very forthright, and would make it quite easy to say that one of ACIP’s recommendations rests on multiple sources of evidence versus limited situations in which only one source of evidence is being used.

Dr. Keitel agreed, and thought that Option 3 would save everyone from having to review footnotes because the information would be stated explicitly up front.

Ms. Ehresmann also agreed, but expressed concern that the third bullet stating “Based on evidence from observational studies, or from randomized trials with very serious limitations” almost sounded worse than “based on expert clinical opinion.” She wondered whether another term could be used that suggested that the limitations are greater than the prior statement. “Very serious” sounded concerning.

Dr. Temte replied that those specifics could be adjusted within the methodology. He emphasized that the GRADE methodology is a very exquisite, well-used, well-oiled, methodology. There is flexibility. These are just examples of the language. The idea would be to try to make a very precise statement regarding what evidence is being used or what the typology is of the evidence being used.

Dr. Baker agreed, pointing out that the use of adjectives is unnecessary in a lot of policy statements.

Dr. Duchin reiterated his strong support for ACIP adopting one of the schemes. He wondered whether there would be a synthesis of evidence in Options 1 or 2.

Dr. Temte responded that the synthesis would be included in either of those options. The difference would be in whether the first bullet of the recommendation included a single 1, 2, 3, 4; A, B, C, D; or a more extensive narrative that captures that information but in a more complete manner.

Dr. Cieslak supported Option 3. One of his concerns was trying to apply this rather stilted grading system to things like harmonizing the schedule for rotavirus vaccines for which there are RCT data, but for which they would allow other vaccines to be used. He found the AAP statement to be very confusing, and thought that tying themselves to grading different levels of evidence would be unhelpful.

Dr. Schaffner (NFID) suggested in the next to the last bullet in Option 3 using the word “notable” instead of “very serious.” “Based on expert clinical” seemed very limited and should be expanded (e.g., clinical, public health, epidemiological, and immunologic opinion).

Dr. Temte emphasized that these were just examples as opposed to having everything fit into one of these narratives. For example, it could be based on expert public health opinion.

Dr. Judson also favored Option 3 and thought they were making progress; however, a statement on impact was missing: Who does the recommendation affect? What does it cost? Who are the proposed payers? Once the recommendation leaves the room, it comes down to healthcare delivery systems and state and local public health. The strength of the evidence is clearly one-sided, and he thought they could no longer ignore the cost and programmatic impacts that ACIP recommendations have.

Dr. Langley (NACI) said she did not hear mention of the publication of the knowledge synthesis tables with whatever statement is published. She suggested that publishing the literature syntheses on the internet would be of great service to readers, including international readers. Looking at the whole table would offer a gestalt impression of the magnitude of the effect, the direction of the effect, and so forth. WHO and the Gates Foundation have been engaged in an 8-year initiative to encourage international publication of knowledge syntheses in order to avoid duplication of efforts around the world, and so that all countries may have access. She also pointed out that in addition to evidence (e.g., scientific studies about vaccine efficacy, disease burden, safety issues, et cetera) there are other issues such as equity, feasibility, et cetera that are not amenable to a literature synthesis and evidence grading. Evidence is an important part of formulating a recommendation, but other issues that help to form a recommendation should also be stated.

Dr. Ahmed responded that the group agreed with those suggestions. They still propose to use the evidence tables he showed the previous day. The evidence grade is only one component. The other components include the balance of benefits and harms, values, and cost-effectiveness, et cetera.

Dr. Baker requested that prior to a vote, any conflicts of interest be disclosed. The following conflicts of interest were declared:

- Dr. Janet Englund: Research support to her university from MedImmune, sanofi pasteur, Novartis, Admark, Adamas, and Chimerix.
- Dr. Wendy Keitel: Her university receives clinical trial support from Novartis
- Dr. Cody Meissner: Payments made to Tufts Medical Center by MedImmune and Pfizer for participation in multi-center clinical trials
- The remainder of the ACIP members declared no conflicts

Motion: GRADE Framework

Ms. Ehresmann made a motion to accept Option 3. Dr. Keitel seconded the motion. The motion carried with 13 affirmative votes, 0 abstentions, and 0 negative votes.

Day 1 Public Comments

Lyn Redwood
Executive Director
SafeMinds

SafeMinds supports the adoption of standardized, transparent, and systematic approaches to assessing future and past ACIP policies of vaccination. We ask for these components to be incorporated into ACIP evidence as part of the appraisal process; that the appraisal be conducted by independent entities without financial or career investment in vaccine programs; that the appraisal include all clinical research on vaccines, including Phase 1, 2, and 3 trials as well as post-licensure studies; that results on adverse effects be combined across all such trials in order to more accurately characterize relatively rare events that may not be identified; that studies which compare vaccine groups to a no vaccine group rather than a different vaccine group, a true placebo group, are ranked as higher quality when assessments of harm are calculated; that a gray literature search be conducted to capture all potential studies and reduce publication bias; that the risk of biased evaluation be included for any study in a summary included in the review; that appraisals utilized independent, systematic reviews when available; that patient-important and real-world effectiveness outcomes be used; that these reviews be published with all supporting evidence as is done with Cochrane systematic reviews to ensure transparency; that the public and scientific communities be allowed to comment on the appraisal prior to consideration by ACIP; that the appraisal be conducted retroactively for current vaccines and not just future vaccines as currently proposed; and that knowledgeable consumer advocates be included in the process, including patient safety advocates, to better assess the needs of patients, especially with regard to values. SafeMinds further asks that guidelines be developed for the appraisal that includes comparative effectiveness or other approaches that vaccines are preventing the mortality and morbidity of the targeted disease and that the cost-benefit comparisons be an important factor. Money for vaccine programs reduces funding for other critical treatments. Finally, we ask that ACIP more widely utilize guidelines calling for an

“optional” use rather than universal recommendation in order to better allow clinical judgment and patient values to be incorporated into vaccination decision making in the clinical setting.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat called everyone's attention to the week's *MMWR*, which included an update on the global immunization situation, highlighting the increase in routine coverage and increase in uptake of hepatitis B and Hib vaccine, with more countries adopting pentavalent formulations. Still, more than 20 million children are not receiving immunizations in terms of the first year series. In light of their day deliberating about meningococcal vaccine in the US, Dr. Schuchat said she was delighted to inform everyone that through a public / private partnership funded by the Gates Foundation and the Serum Institute of India, a dose of meningococcal A conjugate at forty cents per dose has been initiated in campaigns in Burkina Faso, Niger, and Mali. 1.3 million people between the ages of 1 and 29 have been immunized in pilot districts where active efforts at safety evaluation are being conducted. In December 2010, there will be a launch of full campaigns for that age population in those three countries, either nationwide or in larger areas. This is the beginning of a multiyear effort to try to eliminate epidemic meningococcal A in Africa, which causes hundreds of thousands of cases and thousands of deaths when periodic epidemics occur.

Centers for Medicare and Medicaid Services (CMS)

Linda Murphy reported that HHS has been working on an influenza package to outreach to seniors and to get more children immunized. A poster would soon be available on the CMS website and several articles will be distributed. About 3,000 CMS partners will receive the packages. The package is in English and Spanish and addresses the idea for grandparents to take their grandchildren to be immunized when they acquire their own influenza vaccine. This poster has a lot packed in it because it combines Medicare, Medicaid, and the Context of HIV Infection Project (CHIP) and has the website as well as the 1-800-Medicare number. She called the number herself which includes a prompt to be linked to Medicaid and then the specific state of interest. That Medicaid number also includes CHIP information. Ms. Murphy received an email asking about a national statement regarding a pertussis outbreak. There is no national statement at this time regarding the pertussis outbreak in California. Medicare is following ACIP guidelines regarding Tdap. However, there may have been a local determination. Providers were instructed to contact their A and B Medicare for California to determine whether there had been any local changes. The preventive vaccines covered under Medicare part B include influenza, pneumococcal pneumonia, and hepatitis B. Tetanus or Tdap is only coverable under part B in limited circumstances when determined to be medically necessary for the beneficiary by the local Medicare contractor. If the provider feels that the Medicare beneficiary needs Tdap, this can be administered with no problem. Under Medicaid, while she knew everyone was anxious to know what the new rates would be, because the Vaccines for Children (VFC) had not been published in the *Federal Registry* yet, CMS could not release the rates. However, they expect publication in January 2011.

Department of Defense (DoD)

Wayne Hatchet reported that this year, the DoD had purchased more vaccine than ever before (n=over 4.3 million doses). Thanks to the manufacturers, they received the vaccine earlier than ever before as well. In addition, TriCare has established a new initiative that permits any DoD TriCare beneficiary to obtain their influenza vaccine from any retail pharmacy in the TriCare network whether they are active duty, dependent, or retiree. That significantly increases access. Following about 3 years of laboring, they are very close to standing up the Tri-Service Immunization Tracking System. They will have a unified way of determining who has received which vaccines across the spectrum of DoD beneficiaries. In the past, tracking has been service-centered. Some systems captured dependents, but others did not. As October 26, 2010, DoD was at 54% immunization for influenza placing them well on their way to the goal of 90% percent by December 1, 2010. Dr. Baker congratulated DoD on their accomplishments regarding influenza vaccine and the progress on the immunization registry.

Department of Veterans Affairs (DVA)

Terry Murphy reported that DVA's immunization campaigns were well underway across its healthcare system, which includes over 150 medical centers and greater than 900 community-based outpatient clinics. DVA has ordered over 3 million doses of influenza vaccine. In addition to all of the usual strategies that they implement each year, they are also encouraging facilities to work collaboratively with local health departments to set up arrangements to immunize families of veterans as they present with the veteran for healthcare. Dr. Baker congratulated DVA as well.

Food & Drug Administration (FDA)

Dr. Baylor informed everyone that on November 16, 2010, the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) would meet in open session to review and discuss the pathway to licensure for protective antigen-based anthrax vaccines for post-exposure prophylaxis indication using the animal rule. On November 17, 2010, VRBPAC would meet to discuss the effectiveness of vaccinating males and females with Gardasil® manufactured by Merck for the prevention of anal dysplasia and anal cancer. They hope to have the background material available two days prior to the meeting for the public.

Health Resources and Services Administration (HRSA)

Rosemary Johan-Liang for the National Vaccine Injury Compensation Program (VICP) of HRSA reported that fiscal year 2010 saw the largest number of claims for non-autism cases. Approximately half alleged injury from influenza vaccines and nearly 60% percent were filed on behalf of adults. Over 5,600 autism claims were filed as of October 1, 2010. At the time of this ACIP meeting, it was anticipated that approximately 800 had been dismissed at the request of the petitioners or dismissed by the court because of jurisdictional issues. The Autism Omnibus Proceedings (OAP) that began in 2007, with three theories of causation, have moved through all levels of the appeal process and the decision of the court in favor of HHS was affirmed. In February 2009, the Special Masters of the US Court of Federal Claims ruled in favor of HHS in all three test cases. In July and August of 2009, all of these cases were affirmed by the Judge of the Court of Federal Claims upon appeal. In May 2010, one of the three test cases, Hazlehurst, was affirmed by the next level of appeal, the Federal Circuit Court. The decision for the first claim compensated under the OAP contains redactions of the name of the petitioner and other personal identifiers, and states that HHS conceded that this was an injury on the vaccine injury table. The court has begun the process of resolving the remaining approximately 4,800 autism claims. On October 8, 2010 the court posted a copy for the Notice to Council letters being sent to petitioner attorneys. After noting the outcomes of the appeal for the OAP

theories, they requested them to begin contacting their clients to ascertain how they wish to process their claims.

Over the lifetime of the program, \$2.1 billion has been awarded thus far and the current trust fund stands at \$3.25 billion. On October 12, 2010 the US Supreme Court heard arguments in *Bruesewitz versus Wyeth*. The Bruesewitz family has filed a claim with the VICP alleging injury to their daughter Hannah following a DTP vaccination in 1992. The claim was eventually dismissed by the court and the family then filed a lawsuit against Wyeth, the vaccine manufacturer. The key legal issue regards whether the National Childhood Vaccine Injury Act protects vaccine manufacturers from liability for injuries caused by their vaccines, and specifically whether that immunity applies when the victim claims that the design of the vaccine created an avoidable and unnecessary risk to patients. Both sides defer over the meaning of the language in the act dealing with what is known as design defect claims and what Congress meant by the phrase "unavoidably safe." The Institute of Medicine (IOM) committee contract is on-going for the review of adverse events of vaccines. There are 8 vaccines being reviewed currently. The primary goal of this contract is to assist their program as they begin to update the vaccine injury table, which will start when the IOM submits their final report in mid-2011. Concurrent with the IOM's comprehensive review of the current literature, the VICP is performing systematic analysis of the claims data for relevant adverse events and vaccines.

Indian Health Services (IHS)

Jim Cheek indicated that IHS is gearing up for the coming influenza season. They continue to refine their electronic surveillance system for influenza-like illness (ILI), which is an automated system that is based on their electronic health records. This system collects data on potential risk factors as well as vaccination coverage.

National Institutes of Health (NIH)

Richard Gorman reported that NIH continues its focus on basic research studies to determine how microbes survive and multiply, elucidate complex hosts-microbial interactions, and increase understanding of how hosts responds. Basic research provides the knowledge essential for developing safe and effective vaccines, diagnostics, and therapeutics. Conditions or diseases of special interest to NIH's National Institute of Allergy and Infectious Diseases (NIAID) include antimicrobial drug resistance, biodefense and related programs, emerging infections, food allergies, HIV / AIDS, influenza, malaria, sexually transmitted infections, and tuberculosis. In upcoming major events, the AIDS Networks are coming up for re-competition. These networks are massive clinical enterprises, and the leadership is trying to keep the research community updated about the present thinking for refocusing these networks through Blue Ribbon Panels, the blogosphere, and town hall meetings. The 9-year Herpevac Study, with greater than 8000 women, conducted by NIAID and GSK has completed. Women had to be serologically negative for herpes simplex virus-1 (HSV-1) 1 or HSV-2 at enrollment. The vaccine was administered at enrollment, 1 month, and 6 months. The primary outcome was breakthrough infections of general herpes after the second vaccine administration. The vaccine estimate was shown to have a point estimate of efficacy of 20% percent, which was not statistically different from zero. There is a study ongoing comparing the immune responses of three thousand adolescent women who get Gardasil® per recommendations compared to those outside the recommended dosing intervals. There is also a randomized, double-blind, placebo-controlled, phase II study to assess the safety and efficacy of the cytomegalovirus glycoprotein B (gB)/MF59 vaccine in preventing systemic cytomegalovirus infection (CMV) in healthy adolescent females. The primary efficacy objective is to assess whether injection with 3 doses of the CMV gB/MF59 vaccine will reduce the acquisition of a systemic CMV infection in healthy CMV-seronegative adolescent females. This will be accomplished by comparing the rates of acquisition of

systemic CMV infection, defined as detection of CMV in the urine or blood, between the placebo and CMV vaccine recipients beginning 1 month after the third dose of vaccine. The primary safety objective is to assess the local and systemic effects of immunization and adverse events (AE) with the CMV gB/MF59 vaccine when administered to female adolescents on a 0-, 1-, and 6-month schedule [<http://www.clinicaltrials.gov>; study NCT00133497]. Enrollment has been completed of 400 adolescent women. Two of the five dengue vaccine candidates are presently in clinical trials with NIAID, one of which is a quadrivalent live attenuated vaccine. Two influenza trials are on-going this pre-influenza season. One will assess the comparative immunologic response to different currently recommended inactivated trivalent vaccines in pregnant women, while the will examine the reactogenicity and immunogenicity of the 7.5 microgram and 15 microgram dose in infants less than 36 months of age. NIAID is also involved in a Phase 1 trial of a new TB drug, and is in the process of conducting a QT study, which is the last required study for National Voluntary Accreditation (NVA) for this new tuberculosis drug. In addition, the agency has a candidate DNA vaccine for malaria in Phase I testing, which is going to be delivered by electroporation.

National Vaccine Advisory Committee (NVAC)

Dr. Birkhead summarized the September 2010 NVAC meeting, which was primarily informational with no votes taken. A highlight of the meeting was that Secretary Sebelius addressed the group. She spoke on the unprecedented national and international response to the H1N1 pandemic, the activities of NVAC coordination through the Vaccine Safety Working Group, and H1N1 vaccine safety oversight. She also spoke about the medical counter measures review underway in the Office of the Assistant Secretary for Preparedness and Response (ASPR), coverage for preventive services under PPACA, and the upcoming first season of the universal influenza vaccine recommendation.

The Assistant Secretary for Health (ASH) to NVAC issued three recent charges. First, the ASH has asked NVAC to begin a process of annual review of the Healthy People 2020 goals to identify barriers, suggest solutions, monitor progress, and provide annual reports regarding the findings. This is an area in which NVAC could benefit from ACIP's input. Second, the ASH asked NVAC to evaluate reduction and elimination of health disparities, particularly focusing on adult influenza vaccination. NVAC now has an Adult Immunization Working Group that will incorporate this charge into its work. Third, the ASH asked NVAC to review and comment on the materials from the Interagency Viral Hepatitis Working Group.

In addition, NVAC has received two recent charges from the National Vaccine Program Office (NVPO). First, NVPO was asked to provide a review of the first year of universal influenza vaccination recommendation, to review the performance of the influenza universal program, and develop a report. The full committee will be working on this charge and anticipates a report by June 2011. Second, NVPO asked NVAC to assess at healthcare worker influenza vaccination issues, and to develop recommendations to improve vaccination of healthcare personnel, including a consideration of mandates for influenza vaccination. NVAC will establish a sub-group of its Adult Vaccination Working group to fulfill this charge. They have asked for representation from other groups as well. Dr. Duchin has agreed to represent ACIP on that working group.

With regard to the on-going work of NVAC, the Vaccine Safety Working Group (VSWG) is in its second phase of broadly assessing improvements in the national vaccine safety system. This working group is developing recommendations, will go through a period of public comments, and hopes to have recommendations ready for adoption during the June 2011 meeting. In addition, NVAC has hosted the Vaccine Safety Risk Assessment Working Group (VSRAWG), which has had on-going activity under the chair of Marie McCormick to review the efforts to coordinate H1N1's vaccine safety data. The VSRAWG continues to meet and expects to receive reports in November 2010 from the Federal Task Force. A final report on the H1N1 pandemic vaccine safety campaign is anticipated to be presented during the February 2011 meeting. NVAC has also continued in its interest in vaccine financing and healthcare reform. They participated in the second National Immunization Congress hosted by AMA, ASTHO, AAP, and other groups in Chicago in September. They had an update on the impact of health reform. Sara Rosenbaum has presented similar information to ACIP. This continues to be an area of interest for NVAC. The Adult Immunization Working Group continues to meet and hopes to have a set of general recommendations to improve adult immunization by the June 2011 meeting.

National Vaccine Program Office (NVPO)

Dr. Gellin reminded everyone that NVAC advises NVPO, so much of what Dr. Birkhead reported reflected the current priorities of the program. Influenza has been an ongoing, daily activity 24/7 throughout the year. It is always influenza season at HHS. Led by the Assistant Secretary for Health, there has been cross-departmental coordination of a range of efforts. The focal areas are healthcare workers as recipients for vaccines and as advisors to their patients on vaccines; reducing disparities; pregnant women; and uptake in the workplace. The National Vaccine Plan (NVP) is currently in clearance. Given that the NVP has a 10-year vision, NVPO has contracted with the IOM to begin working on elements of the plan. Current work pertains to new vaccine targets and development of an evidence-based approach and methodology for identifying and prioritizing targets for the future. NVPO is in the process of finalizing the launch of the vaccines.gov website by the end of 2010. This is essentially a portal that syndicates information from HHS. Other such sites include aids.gov, healthreform.gov, et cetera.

Zoster Workgroup Update

Paul Cieslak, MD
Medical Director, Oregon Immunization Program
Chair, ACIP Zoster Work Group

Dr. Cieslak briefly reviewed the activities of the Zoster Working Group. Zoster is a reactivation of varicella zoster virus among people who have had chicken pox in the past. The risk overall among seniors is about 1% per year, and about one million episodes annually in the US among persons of all ages. The median age is 55 to 60 years. Common consequences of zoster include acute pain, post-herpetic neuralgia (e.g., pain, often disabling, lasting weeks, months, even years), and ophthalmic zoster that can permanently impair vision.

The zoster vaccine was first approved in May 2006 by the FDA and was recommended by ACIP for persons aged 60 years and older in 2007. This was based on the results of a large multi-center RCT conducted with recruitment through VA medical centers, with a fairly balanced group of males and females. The vaccine is comprised of the live attenuated Oka-strain used in

the chicken pox vaccine, but contains about 14 times the amount of virus. This vaccine was found to be 51% effective in preventing the zoster, and 67% effective in preventing post-herpetic neuralgia. ACIP recommended this vaccine based on the trial conducted with persons 60 years of age and over. New clinical trial data are now available from Merck on zoster vaccine among persons 50 through 59 years of age.

The Zoster Working Group's tentative terms of reference are to review new data regarding use of zoster vaccine among persons 50 through 59 years of age and to consider whether the current zoster vaccine recommendations should be revised; and to review new information on zoster and zoster vaccine three years after publication of the original zoster vaccine recommendations to determine whether refinements are needed. At this stage, it is probably unlikely that there will be duration of efficacy data far enough out to make any definitive statements about duration of protection, but the group will review these data. In addition, the group will hear presentations from Merck and from CDC economists regarding cost-effectiveness data.

The Zoster Working Group began convening conference calls in August 2010. They anticipate reviewing the clinical trials data in December 2010 and the economics data in January and February 2011. An informational session will be included on the February 2011 ACIP meeting agenda. A zoster session, with the possibility of vote on new or revised recommendations, is anticipated during the June 2011 ACIP meeting. All of this, of course, is contingent on FDA approval of the vaccine in the younger aged cohort.

Discussion Points

Dr. Meissner pointed out that there are currently shortages of zoster vaccine. With a new plant being built for production of this vaccine, he requested that Merck address the question of supply of the vaccine and whether they anticipated being able to meet the demand.

Dr. Cieslak replied that the shortage of vaccine is one of the many reasons that the current uptake, based on the existing recommendation for persons over 60 years of age is only about 10%.

Dr. Bresnitz (Merck) responded that Merck recognizes that there have been some problems with delivering vaccine over the last year or so. They are planning to release several hundred thousand doses of vaccine later this year. The plant is currently being built, and there are additional measures expand supply over the coming years. He anticipated that by the time of the vote, Merck would be able to provide more information about future supply expectations.

Human Papillomavirus (HPV) Vaccines

Introduction

HPV Vaccine Session

Janet Englund, MD

Chair, ACIP HPV Vaccine Workgroup

Dr. Englund explained that during this session, presentations would be offered regarding vaccine safety and quadrivalent HPV vaccine for males. She reminded everyone that the last update to ACIP on vaccine safety for HPV vaccine was in October 2008. That session included data from VAERS and a preliminary analysis from the VSD rapid cycle analysis. The first two years of the VAERS safety data were published in August 2009 in *Journal of the American Medical Association (JAMA)*, and the VSD rapid cycle analysis is now complete.

In October 2009, the HPV vaccine was licensed for males 9 through 26 years of age for the prevention of HPV 6- and 11-related genital warts. In October 2009, ACIP stated that HPV vaccine may be given to males 9 through 26 years of age for prevention of genital warts, but this was not included in routine immunization schedule. However, HPV vaccine for males was included in VFC program. A supplementary BLA was submitted by the manufacturer to FDA with efficacy data for anal pre-cancer lesions in males. A review is anticipated before the February 2011 ACIP meeting.

The ACIP HPV vaccine workgroup has reviewed a variety data since September 2010, including cost-effectiveness of routine male vaccination; coverage in 13 through 17 year old females; school-located vaccination and program issues; sexual identity milestones in sexual minority youth; cost-effectiveness of vaccinating MSM; Association of Immunization Managers (AIM) Survey, and a national provider survey regarding male vaccination.

In addition to safety issues, the HPV session included a variety of topics. Because of the impact of coverage of females on cost-effectiveness of male vaccination, was a review of HPV vaccine uptake in females and a variety of program issues. This was followed by a summary of the clinical data from the quadrivalent HPV vaccine trials in men, a report on the data from a national provider survey, a summary of cost-effectiveness data, and a review of some of the considerations and discussion of the working group related to recommendations for males.

Post-Licensure Safety Monitoring of Human Papillomavirus (HPV) Vaccines

Julianne Gee, MPH

Center for Disease Control and Prevention, Atlanta GA

Ms. Gee described CDC's efforts in monitoring the safety of the licensed HPV vaccines. She briefly updated the committee on the reports received for the quadrivalent (HPV4) and bivalent (HPV2) vaccines through VAERS, and presented the findings from the VSD's RCA of the quadrivalent HPV vaccine among females. VAERS is a national passive surveillance system for vaccine adverse events jointly operated by CDC and FDA. VAERS serves as an early warning system for vaccine safety surveillance. Some limitations of this system include the risk of underreporting and other reporting biases, incomplete data, lack of availability of denominator data, and inability to assess causality.

In August 2009, VAERS published a paper in *JAMA* describing reports received by VAERS from June 2006 to December 2008. During the time period of the published *JAMA* surveillance summary, 12,424 reports were received by VAERS following HPV4 of which 6.2% were considered serious. Based on pre-licensure safety data and public attention to reported adverse events, detailed case reviews and separate analyses were conducted for various outcomes, including injection site reactions, syncope, headache, hypersensitivity, GBS, transverse myelitis, motor neuron disease, venous thromboembolic events (VTE), pancreatitis, autoimmune disorders, HPV4 administration during pregnancy, and death [Slade B, Leidel L, Vellozzi C, et al. *JAMA*. Post-licensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine. 2009; 302(7): 750-757]. The findings from this paper were generally not that different from what has been seen in the safety reviews of other vaccines recommended for this age group, and the authors concluded that the safety profile of HPV4 among females was consistent with pre-licensure data, with the exception of VTE and syncope in which disproportional reporting of these two outcomes were noted. Monitoring of HPV4 reports among females has continued in VAERS. Through August 31, 2010, there have been 16,000 reports received by VAERS, of which 8% have been considered serious. Continued monitoring efforts include routine assessments of the adverse events included in the *JAMA* paper as well as for new outcomes of concern. To date, no new adverse events or clinical patterns have been identified.

With regard to HPV4 administered to males, this vaccine was licensed in October 2009. However, prior to licensure VAERS received 64 reports of males receiving HPV4. Since the vaccine has become licensed for males, 98 reports have been received for males. The most common reports have been dizziness (19.1%), wrong drug given (15.4%; most prominent among pre-licensure reports), syncope (13.2%), and nausea (8.8%). There have been 5 serious reports (3.2%), including GBS, severe diarrhea, myocardial infarction, pulmonary embolus, and syncope with seizure-like activity. The bivalent HPV vaccine was licensed for females in October 2009 as well. To date, there has been minimal use of this vaccine in the US, which has limited the ability to assess adverse events. VAERS has only received 9 US reports for females.

In terms of safety monitoring efforts for HPV4 among females within the VSD population, Ms. Gee reminded everyone that the VSD is a collaboration between CDC and 8 managed care organizations (MCO). Using automated data sources that already exist as part of the participating health plans infrastructure, VSD collects medical and vaccination data on more than 9.2 million members annually, which represents approximately 3% of the US population. This project has developed a monitoring system for newly licensed vaccines, RCA, which tests specific hypotheses with well-defined outcomes and relatively short defined risk windows. Each week, the number of events in vaccinated persons are evaluated and compared to the total number of expected events based on a comparison group. Using sequential analyses methodologies, statistical adjustments are made for multiple looks. RCA is a signal detection method for pre-specified events. If an association or a signal is detected in the weekly automated sequential analyses, steps are taken to investigate the potential association appropriately.

The objective of the HPV RCA was to identify associations between HPV4 and a list of pre-specified adverse outcomes (e.g., GBS, seizures, syncope, appendicitis, stroke, venous thromboembolism, anaphylaxis, other allergic reactions) among females 9 to 26 years of age. Data were collected from 7 participating VSD sites in which vaccines were monitored in two age groups, including youth 9 through 17 years of age and adults 18 through 26 years of age. The

analyses began on August 20, 2006 and the formal surveillance period was for three years, ending in October 2009. Each outcome was monitored each week until an association (or signal) was detected; the upper limit was reached (based on the number of events expected after 350,000 doses in the 9 through 17 year olds and 150,000 doses in the 18 through 26 year olds; or until the end of surveillance period was reached.

Adverse events were monitored among the exposed cohort, which were females 9 through 26 years of age who received HPV4. Two comparison groups were used for the selected outcomes, which use different statistical methods based on the rarity of the outcome. For the more rare or less common outcomes in this population (e.g., GBS appendicitis, stroke, and VTE) a historical comparison group was used, which required calculation of the background rates from primarily historical VSD data. For the concurrent comparison group, females in the same age range were compared who had either a preventive care visit or a vaccination visit during the same time period as the exposed group. For this study, sequential analyses were not conducted in weekly monitoring because from previous VSD experience, it was known that the primary ICD-9 code for anaphylaxis was non-specific and generated a lot of false positives. Instead, counts of anaphylaxis identified in the automated data each week were monitored and each case was validated through medical chart review in order to calculate an incidence rate of anaphylaxis following HPV4.

For the historical comparisons, a Poisson MaxSprt analysis was conducted. Using this type of sequential analysis, the observed number of events is compared to an expected number generated from a calculated background rate. A signal using this methodology is detected when the log likelihood ratio (LLR) exceeds an established critical value. [Kulldorff M, et al. A Maximized Sequential Probability Ratio Test for Drug and Vaccine Safety Surveillance. *Submitted for Publication*]. For the concurrent comparisons, a Flexible Exact Sequential Analysis (FESA) methodology was utilized. Each week the observed number of events is compared to an expected number from either a concurrent preventative care visit group or a concurrent vaccination group in which matches are made by variables of interest such as age, site, and / or date of vaccination. A p-value is generated for that week's test. If the p-value is less than the threshold p-value, an association or signal is detected.

In terms of the results from this study, the total number of doses administered to females in this study population through October 4, 2009 were over 600,000 in which approximately 417,000 doses were administered to females ages 9 through 17 years of age. Among adults, no signal was observed for GBS, appendicitis, stroke, or VTE. A signal would have been generated using the Poisson MaxSprt analyses when the LLR exceeded the established critical value, which did not occur. One adult GBS case was identified in the automated data. Through medical chart review, it was determined that it was not an incident case of GBS following HPV4. For the more common outcomes among the 17-26 year olds, using a concurrent comparison group, no signal was generated. A signal would have been generated using this type of analytic method when the binomial test p-value was less than the established threshold p-value, which did not occur. For 9 through 17 year olds, using historical comparison, no signal was generated for GBS, stroke, or VTE. However, a signal was detected for appendicitis. Since VTE was an outcome of concern raised in the VAERS *JAMA* paper as well as other sources, it is important to note that no signal was generated at the time the upper limit was reached. However, the relative risk was slightly elevated, though not statistically significant. This outcome continued to be monitored after the upper limit was reached until the end of the surveillance period. Among the youth, using the flexible exact sequential method, no signal was detected for seizure, new onset seizure, syncope, or other allergic reactions.

As noted earlier in the presentation, each anaphylaxis case identified in the automated data was validated through medical chart review in order to calculate an incidence rate of anaphylaxis following HPV4. Chart review of each of the potential cases among the exposed found that one case was vaccine-related. The majority were miscoded diagnoses with a history of allergy or epi pen refills. The rate of anaphylaxis following HPV4 for this study was approximately 1.7 cases per million doses. Based on previous work conducted within the VSD, what was observed was within the expected rate of 1.5 cases of anaphylaxis following all vaccinations per million doses [Bohlke K, et al. Risk of Anaphylaxis after Vaccination of Children. *Pediatrics* 112(4); 2003].

At the time the upper limit was reached for VTE, 8 cases were identified in the automated data. This outcome continued to be monitored even after the upper limit was reached until the end of the surveillance period, and 13 exposed potential cases of VTE were found in the automated data. Chart review confirmed that 9 of the 13 cases had at least 1 known risk factor (e.g., OCP use, obesity, smoking, hospitalization (spinal cord injury + paralysis), or hypercoagulable disorders). Of those 9 cases, a temporal scan was conducted to look for clustering. A significant cluster was found on Days 2 to 3 in which there were four cases. To further investigate the VTE outcomes, a Self-Controlled Case Series protocol will be conducted to assess the confounding and / or effect modification by other risk factors.

Appendicitis was chosen as an outcome for this RCA because it was a serious adverse event identified in the pre-licensure trials, in which there were 5 cases of appendicitis in the vaccine group and one case in the placebo group. Appendicitis signaled when the LLR exceeded the critical value with Poisson MaxSPRT. Per the study protocol, this potential signal was evaluated to determine whether the association was real or not, so data quality issues were addressed. A temporal scan was conducted on these cases and no significant clustering was found. Additional analyses were conducted, which were finer analyses that could control for things that could not be controlled for through sequential analyses. Through logistic regression, a significant result was not found. To further confirm the secondary analysis results, a case-centered analysis was conducted, which is a non-sequential statistical methodology. Through the additional follow-up of this signal, it was concluded that appendicitis following HPV4 was not a true association [Fireman B, et al. Influenza Vaccination and Mortality: Differentiating Vaccine Effects from Bias. *Practice of Epidemiology*. 2009: 170(5): 650-656].

In conclusion, the major findings of this VSD RCA through the VSD active surveillance confirmed no significant increased risk for any of the pre-specified adverse events after vaccination for either age group. No increase was found in the rate of anaphylaxis following HPV4 as compared to previous studies. This study observed zero confirmed cases of GBS within 42 days of HPV4. Based on a probability of observing 0 cases per 600,558 doses, an attributable risk of > 4.4 per million doses can be ruled out.

With regard to the next steps for monitoring and evaluating the safety of HPV vaccines within CDC, additional analyses will be conducted within the VSD to investigate the elevated non-statically significant risk for VTE among 9 through 17 year old females since chart review in the HPV RCA did suggest that there may be an interaction of other risk factors for VTE. GBS and stroke will continue to be monitored until one million doses administered among females 9 through 26 years of age are reached in the VSD. An RCA will be conducted of HPV4 safety among males. If uptake is sufficient within the VSD MCOs, an RCA will be conducted for HPV2. Through VAERS, reports pertaining to HPV4 and HPV2 will continue to be monitored.

Update: HPV Vaccination Coverage Among US Adolescent Females

Shannon Stokley, MPH
Immunization Services Division
National Center for Immunization and Respiratory Diseases

Ms. Stokely presented an update on HPV vaccination coverage among adolescent females 13 to 17 years of age, and summarized some of the programmatic issues pertaining to adolescent vaccination.

Adolescent vaccination coverage in the US is measured using the National Immunization Survey-Teen (NIS-Teen). This survey uses the NIS sample frame methodology. It is a random-digit-dial (RDD) telephone survey, including a national sample of parents of 13 to 17 year olds. The strength of this survey is that, when consent is given, adolescent immunization histories are verified with immunization providers. NIS-Teen began in 2006. The most recent year of data available is from the 2009 survey. All analyses are limited to adolescents with provider-verified immunization histories. The HPV results Ms. Stokley presented during this session were limited to adolescent females only. In 2006 and 2007, the survey was conducted only during the fourth quarter of the year and could only produce national estimates. In 2008, the survey was expanded such that data were collected during all four quarters of the year. The sample size was increased in order to obtain national and state estimates.

With respect to the results from the 2009 NIS-Teen survey, published in August 2010, coverage for HPV was lower than coverage for the other vaccines routinely recommended for adolescents. Approximately 44% of adolescent females received the first dose of the series, and a total of 27% received all three doses. It is important to note that among the girls who initiated the HPV series and had sufficient time to complete the series before the interview date, 68% received all three doses. To put the current results into perspective, similar to coverage for Tdap and the meningococcal conjugate vaccine, HPV coverage has steadily increased each year. However, the increase in HPV coverage between 2008 and 2009 was only 7 percentage points' whereas, the increase in coverage for both Tdap and MenACWY was greater than 10 percentage points.

CDC has results for 56 grantees from 2008-2009, which include the 50 states, District of Columbia, and 5 other urban cities. Based on these data, coverage varies widely by state, with a low of 23% in Mississippi to a high of 69% in Massachusetts. Another way to evaluate grantee progress with implementing HPV is to assess the change in coverage from the previous year. The change in coverage ranged from a decrease of 5 percentage points to an increase of 25 percentage points. While estimated coverage decreased in 5 areas, the decrease was not statistically significant. Coverage with the first dose of the series did not differ significantly by race / ethnicity. However, significant differences are observed by race / ethnicity when looking at coverage with 3 doses where both Black and Hispanic females have lower coverage than White females. With respect to poverty status, for coverage with the first dose of the series, females living below poverty had significantly higher vaccination coverage when compared to females living at or above poverty. However, there were no significant differences in coverage by poverty status when looking at coverage for 3 doses.

In summary, HPV vaccination is increasing but it does remain low and there is wide variation in coverage at the state level. Completion of the series continues to be challenging and will require additional visits. Factors associated with completing the series may be different than factors associated with initiating the series.

While having a safe and effective vaccine is the first step to protecting adolescents, other programmatic issues have to be addressed to ensure that widespread uptake of the vaccine occurs. Challenges to HPV vaccination can be categorized in one of 3 ways: Do adolescents have access to the vaccine? Are providers recommending and administering the vaccine? Are parents willing to accept the vaccine? In this country, vaccine financing policies vary widely by state. Some states are able to universally provide all vaccines to all children regardless of insurance status, while others may only be able to provide vaccine to eligible children through the VFC program. As a reminder, vaccines provided through VFC can only be administered to children meeting eligibility criteria; that is, they must be Medicaid eligible; uninsured; of American Indian or Alaska Native descent; or if they are underinsured if they receive vaccines at a federally qualified health center (FQHC).

Based on a series of health insurance questions included in the NIS-Teen, each adolescent's VFC eligibility status was determined. Approximately 49% percent of the adolescents are privately insured and 33% percent are VFC-Eligible. Of concern are the 17% who are underinsured, but who are not accessing services at FQHCs. Thus, their ability to obtain vaccines may be limited. With the passage of PPACA it is expected that these adolescents will eventually have complete coverage for vaccines, either through private or public insurance; however, full implementation of health care reform is not expected until 2014.

With respect to provision of HPV vaccine, a national survey of pediatricians and family physicians was conducted by Matt Daley and colleagues to assess current practices. While the majority of physicians administered HPV vaccine, physician practices regarding vaccine recommendations varied by the age of the patient. For both specialties, fewer physicians strongly recommended HPV vaccine for patients 11 to 12 years of age compared to older patients. Since younger adolescents are more likely to make preventive visits than older adolescents, and physician recommendations are known to strongly influence parental acceptance of vaccines, a weaker recommendation for this age group may result in missed opportunities for vaccination [Daley et al. *Pediatrics*. 2010;126:425-433].

Further exploration was made regarding the impact that missed opportunities may have on coverage by analyzing the 2009 NIS-Teen to determine the maximum coverage that could be achieved if all indicated vaccines were administered during existing vaccination visits. For the first dose of HPV vaccine, actual coverage is 44%; however, initiation could be as high as 74% if providers had administered HPV during all eligible visits. Results for receiving all three doses were not presented because few girls had made three unique vaccination visits. That being said, to achieve the maximum coverage for the first dose of HPV, not only do providers have to offer the vaccine, but also parents have to be willing to accept the vaccine. In the 2009 NIS-Teen survey, parents of unvaccinated girls were asked whether they intended to have their daughter receive the HPV vaccine in the next 12 months. While approximately 40% were very or somewhat likely to have their daughters vaccinated in the next 12 months, 51% were not likely to have their daughters vaccinated. When asked why not, the top reasons were that their daughter was not sexually active, lack of knowledge about HPV or the vaccine itself, or the vaccine was not felt to be needed. Less frequently, parents mentioned the lack of provider recommendation or concerns about safety.

A number of projects have been undertaken to identify effective strategies to increase coverage. While all of CDC's adolescent-related projects focus on improving vaccination coverage for all of the vaccines routinely recommended for adolescents, they do not have any vaccine-specific projects. The following projects are underway:

- Evaluating the feasibility of providing vaccines in complementary health settings and the evaluation of reminder / recall strategies
- Assessing the impact the immunization recommendations may have on delivery of other clinical preventive services that are recommended for adolescents.
- Assessing the feasibility of providing vaccines in the school setting and billing third party payers
- Evaluating strategies to increase coverage, focusing specifically on interventions performed in the medical home as well as outside the medical home

While school located vaccination is of interest and this strategy has been used successfully in other countries, in the US there are unique challenges that make implementing school located vaccination clinics somewhat challenging. In the US, schools have not been used as a platform for routine vaccination. The majority of vaccines are provided by primary care providers. Funding for school located clinics may not be feasible for some programs. Funds must be available to purchase the vaccine prior to implementing the clinic. Two-thirds of adolescents are not covered by VFC. Recovering the cost of vaccine and other resources used to plan and implement these clinics can be difficult, but one way to recoup some of the costs is by billing third party payers. This activity alone may be overwhelming for some programs, especially those that do not have infrastructure or experience with billing. Establishing partnerships with schools is critical; however, schools may have different priorities than public health. Moreover, there are logistical issues with regard to obtaining parental consent.

The project that is underway to assess the feasibility of billing third party payers for school located vaccination clinics is being conducted by Denver Health, University of Colorado Denver, and Denver Public Schools. The pilot year of the project consisted of implementing a school located vaccination clinic that offered Tdap to 151 students located at one large middle school. In terms of the results of the insurance billing activity, it cost over \$7,000 to conduct the pilot clinic. Of the costs, 36% were billed to third party payers and 57% (roughly \$1,400) of the billable costs were reimbursed. Overall, the reimbursement from third party payers covered only 20% of the cost of the clinic [Data courtesy of Judy Shlay, Denver Health].

The "Teen Vaccine Jam" project is now in its implementation phase and is providing all ACIP-recommended vaccines in 7 middle schools. The process for submitting claims has been improved based upon the lessons learned from the pilot. They will be conducting a thorough evaluation of the project, as well as reviewing all of the claims that were not reimbursed. The findings from this project are anticipated in the coming year.

In summary, some of the results showed highlight opportunities that exist for addressing the challenges presented. The passage of PPACA is sure to have an impact on the delivery of vaccines, given that most adolescents will have insurance coverage for vaccines. Vaccination coverage could be increased significantly if all indicated vaccines were administered during the same visit. This would require minimal resources since providers would be taking advantage of

visits that are already occurring. Most professional organizations already recommend this strategy, but it would be highly beneficial to help providers recognize the occurrence of missed opportunities that may be occurring in their practices and encourage them to make elimination of missed opportunities a priority. Moving forward, it will be important to focus on identifying the best methods for communicating with parents, determine which messages will be the most effective in motivating them to obtain vaccines, and figure out the best ways to deliver these messages. Several studies are underway that will help to address many of these challenges, and identify effective strategies to address them.

Gardasil® Update: Men (Protocol 020)

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Dr. Haupt provided data from Protocol 20, the Gardasil® clinical study of safety and efficacy in males, including information pertaining to efficacy (e.g., external genital lesions (EGL) endpoint; anal intra-epithelial neoplasia (AIN) endpoint; AIN case assignment analysis; persistent anal HPV infection (6-month) endpoint; and AIN intention-to-treat analyses); immunogenicity; and safety.

As is true with all Gardasil® studies, Protocol 20 was a double blind, randomized, placebo-controlled, international study. Approximately 4000 men around the world were enrolled, approximately 3500 of whom were heterosexual men, and about 600 of whom were men having sex with men (MSM). The primary objectives of the study included safety, immunogenicity, and efficacy endpoints. There were two primary efficacy endpoints: 1) Efficacy of Gardasil® against the combined endpoint of HPV 6/11/16/18-related external genital lesions in heterosexual males and MSM; and 2) Anal intra-epithelial lesions (AIN) in MSM only.

As this study involved a specific sub-study to evaluate the efficacy of Gardasil® against anal endpoints, it is important to understand why the decision was made to study MSM. As is typically done in clinical trials, a population that is more highly susceptible to a given specific condition or disease is often studied with the understanding that the results of how that population would be generalized to a broader population. It is well-recognized that MSM have higher incidence rates for anal HPV infection; however, both men and women get anal HPV infection. Anal cancer rates have been increasing in both men and women over the past two decades, and the pathophysiology of HPV infection / disease of the anal canal is similar in both men and women. Therefore, the efficacy results of the MSM AIN study can be extrapolated to the general population of men and women.

In the past, Merck has focused on two populations of analyses. The primary population to demonstrate efficacy is the per protocol efficacy population (PPE). This group is comprised of the subjects enrolled at baseline who are negative by HPV DNA and serology to the relevant HPV type. They remain HPV DNA through the completion of the vaccination series, roughly through month seven. Case counting begins after month seven. Protocol violators are excluded from that analysis. Supportive analyses are also conducted in the intention-to-treat population, termed the full analysis set (FAS). This involves all enrolled subjects who received at least one dose of vaccine or placebo, who had at least one follow-up visit. Case counting begins after Day 1. This population involves subjects who may already be infected with HPV (vaccine and non-vaccine types) at baseline. The efficacy is expected to be lower in this

population. In terms of vaccine-related endpoints, this group includes subjects who may have been infected at baseline, but even if they were not infected, cases are accrued before the completion of the three-dose vaccination series are being assessed.

In terms of the end of study results for the primary end point of vaccine types 6/11/16/18-related external genital lesions, vaccine efficacy was approximately 91%. Most of the endpoints were external genital warts or condyloma for which vaccine efficacy was about 89%. Both of those are highly statistically significant. There were insufficient endpoints for PIN to make any conclusions about efficacy against that endpoint. Regarding the end of study results for the vaccine type related AIN endpoint, the primary pre-specified hypothesis was based on the prevention of AIN of any grade related to HPV 6/11/16/18. Vaccine efficacy was approximately 78% percent. Efficacy was equally high for both low and high grade AIN. There were 4 cases of AIN1 and 3 cases of AIN 2/3. The composite endpoint total is only 5 because an individual subject can have more than one lesion (i.e. an AIN and an AIN 2/3 lesion). While each endpoint would be counted in the specific disease grade endpoint, a subject is only counted once for the composite endpoint of vaccine type related AIN of any grade. In the vaccine arm, 2 subjects had an AIN1 and an AIN2/3 lesion.

Although the study was designed specifically to assess AIN of any grade related to the vaccine types, once the pre-specified hypothesis was met for that endpoint, the further evaluations were undertaken to determine vaccine efficacy against the high risk types HPV 16/18 for high grade AIN 2/3, which is recognized as being the precursor to anal cancer. In this exploratory analysis, vaccine efficacy of approximately 87% was demonstrated against HPV 16/18 related AIN 2/3, and it was just barely statistically significant.

As in all of Merck's clinical trials, we sought to understand vaccine efficacy more completely. In evaluations to more fully understand the observed efficacy of 78% against any grade AIN, it was observed that the AIN sub-study group of MSM were highly co-infected with other non-vaccine types. HPV 6/11/16/18-related AIN endpoints are defined by the following algorithm: (1) An AIN lesion has been adjudicated by the consensus panel as an endpoint (AIN 1, 2, or 3), (2) HPV 6, 11, 16, or 18 is found in the adjacent tissue section of the same block, then (3) This AIN lesion is adjudicated as a vaccine type related endpoint. The presence of non-vaccine HPV types that may occur in that AIN lesion are not considered in the pre-specified endpoint adjudication. However, our analyses demonstrated that anal HPV infection was very common in MSM. Many MSM were infected at baseline with both non-vaccine and vaccine types. It was observed that in some of the AIN lesions where there was co-infection with vaccine and non-vaccine types, and there was often evidence of preceding infection with the non-vaccine type leading to the development of the AIN lesion in the absence of preceding infection with the vaccine type to which the endpoint was attributed.

Given this information, a case assignment analysis was undertaken to better understand the potential causality of the HPV types found in the AIN lesions. Regarding the methodology of the case assignment analysis, any AIN lesion that was co-infected with both vaccine and non-vaccine HPV types was assessed. Detection of HPV DNA from anogenital swabs from the two preceding study visits leading to the development of the AIN endpoint were evaluated. If the same HPV type was found in one of those study visits as was seen in the AIN lesion, causality of that AIN lesion was attributed to that HPV type. If no different HPV type was seen in the preceding anogenital swabs, whatever was found in the lesion was attributed as the HPV found in that lesion. Analyses were conducted on all 29 cases and vaccine efficacy was calculated.

An example of the confounding of co-infection was demonstrated. A case of HPV 6-Related AIN 1 was adjudicated as an AIN endpoint from the Gardasil® arm. The lesion was co-infected with HPV6, HPV35, and HPV56 (All 10 other HPV types tested for are high risk oncogenic types). At Day 1, this subject was infected with HPV45, 51, and 56. For HPV45 and 56, he remained fairly persistently positive throughout the entire study period. He was also positive for the first time with HPV35 at month seven, when it showed up in the lesion and continued to be persistent after that. Based on the case assignment methodology, given that HPV6 showed up only one time in the lesion, this case would be reassigned to either HPV35 or 56 as the causal HPV types. This methodology was subsequently applied to all 29 lesions. Ultimately, 3 of the Gardasil® cases were reassigned to non-vaccine HPV types and zero of the placebo cases were reassigned. That is because this pattern that I just showed you was really not seen in the placebo arm. In the placebo arm, a vaccine type could be assigned in every case as causal because the same vaccine HPV type was present in anogenital swabs in study visits leading up to the lesion development. When calculations were made taking into account these kinds of case assignments, vaccine efficacy was approximately 91% and was equally high across all grades of disease endpoints.

Assessment of vaccine efficacy against six-month anal persistent infection lends support to the case assignment analysis, because efficacy against a persistent infection endpoint is not subject to the confounding of finding multiple HPV types in a given disease lesion. This efficacy is a measure of the vaccine effect against a single specific HPV vaccine type occurrence. Given that HPV infection is the necessary first step in the development of HPV-related disease, this provides evidence for a mechanistic effect of the vaccine's protection against both infection and disease caused by those HPV types. In terms of anal HPV persistent infection, there was very high efficacy in the study of about 95% for the composite of any 4 vaccine HPV types, and was equally high across all 4 vaccine types individually.

Moving to the intention to treat analysis (e.g., the full analysis set), the vaccine efficacy against any grade AIN regardless of HPV type was about 26%. This was fairly similar for both low and high grade lesion endpoints. Most of the AIN lesions attributed to HPV 6, 11, 16, or 18 that occurred after Day 1 were related to infection that was already prevalent at Day 1. These subjects were positive at baseline by either PCR or serology. Baseline HPV vaccine status was about 23% positive by serology, 30% by PCR, and almost 39% one or the other. Similar analyses were done to assess efficacy against non-vaccine HPV types (HPV types 31/33/35/39/45/51/52/56/58/59). In the intention-to-treat analysis against those types, no efficacy was demonstrated.

The peak response anti-HPV GMTs among males 16 through 26 years of age were very high, and seroconversion rates were close to 100%. Dr. Haupt clarified that each type-specific assay has its own internal control, so the GMTs are not equivalent across the types. Thus, the amount of GMT for 16 and 6 cannot be compared. Likewise, GMT levels generated in Merck's assay cannot be compared to other serological assays. In terms of the peak response anti-HPV GMTs among males 16 through 26 years of age, with the exception of the responses to HPV16, the men overall were slightly lower than the women. The immune response observed in the MSM subset of the male study was lower than that observed in the heterosexual males. The seroconversion rates in the MSM were virtually 100%, similar to what has been observed previously.

Based on these results, it appears that a limited amount of antibody is needed to achieve protection. A robust immune responses has been observed across a wide range of age groups in different populations. Virtually 100% seroconversion rates have been observed, and all GMTs, even those that are nominally lower, are well above what is observed with natural infection. Very high efficacy has also been demonstrated against multiple disease endpoints across a wide range of those GMT levels. To date, given the limited number of breakthrough cases in the Gardasil® clinical trials, it has not been possible to establish an immune correlate of protection. The reality is that the differences observed in the GMTs have no impact and no clinical relevance as related to the efficacy afforded by Gardasil®.

In terms of adverse events observed in males in Protocol 20, safety results were highly consistent with what has been observed in other populations. The safety profile is generally favorable, with the most common adverse event being injection site reactions (e.g., typically pain, swelling, and / redness). Serious adverse events were uncommon and occurred equally in the vaccine and placebo groups. In the male study, none of the serious adverse events were deemed to be related to the study therapy.

The overall conclusions are that to date, high efficacy of Gardasil® has been demonstrated against HPV 6, 11, 16, 18-related HPV persistent infection and disease (high-grade and low-grade) at multiple anogenital sites (e.g., cervical, vulvar, vaginal, anal, genital warts). High efficacy has been demonstrated at both mucosal and keratinized epithelial sites, and in both women and men. The pathophysiology of persistent infection of HPV of the basal keratinocyte of stratified squamous epithelia is similar regardless of tissue. Consistently high vaccine efficacy has been observed across all tissue sites. The totality of this means that vaccination with Gardasil® is going to provide a substantial benefit to both men and women through protection and prevention of HPV 6/11/16/18-related infection and disease.

HPV Vaccine for Males: Physicians' Knowledge, Attitudes and Practices

Mandy Allison, MD, MSPH
The Department of Pediatrics, University of Utah
And Children's Outcomes Research Program
The Children's Hospital Aurora, Colorado

Dr. Allison discussed the Children's Outcomes Research Program's survey of physicians' knowledge, attitudes, and practices regarding HPV vaccine for adolescent males. The objectives of this survey were to describe pediatricians' and family medicine physicians' current practices related to the HPV vaccine in adolescent females and males, practices related to sexual health in adolescents, knowledge and attitudes about the HPV vaccine for males, and intention to recommend the HPV vaccine for males if recommended for routine use by the ACIP and other professional organizations, using wording similar to the current recommendation for females.

Physicians were surveyed between June and September 2010. Surveys were conducted in existing sentinel networks as part of the Vaccine Policy Collaborative Initiative (VPCI). The samples were recruited from random samples of AAP and AAFP. Only respondents practicing at least half of their time in primary care were included in these networks. A previous study compared these networks to the AMA master file. Importantly, regarding questions related to vaccine delivery, their responses did not differ. The survey was developed jointly by the study team and CDC collaborators. It was pre-tested in a community advisory panel and pilot-tested in a group of physicians from AAP and AAFP who were not part of the sentinel network. The

survey was administered by mail or through the Internet, based upon provider preference, using methods known to help achieve high response rates. There was a 72% response rate overall, with 82% of pediatricians and 63% of family medicine physicians responding. Respondents were similar to non-respondents for practice setting, region of the country, and urbanicity with a few exceptions. Overall, respondents were more likely to be women and for family medicine, respondents were more likely to practice in an academic, community, or public health center setting.

In terms of physicians' current practices regarding administration and recommendation of the HPV vaccine for adolescent males and females, 97% of pediatricians and 86% of family medicine physicians said that they are currently administering the HPV vaccine to females in their office, and 37% and 23% respectively are currently administering to males in their offices.

With respect to the current strength of recommendation for females, family medicine and pediatricians were combined. For the most part, any differences between them were not statistically significant. Overall, the investigators did not believe that these differences were clinically significant. For 11 to 12 year old females, 51% of physicians indicated that they strongly recommend the vaccine; 36% recommend, but not strongly; 8% make no recommendation; and 2% recommend against the vaccine. Physicians are more likely to strongly recommend the vaccine for older age groups, with 79% strongly recommending for 13 to 15 year old females and 85% strongly recommending for 16 to 18 year old females. For 11 to 12 year old males, 14% of physicians strongly recommend; 18% recommend, but not strongly; 60% make no recommendation; and 4% recommend against. Once again, physicians are more likely to strongly recommend in older males, with 21% percent strongly recommending for 13 to 15 year old males and 22% strongly recommending for 16 to 18 year old males.

Regarding physicians' practices related to adolescent sexual health, physicians were asked whether they routinely discuss sexual activity at health maintenance visits. This was asked for females and males and different age groups. None of the differences between females and males were statistically significant. For 11 to 12 year olds, about 30% routinely discuss sexual activity at health maintenance visits, while 83% routinely discuss this at 13 to 15 years and greater than 90% routinely discuss it at 16 to 18 years. A question was also asked about discussion of sexually transmitted infections, and had very similar results. Physicians were also asked whether they routinely discuss sexual orientation at health maintenance visits in males and females in different age groups. Only 11% routinely discuss this at 11 to 12 years, about 35% at 13 to 15 years, and 51% at 16 to 18 years.

Many questions were posed about physicians' knowledge and attitudes about the HPV vaccine for males. Dr. Allison focused on the responses that the investigators believed to have the most relevance for policy. Of the physicians surveyed, 63% correctly disagreed that the incidence of HPV-associated anal cancer is similar among MSM compared to men overall (notably, 30% admitted that they did not know the answer); 73% percent correctly agreed that the quadrivalent HPV vaccine is efficacious for preventing genital warts in males; 79% correctly agreed that the quadrivalent HPV vaccine is licensed for both males and females aged 9 to 26 years; 52% correctly agreed that the quadrivalent HPV vaccine has been approved by the VFC program for males and 41% indicated that they did not know; and 21% correctly disagreed that CDC's ACIP has recommended the vaccine for routine use in males and 30% indicated that they did not know the answer. In addition, 53% of physicians strongly agreed and 36% somewhat agreed that because HPV is commonly transmitted from males to females, the severity of HPV-associated diseases in females justifies the routine use of HPV vaccine in males; 31% strongly and 42% somewhat agreed that HPV-associated diseases are severe enough in males

themselves to justify routine use of the HPV vaccine in males; 36% strongly and 32% somewhat agreed that it would be easier to administer the HPV vaccine if it were recommended for routine use in both genders; 35% strongly and 37% somewhat agreed that recommended adolescent vaccines overall have made male patients more likely to come in for a preventative health visit; 20% strongly and 33% somewhat agreed that it is necessary to discuss issues of sexuality prior to recommending the HPV vaccine to male patients; 14% strongly and 54% somewhat agreed that the parents of male patients will not think it is necessary to vaccinate their sons since they think that HPV infection is primarily of concern in females; and only 4% strongly agreed and 15% somewhat agreed that vaccination efforts should be targeted at females only and not males since HPV infection is primarily of concern in females. Physicians were also asked what they would emphasize when discussing HPV vaccine for males. Focusing on what they said they would strongly emphasize, 63% would strongly emphasize prevention of genital warts in the patient himself, 62% would strongly emphasize prevention of cervical cancer in his partners, 58% would strongly emphasize the safety of the vaccine, 55% would strongly emphasize efficacy, and 48% would strongly emphasize the prevention of genital warts in the males' partners.

In terms of physicians' intention to recommend the HPV vaccine for males if recommended for routine use by ACIP and other professional organizations using similar wording to that for females, 35% of physicians would strongly recommend the vaccine for 11 to 12 year old males; 40% would recommend, but not strongly; 17% would make no recommendation; and 3% would recommend against. Physicians are more likely to strongly recommend at older ages, with 59% strongly recommending at 13 to 15 years of age, 69% at 16 to 18 years of age; 81% would strongly recommend for 11 to 18 year old males who they knew to be homosexual or bi-sexual. In comparison to current recommendations for females, it appears that physicians may be more likely to strongly recommend the vaccine for females, even if it is recommended by ACIP for males.

The survey has some limitations. The respondents may have differed slightly from non-respondents; sentinel physicians may differ from physicians overall, though prior work suggests not; and most importantly, the survey results report what physicians say they would do. Their actual practices have not been observed.

In summary, while the vast majority of physicians are currently administering the HPV vaccine to females, only about one-third are administering to males. About half of physicians are confused about whether VFC covers the HPV vaccine for males and about half think that the HPV vaccine has been recommended for routine use in males by ACIP. Physicians are more likely to recommend the HPV vaccine for females and males 13 years and older. Physicians emphasize prevention of HPV-related diseases in partners when discussing the vaccine with males, which differs from their approach with females. The majority of physicians recognize the increased risk of HPV-related diseases in MSM; however, about 50% of physicians do not routinely discuss sexual orientation, even with the oldest group of adolescents asked about. Therefore, a recommendation focusing on adolescent males based on sexual orientation would be difficult to implement for this and other reasons.

Cost-effectiveness of Male HPV Vaccination in the United States

Harrell Chesson, PhD
NCHHSTP / Centers for Disease Control and Prevention

Dr. Chesson reported that the routine vaccination of 12-year old girls in the US is a cost-effective use of public health resources. This result is consistent across a wide range of published studies. The reason for this consistency across the models is that estimates of the cost-effectiveness of vaccination of 12-year old girls are not particularly sensitive to uncertainty in the natural history and epidemiology of HPV. In contrast, there is more uncertainty and less precision in the cost-effectiveness estimates for vaccination of adult women, and for vaccination of males as presented during previous ACIP meetings. During this session, Dr. Chesson provided a review and update of issues related to the cost-effectiveness of HPV vaccination of males.

With regard to cost-effectiveness ratios and QALYs, cost-effectiveness ratios simply show the change in costs divided by the change in health outcomes. The change in cost reflects vaccination costs and administrative costs minus the medical costs averted by vaccination. The change in health outcomes typically are calculated as the number of QALYs gained by vaccination. QALYs account for quality and length of life. A QALY is one year of life in perfect health. Death is given a value of 0 QALYs, while one year of life in less than perfect health is given a value between 0 and 1 QALYs depending upon the severity of the health issue. For example, for some of the HPV outcomes, in the recent cost-effectiveness studies, the QALY weights are approximately 0.93 for genital warts and 0.50 for cervical cancer [See Dasbach (1996)]. QALY weights are approximations based on recent cost-effectiveness studies].

Currently, there is no consensus on the appropriate cost-per-QALY threshold for determining the cost-effectiveness of public health interventions in the US. Likewise, there is no official ACIP cutoff for determining the cost-effectiveness of vaccinations. The \$50,000 to \$100,000 cost-per-QALY threshold has often been cited; however, it has been described as arbitrary, lacking empirical or theoretical justification. Another way to think about cost-effectiveness thresholds for vaccination is to look at the cost-per-QALY of recommended vaccines. This table shows the cost-per-QALY for childhood vaccines in the US and the first five listed, from DTaP to Varicella, have been found to be cost saving whether considered individually or as a group. The remaining cost-effectiveness estimates range from \$10,000 to over \$100,000 per QALY. HPV vaccination of 12-year old girls is \$3,000 to \$45,000 per QALY, which compares favorably to other vaccines. As Dr. Ortega-Sanchez noted the previous day, some cost-per-QALY estimates can exceed \$100,000.

With respect to the available estimates of the cost-effectiveness of vaccination of males in the US, all of the models that have looked at routine vaccination of males in the US have taken into account the indirect effects of vaccination (e.g., herd immunity). However, there are differences in models and how this is done. The approaches used to simulate the changing dynamics after the introduction of the vaccine in the population are different. For example, assumptions regarding the degree and duration of naturally acquired immunity can have a major effect on cost-effectiveness estimates. Estimates are also sensitive to the health outcomes included in the study; the quality-of-life assumptions regarding HPV-associated health outcomes; and vaccine cost, coverage, and efficacy. Male vaccination depends critically upon female vaccine coverage, given that as female vaccination coverage increases, the indirect protection of males increases as well. That leaves little room for additional male impact of vaccination.

The first study of the cost-effectiveness of male vaccination was by Taira and colleagues who included only cervical outcomes in their analysis. They found in their higher coverage scenario that the cost-per-QALY of male vaccination was roughly 10 times greater (\$41,000 versus \$442,000) than in their lower coverage scenario. The next generation of studies included cervical outcomes as well as genital warts in both males and females. The Elbasha et al study found that female coverage did have an impact on the cost-per-QALY estimates for male vaccination. The Jit et al study from the UK only assessed one coverage scenario, but found that at high coverage levels, male vaccination could exceed \$1,000,000 per QALY gained. The most recent studies have included cervical outcomes and genital warts, but have also included non-cervical cancers (such as anal cancer) and recurrent respiratory papillomatosis (RRP). In each of these studies (Kim & Goldie [2009], Elbasha & Dasbach / Merck [2010], and Chesson et al), the cost-per-QALY gained by male vaccination increases as female coverage increases; however, for a given coverage scenario, the estimates can vary across the models. This is shown especially in the higher coverage scenarios.

Preliminary, unpublished data from Chesson et al model show how some results can change when key assumptions are changed. Three coverage scenarios were assessed which correspond to 35% coverage; 55% coverage, and 90% coverage of females by age 26. Coverage by age 12 in the three scenarios was 20%, 30%, and 75%. The cost-per-QALY for female vaccination was less than \$15,000 in all of these scenarios. For male vaccination, it ranged from \$30,000 in the low scenario to over \$200,000 in the high coverage scenario. Using a range of cost per vaccine series from \$200 to \$600 for male vaccination, when the vaccine cost per series is \$200, the cost-per-QALY is roughly \$3,000 in the low coverage scenario and less than \$100,000 in the high coverage scenario. Cost per QALY assumptions can change when assumptions are varied about the cost and quality of life impact of HPV-associated health outcomes. Assuming \$500 cost per vaccine series, changing the assumptions regarding QALYs and cost of the outcomes had very little impact on the cost-per-QALY estimates for female vaccination, but had a much greater impact for male vaccination, particularly in the higher coverage scenarios.

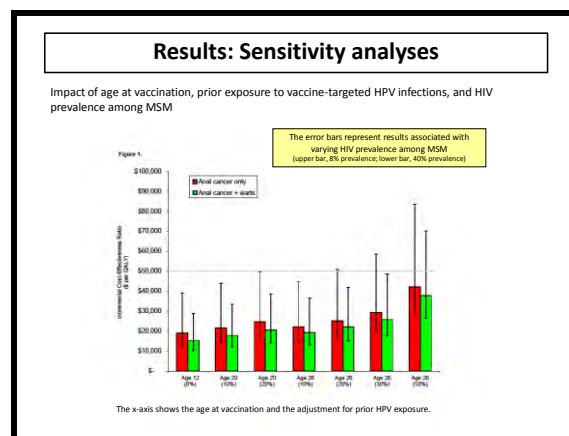
In terms of the cost-effectiveness of male vaccination versus increased female coverage, the published studies of the cost-effectiveness of male vaccination typically focus on adding male vaccination to a female-only vaccination program. An alternative option is to perhaps increase vaccine coverage of females rather than to vaccinate males. An important public policy question to ask is: What is the cost-effectiveness of male vaccination compared to a strategy of increased vaccine coverage of females? To examine this, Chesson et al assessed three vaccination strategies:

- Strategy A: Female only vaccination with 30% coverage of 12 year old girls
- Strategy B: Female only vaccination with 45% coverage of 12 year old girls
- Strategy C: Male and female vaccination with 30% coverage of girls and boys

The typical approach in the published studies would be to compare strategy C to strategy A to determine the cost-effectiveness of male vaccination. In doing so, the cost per QALY estimate is about \$31,000. In a comparison of male vaccination to the strategy of increased coverage of females (Strategy C versus Strategy B), the cost per QALY estimate is about \$185,000. Of note in this particular example is that the increased female vaccination strategy could incur outreach costs of about \$400 per additional girl vaccinated and it would still be as cost-effective as male vaccination.

In a forthcoming study of the cost-effectiveness of HPV vaccination of MSM in the US by Dr. Jane Kim of Harvard, HPV vaccination was assessed of a single MSM cohort with vaccination occurring either at age 12, 20, or 26 years. Previous models was adapted to examine the burden of HPV among MSM with and without HIV. The health outcomes included anal cancer attributable to HPV 16/18 and genital warts attributable to HPV 6/11. The incidence rates and survival probabilities for anal cancer were stratified by HIV status. The vaccine assumptions include 50% coverage, 90% efficacy against 6/11 genital warts, 90% efficacy against 16/18 anal cancer 90%, lifelong vaccine duration, and \$500 cost per series.

An estimate of \$15,290 per QALY for vaccination at age 12 when there is no previous exposure to HPV can be thought of as the lower bound of the possible cost-effectiveness of vaccination of MSM, assuming they could be reached at age 12. For vaccination at ages 20 and 26, the model took into account the possibility of previous exposure to the HPV vaccine types. To do so, the benefits of vaccination were reduced by 10%, 20%, or 50%. In the 10% percent adjustment scenario, vaccination cost about \$17,000 at age 20 and \$19,000 at age 26. These estimates increase to about \$35,000 and \$37,000 respectively in the 50% scenario. Thus, even though vaccination in the mid-twenties of MSM could be cost-effective, it would be more cost-effective at younger ages and would have a greater health impact. The sensitivity analyses, illustrated in the following graphic, show how the results change when changing the age at vaccination, assumptions regarding previous exposure to HPV, and HIV prevalence among MSM.



To summarize, the estimates of cost-effectiveness of male vaccination can vary within a given model when key assumptions are changed, and also across models due to differences in model structure and assumptions. The cost-effectiveness of male vaccination depends upon the health outcomes included in the analysis. As one would expect, the most favorable scenario is when all the potential health benefits of vaccination are included. The cost-effectiveness of male vaccination depends upon vaccine coverage of females. The most favorable scenario for male vaccination is when female coverage is low. For example, in the two most recently published studies, the cost per QALY of male vaccination was \$26,000 and \$62,000 when female coverage was less than or equal to 50%. This compares favorably to many other recommended vaccines and other interventions. However, improving vaccine coverage of females may be a more effective and cost-effective strategy than male vaccination for reducing the overall burden of HPV in the population. HPV vaccination of MSM appears cost-effective, at least in the first and only study to address this issue. Dr. Kim found cost-per-QALY estimates

that were consistently less than \$50,000 over a range of assumptions about age at vaccination and prior exposure to HPV.

Considerations: HPV Vaccine for Males

**Lauri E. Markowitz, MD
NCHHSTP, CDC**

In anticipation of reconsideration of recommendations for males and a possible vote at a future ACIP meeting, Dr. Markowitz reviewed some of the considerations and options regarding HPV vaccine for males discussed by the working group over the last few months. In October 2009, the quadrivalent vaccine was licensed for use in males for prevention of HPV 6/11-related genital warts [<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm>]. ACIP provided guidance that vaccine may be given to males 9 through 26 years of age to prevent acquisition of genital warts, but the vaccine is not included in the routine immunization schedule for males [MMWR 2010; 59: 630]. Quadrivalent HPV vaccine was included in the VFC program, enabling providers to vaccinate eligible males.

Additional information requested by ACIP in October 2009 included efficacy for prevention of anal pre-cancer lesions, further cost-effectiveness analyses, and vaccine coverage in females in 2009 to determine how the program was progressing. Information was subsequently requested on current provider practices and program status after ACIP issued guidance for males. Much of these data were presented earlier in this session, which Dr. Markowitz reviewed. The quadrivalent HPV vaccine has high efficacy for prevention of vaccine HPV type-related anal pre-cancers, genital warts, and persistent infection in males in the per protocol population. Data from the clinical trials in males showed that the vaccine has a good safety profile. Data from the Vaccine Safety Office showed that there were no confirmed safety signals in VSD rapid cycle analysis for females. The national provider survey found high acceptability of male vaccination among providers, although this was lower than that in females. Of note, 36% of pediatricians and 24% of family medicine physicians are currently administering the vaccine to males. The cost-effectiveness of adding male vaccination to a female program depends upon coverage in females, with models showing that at current coverage levels, it is cost-effective to vaccinate males, but not at higher levels. Vaccination of MSM through age 26 years appears to be cost-effective.

With regard to immunization programs, data are available from an AIM survey that was conducted in June 2010 to assess some programmatic issues related the permissive recommendation [Courtesy of Katelyn Wells, AIM survey 2010]. Almost all programs had requested VFC funds for males, and some reported confusion in interpreting the permissive recommendation. All were making vaccine available for males; 70% reported that they made HPV vaccine available to VFC eligible, but did not promote its use in males; and 30% promoted as if there was a routine recommendation. Regarding vaccine uptake, there are no data yet from the NIS, but there are data from Immunization Information Systems (IIS) sentinel sites showing that uptake among males is low. In these 8 sites, less than 1% of males 11 to 17 years had initiated vaccination by the second quarter of 2010 [CDC data, Courtesy of Laura Pabst, CDC].

In terms of the burden of HPV-associated invasive cancers in women and men, data were discussed in detail during the October 2009 ACIP meeting with respect to the average annual number of invasive cases from 1998 to 2003 (identified by histology and anatomic site from the cancer registries in the US). These data showed that while essentially all invasive cervical

cancers are due to HPV, a variable percent of the cancers at other sites are due to HPV. These percentages may vary as more data become available from recent studies on the percent of cancers at these sites associated with HPV. Overall, approximately 15,000 HPV-associated cancers occur in females each year and about 5,000 occur in males. The estimated number due to HPV 16 and 18 are 12,300 for females and 4600 for males. Again, the vast majority HPV-associated cancers at all sites are caused by HPV 16 or 18.

As was mentioned earlier, the incidence of anal cancer is increasing in the US. Between 1992 and 2004, the incidence increased about 2.7% per year, and the incidence is higher in females than males. MSM have a higher risk of anal cancers than heterosexual males. Although these data are not available from cancer registries, there are estimates from various studies indicating the incidence in MSM may be as high as 37 per 100,000. While some providers advocate for cytologic screening for anal cancer in this population, currently there is no recommendation for anal cancer screening in this or any other population. HIV-infected MSM have a higher risk of anal cancers than MSM without HIV infection, which was the reason for the importance of the sensitivity analyses that Dr. Chesson discussed. There has been no decrease during the highly active antiretroviral therapy (HAART) era. In fact, many studies that have examined this have found an increase in anal cancer incidence in these HIV-infected persons in the HAART era compared with the pre-HAART era.

Given what is known, one option being considered by the working group is to retain the current guidance that males may be vaccinated, but vaccination of males is not included in the routine immunization schedule. The second is to recommend routine immunization of males at age 11 or 12 with catch-up. With either of these options, there could be a specific recommendation for vaccination of MSM. There is no consensus on the workgroup at present concerning whether there should be a recommendation for routine vaccination of males, or whether there should be a specific recommendation for vaccination of MSM.

Among working group members who support routine vaccination of males, the reasons for support include safety and efficacy of the vaccine in males, the burden of disease, and issues of equity. Protection of MSM was also a reason for some members to support routine vaccination. In addition to protection of heterosexual males and their female sex partners, some felt that routine vaccination of males is the best way to reach males with this sexual orientation at an age when they could most benefit, and without requiring disclosure of sexual orientation. Some working group members also felt there would be programmatic benefits to a routine recommendation for males, making it easier to vaccinate both females and males. Most working group members who supported a routine vaccination felt that it is cost-effective to vaccinate males at current coverage levels, and that although coverage is increasing, male vaccination would remain cost-effective into the foreseeable future.

Among workgroup members not supporting a routine recommendation for males, some felt there are programmatic challenges at the state and local levels, and that the cost of vaccine prohibits reaching all females. Most of the burden of disease is in females, and priority should be given to vaccinating females. Most working group members who did not support a routine recommendation for males felt that for protection of MSM, a recommendation should be made for MSM specifically. Those not supporting a routine recommendation also felt that if coverage of females is high, it is not cost-effective to vaccinate males, and if coverage of females is low, it would be more cost-effective to increase coverage of females than to vaccinate males.

Cost and cost-effectiveness impacted considerations for most working group members. Of the members who do not support of a routine recommendation for males, most would reconsider if the vaccine price was lower. Vaccine price for quadrivalent HPV has increased in the US since first licensure in 2006 from \$96 per dose to \$108 per dose on the VFC contract.

Concerning MSM, the working group did not feel that it would be feasible to target young adolescent males based on sexual orientation, and acknowledged that there are programmatic challenges in reaching this group at an age when they would benefit most without a routine recommendation. However, for those males who have disclosed their sexual orientation, HPV vaccine could be recommended or a strong guidance provided. Concern was expressed that a large percentage of MSM seeking care may already have been infected or exposed to HPV vaccine types. However, the model described during this session showed that vaccination into the 20s appears to be cost-effective for MSM, even after taking into account prior exposure. Some working group members, particularly those supporting a routine recommendation, expressed concern about stigma if there is a specific recommendation for MSM that might impact the overall program.

The future plans for the workgroup are to await FDA review of the BLA. The workgroup will have further discussion of options for HPV vaccine use in males, and will hopefully reach consensus. CDC plans to review additional data with the working group as well as the full ACIP membership, including more information about HPV-related disease in males. Data will also be reviewed that are now available from a few immunogenicity trials of HPV vaccine in HIV-infected individuals. It is anticipated that there will be further discussion and consideration for a vote at future ACIP meeting. The working group specifically requested that ACIP offer feedback on the following:

- Feedback on options proposed
- Other issues that require discussion
- Additional data for ACIP review

Discussion Points

Dr. Marcy reported that he has National Cancer Institute (NCI) data that were much different for cancer. His data show 25,240 oral cavity / oral pharyngeal cancers; and 6300 HPV-related. With larynx, anus, and penile, he has 11,200 HPV-related cases in males, which is almost exactly same number as the 11,200 cases of cervical cancer predicted for 2009. He thought an update on the cancer incidence in males would be important.

Dr. Markowitz replied that they have been discussing these issues. Their working group member from the Cancer Division was not present to comment. One of the issues is that some of those numbers are based on all cancers at those sites. For cervical cancer, almost 100% of cervical cancers are due to HPV. However, not all oral, pharyngeal, head, and neck cancers are due to HPV. There is some confusion regarding the terminology, and they know this needs to be clearer. The numbers she showed are from CDC's cancer registries. She agreed that everyone needed to get together on this because there are some differences on the various cancer websites.

Dr. Marcy wondered whether a QALY would be the same for an unemployed black male in inner city Detroit as would be for a former CEO, and who determined that genital wart have a QALY of 0.93? Out to two decimal points is impressive.

Dr. Chesson responded that there are a variety of ways to estimate the QALY weights. For genital warts, they were primarily based in the initial studies on expert opinion. Recently, there have been some surveys of the general population and people with genital warts to assess the burden of disease using established instruments in health economics. The surveys more or less assess all socio-economic groups. Often a convenience samples from STD clinics is used. A QALY is a QALY regardless of who it is.

Dr. Keitel requested clarification from Dr. Chesson regarding the costs per QALY gained by HPV vaccination in the three coverage scenarios where males and females were dichotomized in terms of whether the assumption was that the other gender was not being vaccinated.

Dr. Chesson replied that for female vaccination, they assumed female only vaccination. The cost per QALY estimates for male vaccination assumed that females were being vaccinated, so they were adding male vaccination to female vaccination. The coverage scenarios for their model are similar for males and females when both are being vaccinated.

Dr. Judson thought that because the QALY figures for genital warts would always be subject to debate, he thought this should be separated out, at least for men, so that people could see what part of the QALY costs are attributable to cancers and what part are attributable to genital warts. He agreed with Dr. Marcy. From decades of treating patients in an STD clinic, most genital warts are relatively small, not the ones seen in the textbook, and are relatively of little concern in patients. In fact, 50% of patients who are diagnosed with genital warts in an STD clinic did not even notice them. Once it was brought to their attention, they did not seem to be very concerned about it. He thought they probably had also been over-diagnosing genital warts in STD clinics as time went on. Related to future cost-effectiveness, trends in cervical cancers in the US appear to have decreased from 12,000 to 10,000. Deaths have decreased from 5,000 to 3,800. If these data are current, the trends have been very favorable and may begin leveling off. The same may be true for anal cancers in reverse, in which they appear to be increasing, which he would attribute to HIV infection. With extended survival and treatment, AIN deaths may be actually increasing. That would be expected because until 1995, HIV patients were dying much faster, so there was not time for the development of long-term HPV AIN.

Dr. Markowitz responded that there are some differences in the literature about the some of the QALY issues regarding genital warts. These data certainly can be presented to the committee. There are data showing that there are more issues around quality related to those than maybe Dr. Judson was indicating. She thought his interpretation of the increase of anal cancer in HIV-infected MSM was correct. HIV-infected persons are living longer and may have more chances of HPV exposure as well.

Regarding immune response among MSM to the 4 serotypes in Dr. Haupt's presentation, Dr. Meissner inquired as to how seroconversion was defined if they did not know what the correlate of protection was. He wondered whether Dr. Haupt had any data on the decay of antibodies and whether a booster may be necessary.

Dr. Haupt replied that the serostatus cutoffs were established in the assay years ago based on serological specimens of likely positives and likely negatives. They arrived at a serostatus cutoff in their assay based on trying to define a cutoff that was very specific to defining whether a subject was likely to be negative or likely positive. Status would likely be positive based on clinical history and known HPV DNA status. That is how the serostatus cutoff is established, and this has been very useful as a way to develop a highly specific assay. Granted, the

serostatus cutoff is not correlated necessarily with a known immune correlate of protection. They are starting to observe that if subjects seroconvert, they have very high efficacy and rarely is there any breakthrough disease. It may be that the serostatus cutoffs defined years ago are fairly close to an immune correlate. It has been fairly well-established that the amount of antibody required to prevent infection is very small. They are generating immune responses with their vaccines that are much greater than is probably required. There is a very similar pattern for all 4 types in all populations. The peak after month seven appears to decrease somewhat over the next 18 months. By about 2 years out, many people arrive at a relatively stable plateau phase. To date, most of Merck's data have been from their studies in women. There is no evidence whatsoever of any breakthrough disease occurring a longer time out following vaccination, irrespective of the antibody level at that time.

Dr. Sawyer said that the significant decrease in predicted vaccine efficacy in the intent-to-treat population as opposed to the per protocol population said to him that in order for vaccination to be effective, they would have to target very young males below the age in the clinical trial. Otherwise, he did not believe the intervention would be nearly as effective. Based on Dr. Allison's presentation, it was clear that they would have to get that message to providers as well, because they are not focusing as much on the very young population. He also wondered whether Dr. Chesson's sensitivity analyses included efficacy calculations based on the much lower efficacy in the intent-to-treat population.

Dr. Haupt reiterated that from the clinical studies, the age group of the vaccine participants was 16 to 26 years of age. The baseline HPV status for the MSM subjects for the vaccine types was about 22% positive by PCR, and about 39% serology positive. That means that about 60% of the 16 to 26 year old sexually active MSM were negative to all 4 types in the vaccine by either methodology of detection. There is less benefit at the intent-to-treat level, because there are men who are already exposed and infected. He also pointed out that vaccine efficacy in the intention-to-treat for the vaccine types was about 50% for high grade AIN 2/3. That very much aligns with what was observed for prevention of CIN 2/3 in the women's studies in a similar intention-to-treat population.

Dr. Chesson indicated that in their model, they assume that there was no efficacy against a vaccine type if the person had been exposed to that type prior to vaccination. The more complex models also addressed this issue, but in a different way.

Dr. Temte pointed out that as a clinician, it is a rare event that he would identify an adolescent male being potentially MSM. He wondered if there were any data about the preventative care seeking behavior of MSM and clinical practice in terms of 16 year-olds.

Dr. Markowitz was not aware of any data. She thought there would be some data from the BRFSS surveys that include some general information about sexual orientation disclosures. However, she did not think these included specific questions on healthcare seeking behavior.

Dr. Keitel wondered whether, among the women and men Merck has continued to follow for persistence of antibody, any had actually converted to seronegative during follow-up. If so, she wondered what the timeline of that had been. She asked this in the context of concerns expressed about the length of protection that might be expected.

Dr. Haupt replied that depending on the HPV type, some subjects had become nominally seronegative. Merck's assay is a competitive inhibition assay measuring one antibody against a known neutralizing epitope. This assay does not measure the full range of antibodies that are

produced in response to the vaccine. With the Merck assay, they see nominal seronegativity over time, but have not yet seen any breakthrough disease related to that. It may be that immune memory plays a more important role in terms of the durability of the immune response. Importantly, Merck will continue to monitor long term protection, and has extended all of its studies in all populations to follow long-term efficacy over time.

Dr. Duchin requested clarification from Dr. Chesson regarding whether the cost-effectiveness analyses presumed that the duration of protection was lifetime. He also requested that some models be presented in the future that incorporated shorter duration of protection. With respect to incomplete vaccinated persons, it seemed that the models also assumed completion of the series for those persons who are vaccinated. Based on the data presented earlier, about half of the people who had been vaccinated were not completely vaccinated. He wondered whether incompletely vaccinated persons could be incorporated into the model (e.g., a real world scenario).

Dr. Chesson replied that the base case assumption in the Chesson et al and Jane Kim MSM models was that duration of protection was lifetime. He also indicated that they could provide the requested results at a future meeting.

Dr. Englund asked Dr. Haupt the duration of time he had for the follow up for the MSM portion of the Merck study.

Dr. Haupt responded that the clinical study was designed to be a 3-year study. Their Data Safety Monitoring Board (DSMB) had them complete that study earlier. The final results presented represent that time period. The study has been extended to include a 10-year follow-up period. Thus, all subjects are being re-enrolled into Protocol 20 (heterosexual men and MSM) to follow them for a total of 10 years. Effectiveness, immunogenicity, and safety of the vaccine over that time will be evaluated. The MSM who are re-enrolling will have high resolution endoscopy and anal Paps, and AIN lesions will be evaluated as well. Responding to Dr. Duchin's question, the Merck health economic model uses what he would call real world coverage rates, incorporating current female vaccination scenarios in terms of actual coverage and completion of the vaccination series. The Merck model includes the real world calculation of the female vaccination currently, and how it affects male vaccination value.

Dr. Meissner said he did not have a sense of how many people who have genital infection also have anal infection with HPV, and whether anal sex is necessary to have an anal infection. That is, is anything known about the mechanism of how that occurs?

Dr. Markowitz replied that they could present some additional data on that. Cervical infection has been shown to be a risk factor for anal infection, so perhaps there is a field effect. Receptive anal intercourse is a major risk factor for anal HPV infection, but anal infection can occur with contact other than anal intercourse. She did not have data with her regarding how often a heterosexual person who does not engage in anal sex has an anal infection; however, this could be presented at a later meeting as studies have been conducted in heterosexual males to assess infection.

Dr. Judson added that things get moved around a lot in the contiguous anal-genital area. For women with gonorrhea, the anal site is almost as sensitive as the vaginal site for detecting gonorrhea regardless of any history of anal exposure. He was sure the same would be true for highly infectious mobile secretions of HPV.

Dr. Marcy indicated that a paper was published in the *Journal of Infectious Diseases* in 2010 showing the 11.8% of men who have sex with women have anal canal HPV infection.

Dr. Schuchat requested clarification from Dr. Chesson about how the models work when assuming certain coverage among males in terms of the indirect effect to protect females. Most of the vaccination targets are younger people under 26 years of age. She wondered whether the age of the partner was factored into the model in terms of vaccinating younger people.

Dr. Chesson responded that the models take into account that people tend to have sex partners who are near their age or similar in age.

Dr. Turner (ACHA) indicated that he had been on the HPV Working Group for a number of years and that Dr. Judson and he do not see eye-to-eye on the issue of genital warts. Dr. Turner believes that there is a tendency to minimize or trivialize genital warts, and he challenged any male in the room to tell him that diagnosis of the genital wart in themselves would be of no consequence. It is not because of the medical consequences. It is because of the social consequences and what it does to relationships. In his world where of private practice and college students, a genital wart is exceedingly disruptive to a young man and his relationship with a committed person. He has seen marriages, families, and young people's lives extremely disrupted by it. The men he sees would rate a genital wart on the QALY scale of just above death, 0.01 perhaps. He is also an advocate on behalf of the lesbian, gay, bisexual, or transgender (LGBT) community in college health, and they have been lobbied pretty heavily to advocate on behalf of a universal male vaccine. They deal with an extremely bright and educated population who are aware that it is, in fact, cost-effective using the current criteria to universally vaccinate males because there is such a low uptake among females.

Dr. Fryhofer (ACP) indicated that ACP represents over 130,000 Doctors of Internal Medicine and medical students throughout the country. She greatly appreciated the discussion of physicians' attitudes and practices that were described, but it only included family medicine doctors and pediatricians. Many internists see adolescents and many administer vaccines in these age groups. They provide catch-up vaccination, and coordinate care for probably most of the patients who have HPV-related disease when they are older. Thus, she encouraged the inclusion of internists in the future when assessing physician attitudes and behaviors.

Dr. Salisbury (DOH, UK) indicated that they had just published the second year follow-up from their adverse event reporting for the bivalent vaccine. For 4.5 million doses of vaccine, there have been roughly 4500 cards submitted of adverse reports, which is a rate of roughly 1 per 1000. By far the most common reports were the either injection site reactions or events relating to the vaccination rather than the actual content of the vaccine. They have conducted similar analyses for chronic fatigue syndrome (CFS), GBS, and encephalitis using rapid cycle analysis. They have not observed any indication that there is a causal association between those events and the bivalent vaccine. In one tragic event, a girl who was vaccinated in school collapsed about an hour after vaccination and died shortly thereafter. Sadly this was seized upon by some individuals as an indication of the lack of safety of the vaccine. The reality was that this girl had an enormous invasive tumor in her thorax that involved her mediastinum, lungs, right atrium, and had almost given her cooptation of the aorta. It was absolutely clear that the vaccine played no part in her death, but it was not portrayed that way by some individuals. In terms of their program, the catch-up up to 18 years has now been completed, so the UK is only vaccinating the routine 13 year old cohort. Coverage for the first year for ages 12 to 13 was completed a year ago, and was 90% effectively for the first dose and just over 80% for the third

dose. In addition to pride for that achievement, this relates to the economic analysis and cost-effectiveness in terms of vaccinating males. Under those circumstances, their predictions were that it was not going to be cost-effective to vaccinate males. Despite that, they will continue to assess the marginal benefits that would accrue in terms of some of the non-cervical cancers, taking into account the female protective effect on males. They have again assessed the QALY value of warts, and having done some attitudinal work with those who suffered, the QALY value came out very similar to the US QALY value. It was interesting to see in the Colorado data that the force of recommendation increased with the age of the girls. He wondered whether that was because they were not being vaccinated at a younger age, which encouraged people to push the recommendation harder, or whether they should have been recommending vaccination more forcefully at a younger age.

Ms. Stinchfield (NAPNAP) thought that the Colorado information was very helpful, but thought that there was a gap, especially with HPV. In many of the STD clinics, the providers are also nurse practitioners. She guaranteed a high rate of return if nurse practitioners are surveyed. She suggested that CDC increase the funding for this. She also thought Dr. Salisbury should offer a report on how the vaccine rates were so high in Great Britain.

Dr. Lewin (Novartis) inquired as to whether anyone could estimate when they would reach 50% coverage with 3 doses, what efforts are planned to achieve higher rates, and what the costs would be.

Dr. Schuchat responded that the poor 3-dose US completion data are a rallying cry upon which CDC will focus. Efforts are underway to identify best practices for reaching this group, which include a focus on completion of the series. As noted earlier, there is major variation state to state. Few states have done extraordinarily well in the past year or two. CDC is committed to determining how to increase coverage.

Dr. Katz asked whether Dr. Turner had any data on college health programs and the percentage of young women and / or young men who are receiving HPV.

Dr. Turner (ACHA) replied that they, and that it is based on a survey conducted among students every year called the National College Health Assessment. Last year, 39% of students said that they had received HPV vaccine (15% males; 26% to 38% females). There is major uptake among males. ACHA is not pushing this as an organization, but a number of college health insurance plans that cover it do not distinguish between male and female coverage. They also have a very proactive, educated LGBT community who is promoting it among students.

Dr. Marcy asked Dr. Salisbury to speak about whether they are observing syncope in Great Britain, noting that it is a major problem in the US.

Dr. Salisbury (DOH, UK) replied that they have experienced syncope as well. These are categorized as psychogenic. It is not what is in the syringe—it is the syringe.

Prior to Dr. Haupt's presentation, Dr. Pickering pointed out that some of them were very comfortable with the antibody responses observed after HPV, and modeling shows that this may not be long-term. The previous day they engaged in a long discussion regarding meningococcal disease and loss of antibodies. Dr. Haupt mentioned during his presentation that Merck is observing people who become seronegative after being immunized. To follow up on what Dr. Keitel said, Dr. Pickering posed several questions: Is this type specific? Can you give us some quantification about the number? Is there a trend toward loss of antibodies?

What is this time then since the immunizations? Do you have enough of these individuals to offer predictors of this antibody loss?

Dr. Haupt responded that the immune response as measured in the competitive assay is type-specific. They have observed more seronegativity with type 18 over time, which they believe is related to the fact that they are measuring one specific antibody. They are probably not measuring the immunodominant antibody for type 18. For some types, they have not seen any seronegativity over time. The decay curve is very slow after about 2 years out from vaccination, and there is no evidence of vaccine breakthrough in the long-term. As an additional piece of information, Merck has recently developed a total immunoglobulin G (IgG) assay to try to understand and get more sensitivity around immune response using a total IgG assay. In that assay, based on the same kinds of evaluations, 100% seroconversion is observed 5 years out. The individuals who were seronegative on the competitive inhibition assay have antibodies as measured in the total IgG. Dr. Haupt believes this to be a function of the assay used to define the baseline status and to measure a response to the vaccine. He did not think the competitive immunoassay was the type of sensitive assay that would be used to follow long-term response to the vaccine. It is very clear so far that there has been no breakthrough disease even in individuals who have antibodies that cannot be measured. Merck will soon publically present data from one of the long-term studies conducted the Nordic countries. In that study, there have been zero breakthrough cases seven years out in individuals who were vaccinated.

Dr. Baker clarified that there was one difference between the meningococcal discussion and this discussion. For HPV, licensure was based on efficacy. For meningococcal disease in adolescents and adults, licensure was based on serologic correlates of immunity. It would be nice to have that for HPV, but right now, they do not have a correlate.

Vaccine Supply

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

Dr. Rodewald reported on the supply status of adult hepatitis B, adult hepatitis A, MMRV, and zoster vaccines.

Merck is not currently distributing its adult hepatitis B formulation other than the dialysis formulation, which returned to the market in August 2010. The adult formulation is not anticipated to be available until the first half of 2012. Production and supply of GSK's adult hepatitis B vaccine (prefilled-syringe presentation) and hepatitis A / hepatitis B combination vaccine currently are sufficient to meet the demand for routine adult usage of this vaccine. Merck does not anticipate its adult hepatitis A vaccine to be available until the second half of 2012. Production and supply of GSK's adult hepatitis A vaccine and hepatitis A / hepatitis B combination vaccine currently are sufficient to meet the demand for routine adult usage of this vaccine.

Merck began taking orders for MMRV in May 2010. A limited number of doses continue to be available for distribution. Merck has adequate supply of both their MMR and varicella vaccines to meet current demand.

The zoster vaccine is the only vaccine that does not have an alternative. As noted earlier by Dr. Bresnitz, Merck will begin clearing current backorders in December 2010 and expects to release doses more regularly in 2011. Backorders could still occur during early 2011 as Merck works to build inventory of ZOSTAVAX®.

GSK anticipates intermittent supply constraints for individual presentations of KINRIX® vials through early November 2010; KINRIX® syringes through January 2011; and ENGERIX-B® adult vials through March 2011. Alternative products, presentations, and brands are available.

CDC's Vaccine Supply / Shortage webpage is continually updated and is located at the following url: <http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm>

Immunization Schedule: 0-18 Years of Age

Overview

Cody Meissner, MD
Harmonized Schedule Work Group Chair
Tufts Medical Center

Dr. Meissner presented an overview of the activities of the Harmonized Immunization Schedule Work Group in 2010. The childhood and adolescent immunization schedules are revised annually. The intent was that during this session, the proposed wording for the 2011 schedules would be presented and a vote would be taken. While the plan was to move forward with that vote as planned, several changes were voted upon the previous day, so the final version was not available at the time of this session. Typically, approved schedules are published in January in the *MMWR*, *Pediatrics*, and the *American Family Physician*.

The Harmonized Schedule Work Group is one of four permanent working groups. Dr. Meissner recognized the members of the Work Group during 2010 and thanked them for their time. He particularly acknowledged the contributions of Dr. Susan Lett, whose term on ACIP recently ended in June 2010. They look forward to Dr. Renée Jenkins joining the group in 2011. He also acknowledged the contributions of Jeffrey Berg, who represented AIM.

The fundamental approach to the annual childhood and adolescent schedules is to accurately and succinctly reflect existing ACIP recommendations. The schedules should not make new immunization policy, except in unusual circumstances. The version of the schedule presented to ACIP for approval during this session was developed using an iterative process. Input was first obtained from work group members during scheduled monthly conference calls. ACIP recommendations published since January 2010, notably PCV13 and influenza, were added at this stage. The work group-revised document was then circulated among CDC SMEs, and comments provided by CDC SMEs were then discussed during a monthly work group call. A document that consolidated work group and CDC SME revisions was submitted for internal CDC clearance in early October.

The basic layouts of the 2011 schedules are unchanged from the 2010 schedules. There are three separate schedules each with its own footnotes: 0 through 6 years, 7 through 18 years, and catch-up schedules for 4 months through 6 years and 6 through 18 years. The catch-up schedules are for children who start late or whose vaccinations have been delayed by more than one month.

In the past, because of changes made in the text by *MMWR* editors, the version of the schedule published in *MMWR* could differ slightly 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 help ensure that the published version closely matches the version approved by ACIP. Wording changes were made to numerous footnotes in all three schedules to improve clarity and readability. By long-standing convention, each schedule must fit on one side of an 8½ by 11 inch page. Consequently, the space available for footnotes is always limited. As more words were added over the years, the point size of the font was reduced. In an attempt to reduce the number of words in the footnotes and enlarge the font, redundant text was removed. That is, information presented in the grid of the schedule, was removed from the corresponding footnote.

2011 Immunization Schedule: 0-18 Years of Age

William Atkinson, MD, MPH

Harmonized Schedule Work Group CDC Lead

National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

Dr. Atkinson reviewed the specific changes in the schedule for 2011, emphasizing that the events that transpired the previous day this much more difficult in that five separate new recommendations were voted upon—four of which are applicable to the child and adolescent schedule. On October 27, 2010 ACIP approved new recommendations for meningococcal conjugate and Tdap vaccines applicable to the child and adolescent schedule. To be included on the schedule, these recommendations must also be approved by AAP and AAFP. The deadline for submission for the January 2011 publication by AAP and AAFP is December 1, 2010. This serious timeline meant that internal changes had to be approved prior to this meeting. In the last several years, it has been very easy because ACIP had been relatively quiet in October and had not added anything in. That all changed following the votes of the previous day. The original plan was to submit this and the adult 2011 schedules to the *MMWR* editors the week following the ACIP meeting. In order to do so, the five new and important recommendations voted upon the previous day could not be added.

The footnotes must to be created, approved by the SMEs, and approved by ACIP. Given that this would be impossible, it was proposed that publication of both schedules be moved to February 2011. That would give them time to craft the footnotes, which have to be carefully worded to fit into the space available and have them approved by AAP, AAFP, and ACIP. Otherwise, the schedule would have to be sent forward without the changes. Unless there was serious disagreement, the preference would be to move the publication date to February in order to include the new recommendations.

Dr. Atkinson then summarized what was done prior to the votes the previous day, which reflected a summary of the recommendations approved throughout the last year. Proposed changes to the 2011 schedule for children 0 through 6 years were to revise the wording for the yellow bar label, guidance on the hepatitis B vaccine schedule for children who did not receive a birth dose was added (footnote 1), information on the use of PCV13 was added (footnote 5), and guidance on administration of 1 or 2 doses of influenza vaccine based on the child's history of H1N1 was added (footnote 7). Dr. Atkinson noted that the summary document distributed to ACIP members and liaisons indicated a change in the abbreviation for meningococcal conjugate vaccine in both the 0-6 year and 7-18 year schedules from MCV4 to MenACWY. After additional internal discussion, it was decided to leave the abbreviation as MCV4. An error was introduced in the 2010 schedule on the legend for the yellow bar, which stated the range of recommended ages for all children, "Except high risk children" which is not accurate. The yellow bar indicates the recommended ranges for all children, which will be corrected. That was an edit introduced by the *MMWR* that failed to be recognized before publication.

The two new footnotes for hepatitis B are nothing particularly controversial. The new footnote states, "Infants who did not receive a birth dose should receive 3 doses of HepB on a schedule of 0, 1, and 6 months" and the consolidated wording states, "The final (3rd or 4th) dose in the HepB series should be administered no earlier than age 24 weeks."

Regarding 13-valent PCV (PCV13), ACIP's recommendations that were published in the *MMWR* on September 3, 2010 were summarized [*MMWR* 2010;59(No. 6):258-61 (September 3, 2010)]. New footnotes added include the following:

- ❑ A PCV series begun with 7-valent PCV (PCV7) should be completed with 13-valent PCV (PCV13)
- ❑ A single supplemental dose of PCV13 is recommended for all children aged 14 through 59 months who have received an age-appropriate series of PCV7
- ❑ A single supplemental dose of PCV13 is recommended for all children aged 60 through 71 months with underlying medical conditions who have received an age-appropriate series of PCV7 See *MMWR* 2010;59:258-61
- ❑ The supplemental dose of PCV13 should be administered at least 8 weeks after the previous dose of PCV7

Following extensive consultation with the Influenza Division about guidance for the very confusing issue of which children should receive one or two doses, a new footnote was added which states that, "Children aged 6 months through 8 years who received no doses of monovalent 2009 H1N1 vaccine should receive 2 doses of 2010-2011 seasonal influenza vaccine. See *MMWR* 2010;59(RR-8):33-34."

Changes to the 0 Through 6 years meningococcal footnote (footnote 11) are as follows:

11. Meningococcal conjugate vaccine, quadrivalent (MCV4). (Minimum age: 2 years for Menactra and 11 years for Menveo) meningococcal conjugate vaccine (MCV), and for meningococcal polysaccharide vaccine (MPSV4)

- Administer MCV4 to children aged 2 through 10 years with persistent complement component deficiency, anatomic or functional asplenia, and certain other conditions placing them at high risk and those with increased risk of exposure including travel to countries with highly endemic or epidemic disease and during outbreaks caused by a vaccine serogroup.
- Administer MCV4 to children at continued risk of meningococcal disease who were previously vaccinated with MCV4 or MPSV4 or meningococcal polysaccharide vaccine after 3 years if first dose administered at age 2 through 6 years. See *MMWR* 2009;58:1042-3.

These changes are essentially for clarification. Some of the generic wording such as “and certain other conditions” were replaced with very specific wording about what these conditions are. The two new meningococcal conjugate recommendations made the previous day will have to be added to this footnote as well.

Proposed changes to the 2011 schedule for children 7 through 18 Years include revision of the wording for the yellow bar label; removal of the reference to a specified interval between Td and Tdap (footnote 1); “Females” added to HPV in grid and HPV footnotes condensed (footnote 2); guidance on administration of 1 or 2 doses of influenza vaccine based on the child’s history of H1N1 added (footnote 4) (same as 0-6 schedule); and information on use of PCV13 was added (footnote 5) (same as 0-6 schedule). The Tdap footnotes will need to be revised due to the vote the previous day.

The 7 through 18 years meningococcal footnote (footnote 3) will be revised as follows, with the exception that modifications still must be made based on the vote from the previous day:

3. Meningococcal conjugate vaccine, quadrivalent (MCV4). (Minimum age: 2 years for Menactra and 11 years for Menveo)

- Administer at age 11 or 12 years, or at age 13 through 18 years if not previously vaccinated.
- Administer to previously unvaccinated college freshmen living in a dormitory.
- Administer MCV4 to children aged 2 through 10 years with persistent complement component deficiency, anatomic or functional asplenia, or certain other conditions placing them at high risk and those with increased risk of exposure including travel to countries with highly endemic or epidemic disease and during outbreaks caused by a vaccine serogroup.
- Administer to children previously vaccinated with MCV4 or meningococcal polysaccharide vaccine (MPSV4) who remain at increased risk after 3 years (if first dose administered at age 2 through 6 years) or after 5 years (if first dose administered 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;58:1042-3.

No specific changes are proposed to the utterly complicated catch-up schedule, although some minor changes will be made to the footnotes, including the addition of the minimum age for HepB dose 3 (footnote 1), guidance for use of Hib vaccine in persons 5 years and older will be condensed (footnote 4), and information on the use of PCV13 will be added (footnote 5). The Hib footnote will be condensed to read as follows:

4. *Haemophilus influenzae* type b conjugate vaccine (Hib).

• 1 dose of Hib vaccine should be considered for Hib vaccine is not generally recommended for persons aged 5 years or older. No efficacy data are available on which to base a recommendation concerning use of Hib vaccine for older children and adults. However, studies suggest good immunogenicity in persons aged 5 years or older who have sickle cell disease, leukemia, or HIV infection, or who have had a splenectomy. administering 1 dose of Hib vaccine to these persons who have not previously received Hib vaccine is not contraindicated.

Changes made to the 2011 “catch-up” schedule pneumococcal footnote (footnote 5) will be as follows:

5. Pneumococcal vaccine.

- Administer 1 dose of 13-valent pneumococcal conjugate vaccine (PCV13) to all healthy children aged 24 through 59 months with any incomplete PCV schedule (PCV7 or PCV13) who have not received at least 1 dose of PCV on or after age 12 months.
- For children aged 24 through 59 71 months with underlying medical conditions, administer 1 dose of PCV13 if 3 doses of PCV were received previously or administer 2 doses of PCV13 at least 8 weeks apart if fewer than 3 doses of PCV were received previously.
- A single dose of PCV13 is recommended for certain children with underlying medical conditions through 18 years of age. See age-specific schedules for details.
- Administer pneumococcal polysaccharide vaccine (PPSV) to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant, at least 8 weeks after the last dose of PCV. A single revaccination should be administered after 5 years to children with functional or anatomic asplenia or an immunocompromising condition. See *MMWR* 1997;46(No. RR-8).

Dr. Atkinson requested discussion pertaining to the changes shown, as well as the proposed publication delay to February 2011.

Discussion Points

Dr. Baker went on record to say how nimble one part of the government was in terms of delaying publication so that new recommendations could be included.

Dr. Atkinson indicated that this had not previously occurred during tenure. Assuming that it could occur again in the future, there must be an established mechanism for a rapid feedback loop. Perhaps AAP, AAFP, CDC, and all partners could convene ad hoc meetings the next week.

Dr. Baker indicated that she and Dr. Pickering suggested voting on what was presented, distributing the additional changes as soon as possible, and having ACIP subsequently engage in an email vote.

Dr. Meissner suggested vetting the changes through the work group prior to disseminating them to the full ACIP membership.

Dr. Pickering clarified that they would not need to vote specially on the changes, given that nothing would be added to the schedule that had not been voted on.

Dr. Baker pointed out that approval would also be needed by the partner organizations involved in this.

It was not clear to Dr. Cieslak why a vote was needed at all, given that the schedule was merely an encapsulation of the recommendations already made. They had already seen that the *MMWR* editor could make mistakes in the wording even after ACIP voted. He preferred to see this moved into the capable hands of CDC staff, and for there to be consultation with ACIP members on an informal basis in order to produce a document that encapsulated what they had already said in an efficient and useful manner.

Dr. Baker replied that while CDC could consider this, for this meeting, they must vote on the two schedules as presented.

Dr. Middleman (SAM) suggested that for consistency, the 3-dose total should be included for the hepatitis B series just as the 2-dose total was included for the hepatitis A series.

Dr. Atkinson responded that this could be added.

Regarding the meningococcal footnote, Dr. Middleman (SAM) pointed out that the *MMWR* says that people at persistent risk should continue to receive boosters every 5 years, but the footnote implies that there is only 1 booster for those at persistent risk. Many of the people with whom she has spoken have interpreted this as needing 1 booster dose after 3 years if immunized between the ages of 2 and 6. If older, they would receive one booster dose after 5 years. However, the full *MMWR* statement says those at persistent risk should continue to receive booster doses. She suggested making this clearer in the footnote.

Dr. Baker replied that it is very clear in the AAP Redbook that those who continue to be at risk should be re-boosted at either 3- or 5-year intervals. For example, the asplenic person would continue to receive boosters throughout their lifetime. She suggested that Dr. Atkinson take Dr. Middleman's comments under advisement when making revisions to this section.

Dr. Chilton noted that the last dose of hepatitis B vaccine was recommended after 24 weeks. In practice, if a child presented to a practitioner's office that day who was born on May 3, he wondered whether the child could get the third dose.

Dr. Atkinson replied that usually people round it up to 6 months.

Dr. Chilton suggested merely saying 6 months then.

Dr. Atkinson replied that this was debated fairly vigorously with the hepatitis group, who felt very strong about this. When they put 6 months, many errors occurred because vaccines were being administered before 6 months. To try to reduce the number of interval and age errors, the hepatitis group thought that it should be 24 weeks.

Dr. Chilton pointed out that the rotavirus schedule reads 8 months rather than 32 weeks. He thought this should be considered in the future to make it possible for practitioners to calculate fairly quickly.

Dr. Baker added that depending upon when someone was born, 24 weeks may be considerably before age 6 months. She thought this should be taken to the hepatitis work group for continued conversation, because it has been such a point of debate and is a very valid observation. She did think that pediatricians were used to dealing with weeks in terms of recommendations.

Dr. Sawyer requested that immunization information systems be kept in mind, because it is harder for a computer to calculate months than it is weeks.

Regarding the Tdap dosing interval, Dr. Judson noted that 20 to 30 years ago, there was a concern about over-immunization with tetanus and full strength diphtheria. He inquired as to whether there was no longer concern about increased reactogenicity with more frequent dosing with Tdap.

Dr. Baker replied that currently, a single booster dose is recommended. The Pertussis Work Group will be considering whether there should be re-immunization with Tdap. Hopefully, there will be some safety data to inform that for persons of multiple ages.

Dr. Fryhofer (ACP) thanked ACIP for going to all of the extra trouble to ensure accuracy before the adult schedule is published. This is the "Holy Grail" for internists, and there are some major changes that will affect them.

Dr. Campos-Outcalt inquired as to what would occur should one of the parent organizations not endorse one of these changes. For example, what would happen to the harmonized schedule if there was a disagreement on a particular point?

Dr. Baker responded that this was an interesting rhetorical question that she was confident would remain rhetorical.

Ms. Brewer (ANA) asked whether there was a reason that a descriptor of females for the HPV vaccine was not included on the catch-up schedule bar as well. The 13 through 17 section says HPV (females) 3 doses, but the catch-up schedule just says HPV.

Dr. Atkinson replied that it would not be a problem to include this.

Dr. Schuchat asked whether online publication would still occur in January, while the print version would be published February.

Dr. Baker did not believe with the delay *Pediatrics* would be able to do something in January.

Dr. Atkinson added that basically, the entire process would be delayed by one month. That would mean that the deadline for February publication would be January 1.

MMWR does the penultimate editing. AAP and AAFP do not do further edit the schedules. While essentially the final schedules could be posted to the website, they would be "jumping the gun" on AAP and AAFP by a month.

Dr. Schuchat suggested that AAP, AAFP, and ACP take into consideration whether it would be problematic for them if CDC posted the schedules as soon as they were finalized.

Dr. Atkinson indicated that he would discuss this when communicating with the journals.

Dr. Meissner thought that AAP might also be able to publish the schedules electronically on its own website on January 1.

Dr. Atkinson responded that he was told that they generally publish electronically a week prior to paper publication in *Pediatrics*.

Dr. Baker pointed out that this was a *Pediatrics* journal process, not an AAP process.

Regarding the new meningococcal recommendation, Dr. Turner wondered whether there would be an ACIP provisional recommendation posted on the website before posting in the *MMWR*. Most colleges start printing their pre-entrance immunization recommendations in December and January. This is a very time-sensitive issue, given that they start admitting students immediately after the first of the year. Having a provisional recommendation would permit them to insert that into pre-entrance recommendations.

Dr. Pickering responded that they had already spoken to the work group lead staff for pertussis and meningococcal. Given that this will be a Policy Note, provisional recommendations will not be published. The Policy Notes will be published within 3 to 4 weeks, but must go through clearance for publication in the *MMWR*. Policy Notes are typically published fairly quickly. They will speak with both work group leads to try to get this done as quickly as possible, which he was confident Dr. Schuchat would support.

Motion: 2011 Immunization Schedule 0-18 Years of Age

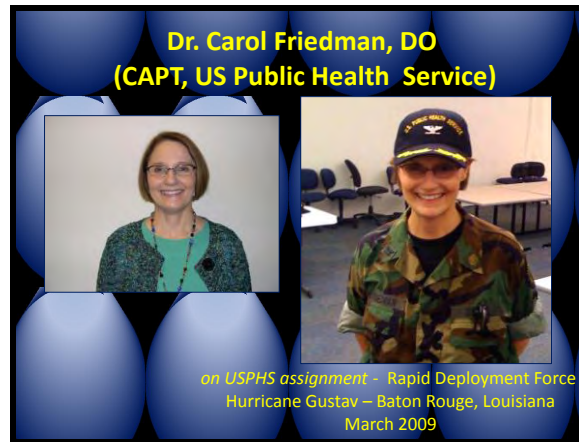
Dr. Judson made a motion to accept the language as presented. Dr. Sawyer seconded the motion. The motion carried with 12 affirmative votes, 0 negative votes, and 0 abstentions.

Immunization Schedule: 19 Years of Age and Older

Tribute to Carol Friedman

**Kristen Ehresmann, MPH
Minnesota Department of Health
St. Paul, Minnesota**

Before we begin our discussion of the adult schedule, I would like to take a moment to pay tribute to the life of Dr. Carol Friedman, Associate Director for Adult Immunization. Carol passed away suddenly on July 27, 2010; since our June meeting:



Carol began as Associate Director for Adult Immunization in 2009 and served as CDC lead for ACIP's Adult Immunization Workgroup, where I had the pleasure of working with her. As you might imagine, Carol had a rich and meaningful career in public health prior to that appointment, and I would like to share that with you.

For 10 years before serving in public health, Carol was a teacher in the Austin School District in East Austin, the poorest area in Travis County, Texas. She later studied medicine at the University of North Texas Health Science Center, and graduated with her Doctor of Osteopathy. She trained in Internal Medicine in Breckenridge Hospital in Austin and was their Chief Resident in 1990. Carol joined CDC as an Epidemic Intelligence Service (EIS) Officer in 1991, serving in the Missouri Department of Health. After her work as an EIS officer, she accepted an assignment at the Texas Department of Health. Her major accomplishments there involved improving the Texas surveillance systems and health assessments.

In 1997, Carol moved to Atlanta to join the Epidemiology Program Office (EPO). While in EPO, Carol led an innovative, multi-year project in which CDC helped General Motors increase their employee's use of priority clinical preventive services. Carol joined the Division of Cancer Prevention and Control in 2003 as a Supervisory Medical Officer. She served as a Team Lead in the Cancer Surveillance Branch, where she played an integral part in reporting and publishing cancer statistics for the nation. In this capacity, she worked with the National Cancer Institute, the American Cancer Society, the American Joint Committee on Cancer, and others to coordinate national surveillance efforts. She also served as the Acting Deputy Division Director.

In 2006, Carol began her tenure as the first Branch Chief for the newly created Comprehensive Cancer Control Branch. The branch has become a critically important force for cancer control in the US. In both her Team Lead and Branch Chief positions, Carol recruited and trained numerous individuals and served as a mentor for many. As a Captain in the US Public Health Service, Carol led a tier one rapid deployment team and led numerous disaster response teams, including ones assisting with Hurricane Katrina. She was a highly decorated officer and provided generous mentorship to fellow Commissioned Corps Officers.

Outside of CDC, Carol was an attending physician in the Dekalb County Health Department's HIV clinic, helping patients to live well with HIV. In her role as Associate Director for Adult Immunization in the National Center for Immunization and Respiratory Diseases, Carol led CDC's efforts to obtain influenza vaccine for nursing homes that were struggling to find enough vaccine for their patients during H1N1. With the American Medical Association, she led the National Influenza Summit, which helps promote influenza vaccination in public and private

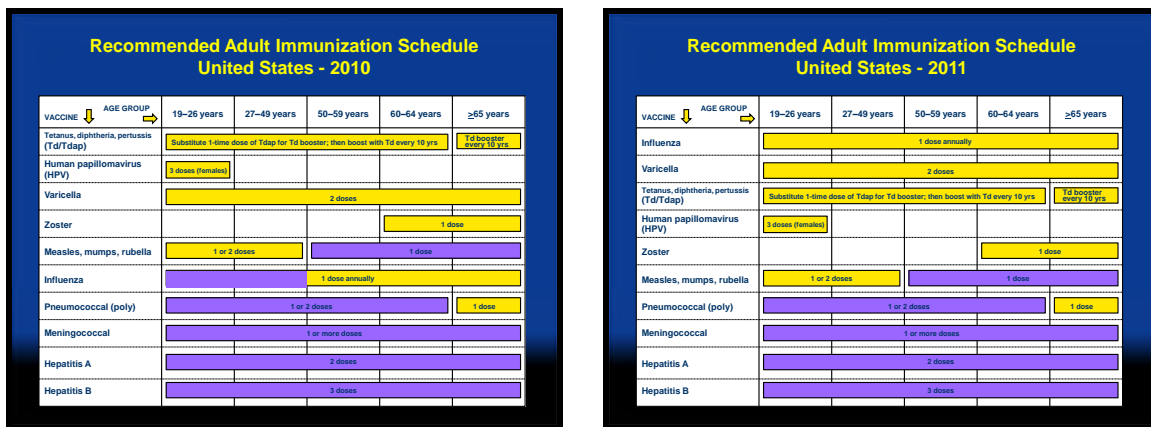
settings. In conjunction with the Centers for Medicare and Medicaid services in HHS, she recently developed and was leading an effort to increase influenza vaccination among healthcare workers.

I think Carol's three favorite charities say a great deal about her values: PAWS Atlanta, Doctors Without Borders, and Richardson Health Center HIV Clinic. Carol is survived by her sister and sister's husband, Charlotte and Paul Myer; many friends; and her beloved cat, Gracie. May our on-going commitment to serving others through public health be a tribute to Carol's life.

Recommended Adult Immunization Schedule United States: 2011 Proposed Revisions

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

Dr. Shefer reviewed the proposed changes to the 2011 Adult Immunization Schedule compared to the 2010 schedule, pointing out that votes which took place the previous day had not yet been incorporated:



The bar in the Figure for influenza vaccination was changed to reflect the universal recommendation. The list of vaccines was reordered to keep all of the universally recommended vaccines together. To the box at the bottom of the medical and other indications, a sentence was added, "A vaccine series dose does not need to be restarted, regardless of the time that has elapsed between doses." This would come before the sentence that discusses issues about the use of combination vaccines. While this has been more of an issue with HPV vaccine, it applies to all vaccines.

There were also some changes to the footnotes. The first was for influenza, reflecting the universal recommendation. The second was that language was consolidated for MMR as a common paragraph at the beginning of that section. In addition, revaccination with pneumococcal polysaccharide vaccine is clarified for 19 through 64 years of age. Meningococcal vaccine is noted as quadrivalent, and the same revision that was made to the childhood Hib footnote will be made to clarify and shorten the language.

Influenza Footnote #1 had been revised to read, “Annual vaccination against influenza is universally recommended for all persons 6 months of age and older, including all adults. Healthy, nonpregnant adults younger than age 50 years without high-risk conditions can receive either LAIV or inactivated vaccine. Other persons should receive the inactivated vaccine. Adults aged 65 years and older can receive the standard seasonal influenza vaccine or the high-dose (Fluzone) seasonal influenza vaccine. Additional information on influenza vaccination is available at www.cdc.gov/vaccines/vpd-vac/flu/default.htm.”

For the MMR footnote, the common language that had been part of each of the three vaccine-component sections was moved into one introductory statement that now reads, “Adults born before 1957 generally are considered immune to measles and mumps. All adults born in 1957 or later should have documentation of one or more doses of MMR unless they have a medical contraindication to the vaccine, laboratory evidence of immunity to each of the three diseases, or documentation of physician-diagnosed measles or mumps disease (documentation of physician diagnosed-disease is not considered acceptable evidence of immunity for rubella.”

Pneumococcal polysaccharide (PPSV) Footnote #8 has been revised to read, “Revaccination with PPSV. One-time revaccination after 5 years is recommended for persons aged 19-64 years with chronic renal failure or nephrotic syndrome; functional of anatomic asplenia (e.g., sickle cell disease or splenectomy); and for persons with immunocompromising conditions. For persons aged >65 years, one-time revaccination is recommended if they were vaccinated >5 years previously and were aged <65 years at the time of primary vaccination.”

As noted also in the child and adolescent schedule, meningococcal will be referred to as MCV4 the first time it is referred to. The last paragraph of Meningococcal Vaccination Footnote #9 has been revised to read, “Meningococcal conjugate vaccine, quadrivalent (MCV4) is preferred for adults with any of the preceding indications who are aged <55 years; meningococcal polysaccharide vaccine (MPSV4) is preferred for adults aged >56 years.”

The results of the votes that occurred the previous day will be incorporated into the 2011 table. This includes the Tdap minimum interval, the Tdap permissive recommendation for over 65 years of age, and the 2-dose meningococcal for medically indicated adults.

Discussion Points

Dr. Keitel pointed out that the MMR footnote revision differed from what was provided in the handout. It says “physician diagnosed” and then it says “documentation is not considered acceptable evidence.”

Dr. Shefer clarified that the statement referred to rubella.

Dr. Keitel suggested that it be removed from parentheses and be included as a sentence itself, “Documentation of physician diagnosed rubella is not considered acceptable evidence of immunity.” An additional suggestion was to begin the sentence with Rubella.

Ms. Stinchfield suggested not including “physician diagnosed only” because this is likely to create unintended consequences. She suggested using either “clinician diagnosed” or “provider diagnosed” in order to be more inclusive. Dr. Baker agreed that for advanced healthcare providers they needed to be more generic in the language.

For universal influenza vaccines, Dr. Baker did not think the adverb “universally” was needed. It is very clear that it is recommended for all persons.

Dr. Campos-Outcalt pointed out that for varicella, the yellow line went all the way through. It was his understanding that someone was born before 1980, they were considered immune but there were some exceptions to that. Therefore, he wondered whether the yellow line should stop at whatever the current year is minus 1980.

Dr. Shefer responded that the line went all the way through in the 2010 Adult Schedule, so this was not a change. She will check with the SMEs regarding Dr. Campos-Outcalt’s suggestion.

Mr. Grabenstein (Merck) reminded everyone that 2 years previously during the October meeting, ACIP voted to recommend pneumococcal vaccination for adults who smoke cigarettes or who have asthma. However, he did not see that reflected on the 2011 table. He wondered whether it was reflected in other areas of the document. There were some other segmental votes such as those for children in American Indian settings that should be attended to.

Dr. Shefer replied that she thought this information was included in the footnote.

Motion: 2011 Immunization Schedule 19 Years of Age and Older

Dr. Keitel made a motion to accept the language as presented, incorporating the revisions suggested. Dr. Sawyer seconded the motion. The motion carried with 12 affirmative votes, 0 negative votes, and 0 abstentions.

Rotavirus

Introduction

Lance Chilton, MD, FAAP
Chair, Rotavirus Work Group

Dr. Chilton reported that the Rotavirus Work Group was active during the time that the two rotavirus vaccines had just been licensed. The group then went on hiatus, but was called back into action during the Summer of 2010 when new developments occurred. He thanked all of the work group members for their many hours of discussion over the previous few months. The group engaged in calls every other week since the summer. The primary reason for reactivation of this committee was that some safety issues arose, although efficacy remained unchanged from the previous discussions of rotavirus vaccine a year or two ago. The two issues that arose were the association of rotavirus vaccine with porcine circovirus (PCV) and a possible increased risk of intussusception (IS).

In Spring 2010, Joseph Victoria and his group, led by Eric Delwart, had the Blood Systems Research Institute (BSRI) in San Francisco published a paper in the *Journal of Virology* indicating that porcine circovirus DNA had been detected in the Rotarix[®] vaccine using new techniques that had not been available before. Porcine circovirus was detected first in RV1

(Rotarix[®]), then in RV5 (RotaTeq[®]) The FDA responded with the suspension of the use of Rotarix[®] out of an abundance of caution, and convened a panel of experts to determine the significance of this finding. Meanwhile, both manufacturers repeated the sensitivity tests and both detected the porcine circovirus. The FDA's expert panel determined that PCV posed no risk to humans, and responded by recommending resumption of the use of Rotarix[®] and continued use of RotaTeq[®].

The first rotavirus vaccine, Rotashield[®], was associated with a 20 to 30 times increased risk of intussusception, or one additional case of intussusception for every 4000 to 9000 doses administered. After this was demonstrated, ACIP retracted its recommendations for use of that vaccine and it was removed from the market. Note that in the pre-licensing trials involving about 15,000, there was no significant increase in intussusception noted for Rotashield[®]. It was only after hundreds of thousands of doses were given that the association became evident. Some may have looked at this episode as a "black eye" on vaccine safety. Dr. Chilton thought that instead, it was just the opposite. It was evidence that the vaccine safety apparatus that is in place determined very rapidly the increased risk of intussusception, and the response was quick and appropriate.

With respect to the two newer rotavirus vaccines, almost five times as many children were enrolled in the safety and efficacy trials as had been for Rotashield[®] and intussusception rates were carefully evaluated. No increased risk was detected with either vaccine. The post-marketing odds ratio was 20-30 for intussusception in Rotashield recipients compared to controls [Trudy V. Murphy, Paul M. Gargiullo, et al. Intussusception among Infants Given an Oral Rotavirus Vaccine. N Engl J Med 2001; 344:564-572]. There are plans to continue post-marketing evaluation.

With regard to the gratifying effects of rotavirus immunization in practice in the US, the test positivity rate has climbed each winter and then fallen every year, producing Rocky Mountain like peaks each year from 2000 through 2006. There has been a decline in the absolute number of rotavirus detections in the labs of the NREVSS, such that the "Himalayan" peaks have come to look like Florida.

GSK Human Rotavirus Vaccine Rotarix[®]: PASS Mexico Study Update

Romulo Colindres, MD, MPH
Head Biologicals Worldwide Epidemiology
GlaxoSmithKline Biologicals

Dr. Colindres noted that as an ex-EIS Officer, it was a special privilege to be back on the CDC campus, and expressed his gratitude for the opportunity to present information from GSK's ongoing Rotarix[®] Post-Marketing Authorization Safety Study (PASS) in Mexico. During this session, he presented background information on the Rotarix[®] Global Development Program; pre-licensure data on reports of intussusception from Rotarix[®] clinical trials; results from the planned interim analysis of GSK's post-authorization safety study in Mexico; an update on the US prescribing information changes as a result of the Mexico study; and overall observations regarding rotavirus vaccination and intussusception.

As a reminder, Rotarix[®] is a live attenuated human rotavirus vaccine administered orally as a two-dose series. Rotarix[®] was the first rotavirus vaccine to be WHO pre-qualified and is currently licensed in over 100 countries, the first of which was Mexico in 2004. The initial license was issued in 2004, and Rotarix[®] was approved by FDA in 2008. As of August 2010,

approximately 76 million doses of Rotarix[®] have been distributed worldwide, representing approximately 67%, or the majority, of all rotavirus vaccine doses distributed. Rotarix[®] has had one of the largest vaccine development programs, which included 11 studies enrolling more than 75,000 infants. Safety was evaluated in all of these studies, including a large safety study (Rota 023 Safety Study) specifically designed to assess the risk of IS.

In the pre-licensure Rotarix[®] clinical trials, there was no evidence of increased risk of IS following vaccination. The Rota 023 Safety Study enrolled more than 60,000 infants in 11 countries in Latin America and Finland. The primary objective of this study was to assess the temporal association between Rotarix[®] vaccination and IS. In the 31 days post-vaccination of either dose, there were very few IS cases observed (n=13), 6 of which were in the Rotarix[®] group and 7 of which were in the placebo group. The relative risks indicated no temporal association. A subset of the Rota 023 Safety Study, comprised of approximately 20,000 infants, was followed through one year of age. During this time, 4 IS cases were reported in the Rotarix[®] group compared to 14 in the placebo group. In the pre-planned analysis, the relative risk was 0.28 and was statistically significant, suggesting a potential protective effect over time. In addition, GSK conducted a pooled analysis of 20 placebo control trials involving over 94,000 thousand infants, the results of which showed no evidence of an association between vaccination and IS. However, given that IS is a rare event that was observed infrequently in the clinical studies, it is a company priority to continue to monitor IS and conduct specific studies as part of post-marketing surveillance.

The PASS study in Mexico is a post-marketing commitment to the European Medicine's Agency to reconfirm the safety profile from the clinical trials when administered as part of routine health care services. The study was planned to have an event-driven interim analysis, the results of which Dr. Colindres presented during this session. The full study is expected to be completed in 2011. Mexico was chosen as a study site because this country has a high background IS incidence rate estimated to be 87 per 100,000, making it more feasible to enroll cases considering that IS is a rare event. Mexico also introduced Rotarix[®] into its expanded program of immunization in 2006 and accordingly, collaboration was established between GSK and the Mexican Institute of Social Security, which provides public health services to approximately 40% of the Mexican population, covering an annual birth cohort of approximately 500,000 infants.

The PASS study covers a network of 66 pediatric hospitals geographically spread throughout Mexico that actively and prospectively enroll cases of IS. At each hospital, designated surveillance nurses or epidemiologists conduct daily reviews of hospital registries in search of potential IS cases. The study's primary objective, which applies to the planned interim analysis and the final analysis, is to assess the temporal association between Rotarix[®] and definite IS as defined by the Brighton Collaboration Working Group occurring within 31 days following vaccination in children less than one year of age. The secondary objectives apply only to the final analysis and will assess the temporal association between Rotarix[®] and definite IS occurring within 7 days following vaccination in children less than one year of age, as well as to monitor yearly incidence rates of IS.

The Mexico PASS uses a self-control case series (SCCS) design. Using this methodology, association between IS and each dose is analyzed separately and sequentially starting with the last dose. The complete observation period starts at Dose 2 and goes through one year of age. The risk period is the 31 days after Dose 2. The control period is the remainder of time through one year of age. This analysis only includes children who have received 2 doses of vaccine. The measure of association derived from the self-control case series is the relative incidence which is the incidence rate in the risk period over the incidence rate in the control period. The

relative incidence is computed using a Poisson regression model that includes age in months as a covariate, allowing adjustment for potential age effect. If Dose 2 has no effect, analysis of Dose 1 can be done. The overall observation period starts at Dose 1 and ends at one year of age. The risk period is the 31 days post-Dose 1 and the control period is the remainder of time through one year of age. It is important to note that one of the limitations of the SCCS methodology is that it quantifies a probable temporal increased risk of the pre-defined specific risk period and may not evaluate the overall impact of vaccination and definite IS occurring over time. In designing this study for the interim analysis, it was calculated that a minimum of 360 vaccinated cases with definite IS would provide a power of 80% to exclude a relative incidence of >4.33 within 31 days after Dose 1 and >2.18 within 31 days after Dose 2. These relative incidences were derived from estimated baseline IS incidence in Mexico plus an additional incidence of 2 cases per 10,000, which represents a consensus risk estimation based on Rotashield[®] data. The interim analysis was adjusted for a type 1 error—alpha of 0.01.

The Mexico PASS interim analysis covers a period from January 2008 to December 2009. During this two-year period, there were approximately 1 million infants under surveillance and a total of 457 subjects with IS were enrolled, for a total of 459 IS episodes. Of note, there were two subjects who each had two episodes of IS reported both after having received the second dose. With regard to the age distribution of the IS cases from the Mexico PASS study, there was a peak between 4 and 6 months of age. This age distribution is consistent with reported background IS data from Mexico and worldwide.

In terms of the primary objective evaluated in the interim analysis, for Dose 1, there were 68 episodes of IS during the risk period. Using the Poisson regression model to adjust for age, this yields a relative incidence of 1.75, which is of borderline statistical significance; however, the upper limit of the 99% confidence interval is a relative incidence of 3.08, which is lower than the relative incidence of 4.33 that the study was powered to exclude. For the second dose, 77 episodes of IS were detected during the risk period. After adjusting for the age effect, this yields a relative incidence of 1.07, showing no association between vaccination and IS. The upper limit of the 99% percent confidence interval is a relative incidence of 1.87, which is lower than the relative incidence of 2.18, which the study was powered to exclude.

It is important to recognize that the Mexico PASS provides the largest active surveillance system for IS worldwide, with approximately 1 million infants under surveillance during a two-year period. The planned interim analysis suggests a temporal association between IS and vaccine within 31 days post-Dose 1 and no temporal association within 31 days post-Dose 2. The results meet one of the primary objectives of the study, which was to reject a relative incidence greater than or equal to 4.33 post-Dose 1. Distribution by time from vaccination to IS onset shows a clustering of cases within 7 days post-Dose 1, and no such clustering is seen post-Dose 2. Also important to mention is that once the results from the Mexico PASS were known, GSK immediately presented and discussed the results with regulatory agencies worldwide. After review with FDA, the US prescribing information for Rotarix[®] was updated in September 2010. Changes were made to two sections in the label: 1) to the already existing IS subsection of warnings and precautions; and 2) to the post-marketing experience.

The existing IS subsection states the following:

“Interim post-marketing safety data ... suggest an increased risk of IS in the 31-day period following administration of the first dose of ROTARIX.”

The post-marketing experience section states the following:

“An interim analysis ... suggests an increased risk of IS in the 31-day period following administration of the first dose of ROTARIX [Relative Risk: 1.8(99% CI:1.0,3.1)]. In this study, within the 31-day period after the first dose, most cases of IS occurred in the first 7 days.

Applying the RR observed from the interim analysis of the PASS in Mexico to estimates of background rates of IS in the US would approximate 0 to 4 additional cases of IS hospitalizations per 100,000 vaccinated infants within the 31 days after the first dose. In the first year of life, the background rate of IS hospitalizations in the US is approximately 34 per 100,000 infants.”

In conclusion, Dr. Colindres highlighted some important observations regarding rotavirus vaccination in general and risk of IS. Rotarix[®] is the only rotavirus vaccine to have sufficient post-marketing experience to detect the low level of temporal IS risk with a degree of precision observed in Mexico PASS. To date, safety data from post-marketing studies and large safety databases in the US for both licensed rotavirus vaccines are not large enough to rule out the level of risk suggested by Mexico PASS. A review conducted in June 2010 by GSK of publically available data from VAERS in the US shows a cluster of IS in first week post-rotavirus vaccination with both licensed rotavirus vaccines. Additional data from the Australian National Immunization Program have also shown temporal clusterings of IS cases shortly post-Dose 1 for both licensed rotavirus vaccines. It is important to note that a temporal increased risk post-Dose 1 does not necessarily indicate an overall increased risk of IS. As was shown earlier, as a pre-defined endpoint of a Rotarix[®] Phase III clinical program, statistically significant protection of Rotarix[®] against IS is observed.

Substantial rotavirus vaccination benefits include prevention of hospitalizations for severe rotavirus worldwide, including the US, and reduction of infant mortality in other less developed parts of the world. Currently, the known benefits of Rotarix[®] outweigh the suggested small, temporal increased risk for IS. Regulatory and public health authorities worldwide (e.g., WHO, PAHO, EMA, and CDC) recommend the use of Rotarix[®] to prevent rotavirus disease in infants. As a vaccine manufacturer, GSK's primary focus is on patient safety. GSK is committed to continue closely monitoring the safety of Rotarix[®]. This will be done primarily through analysis of spontaneous reports; the continuation of the Mexico PASS study, for which final results are expected in 2011; and an on-going US PASS, which was previously presented to ACIP, and for which results are expected in 2013.

Analysis of Post-Licensure Evaluation of Intussusception Risk with Rotarix[®] in Brazil and Mexico

**Manish Patel, MD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Patel presented an analysis of the post-licensure evaluation of intussusception risk with Rotarix[®] in Brazil and Mexico. This study was conducted primarily by Ministries of Health in these two countries with technical support from PAHO and CDC, funded in part by the Program for Appropriate Technology in Health (PATH) and GAVI. A project like this requires the work of many people, whom Dr. Patel acknowledged.

Currently, 17 countries in the Americas have introduced rotavirus vaccine. The majority of countries in Latin American have introduced Rotarix[®], which Dr. Patel referred to as RV1. Brazil introduced Rotarix[®] in 2006, and Mexico introduced this vaccine into their national program in 2007. Prior to that, Mexico introduced this vaccine into the private side in 2006. The reason Brazil and Mexico were selected is simple. The birth cohort for Brazil is 4 million, for Mexico it is nearly 3 million. IS is a very rare event, so a large cohort is required to conduct a study to assess the risk. This is a 2-dose vaccine administered at 2 and 4 months. It is important to note that Dose 1 is restricted to infants ≤ 14 weeks of age, given that this is prior to the potential increased risk with age associated with Rotashield[®], and the potential excess number of cases that would occur if vaccinating older children. This age restriction was recommended by WHO.

IS surveillance was begun in Mexico and Brazil in 2007. The objective of this safety monitoring study was to use the case series and the case-control method. The case series is an attractive approach because it is efficient in terms of not having to find controls and is a great method for an acute event like IS that occurs in a short timeframe following vaccination. However, it is somewhat of a novel approach and has not been widely applied. For that reason, the investigators elected to use a case-control to validate the case series results. The sample size used in the study was to exclude a three-fold relative risk within Week 1 of Dose 1 compared to the background, or approximately 1 / 100,000 Dose 1 vaccinees.

Case ascertainment is a very important step for the case series. For a cases series and a case-control to work, an active surveillance system is required. A passive pharmaco-vigilant system is not sufficient, given that cases must be identified independently of vaccination. Active surveillance was conducted for 2.5 years in Brazil and Mexico in 53 hospitals in Brazil and 16 hospitals in Mexico. Prospective and retrospective searches were made of radiology logs, surgical logs, and emergency room visits in order to have as full a capture of cases as possible, using the well-established Brighton Collaboration Case definition. The vaccination itself was verified to the extent possible with provider cards, and there was pretty good vaccination verification in both countries. The observation period of the cases was 45 to 245 days of the period when a subject is eligible for vaccination. The primary risk period for this analysis was 1 to 7 days after vaccination. This was selected because with the Rotashield[®] experience, the risk was highest during the 3- to 7-day period in the first week following vaccination. It remains unclear why Rotashield[®] caused IS, but one suspicion is that it correlates with the peak replication period of the virus in the gut, which happens to occur in the first week of vaccination. The second and third weeks after vaccination were assessed as well.

The analytic method used was a well-established method by Paddy Farrington of The Open University. It is a conditional Poisson regression model in which age can be adjusted for, which is crucial because IS rates vary markedly during the first 6 months of life. Age was adjusted for in 30-day bands; however, the analyses were also done adjusting age in 7- and 14-day bands. Though Dr. Patel did not show those results, they were very similar to the 30-day age adjustment. The healthy vaccine effect was taken into account. Essentially, if a child presents with IS who is unvaccinated, the likelihood is that the provider or the parent may choose not to vaccinate after developing IS. If they are included in the analysis, the pool will be enriched with a lower IS incidence. This was accounted for by using only post-exposure time in the model.

Case-control methods and analyses were pretty standard. Enrollment was of neighborhood controls matched + / - 30 days on the case's date of birth at enrollment. Age was further adjusted for in the analysis in that the cases and the controls were made the same day in age. Details were provided in the ACIP members' handouts as a conditional logistic regression model. An important point for Mexico and Brazil was the age restriction for Dose 1. By 14

weeks, a majority of the children had received Dose 1 amongst the children who were vaccinated. A second important point is that although the children received the vaccine by 14 weeks and the second dose by 25, there was an age distribution of when they received vaccines. Children are vaccinated at different times between 6-14 weeks of age, versus all being vaccinated at two months of age. It is crucially important to have an age distribution for the case series to work.

In terms of the results, in Brazil 330 cases met the definition and there were 1311 controls. Of the cases, 57% were males, while 51% of the controls were male. All were hospitalized in Brazil, and 4.6% (n=16) cases died in the hospital. Of the cases and controls, 95% had a history of breastfeeding. 95% of the controls and 97% of the cases were ever vaccinated in the first 8 months of life, and this is independent of their IS status. A card confirmed vaccination status was obtained on most. Surgery was pretty high in Brazil, with 95% of the cases undergoing surgery. Of those, 50% had a bowel resection, and 50% had manual reduction of their IS. This is higher than other places. For comparison, in the US surgical rates tend to be 40% to 50%. It is believed this is probably the practice in Brazil. There is another paper of IS surveillance published in 2004-2005 that showed similarly high surgical rates in Brazil. Dr. Patel believes that because barium enemas are not commonly available in hospitals in Brazil, surgical management is the treatment chosen.

Comparison of the 6 or 7 cases that occur within a week of vaccination to the number of cases further out from vaccination constitutes the case series. There was no real signal apparent to the eye with the first dose. With the second dose, there was some grouping of cases in the first week after the second dose, but nothing too remarkable. The case series essentially reflects what can be seen with the naked eye. There was no signal after Dose 1 in Brazil, with pretty reasonable confidence limits. With dose two, there was a slight signal during Week 1 vaccination for both the case series and the case control of 1.6, 1.9. There was a small signal within Week 1 after Dose 2.

In Mexico, thus far there are 281 cases and 578. The mean age was 5 months. 61% of the cases and 51% of the controls were male. All were hospitalized. The death rate was lower than in Brazil, with 2 cases (1%) dying. The surgery rate was also somewhat lower, with 75% having surgery and a quarter of those a resection. The number ever vaccinated with Rota 1 was also high, though somewhat lower than Brazil at 87% cases and 92% percent controls. The clustering or grouping of cases within Week 1 after the first dose in Mexico is very similar in our study compared with GSK. The surveillance system in Mexico is independent of the surveillance system conducted by GSK. This was set up in the Mexico Ministry of Health hospitals; whereas, the GSK surveillance system was set up in the IN system, which is the private system in Mexico. With Dose 2 in Mexico, there was no grouping of cases. Cases were pretty well-distributed from Day 0 to Day 60 after vaccination.

In the Dose 1 analysis, a signal was observed within Week 1 of vaccination with the case series and the case controls. This is approximately a 5-fold relative risk compared to background, with confidence limits ranging from 2 to 8 for the case series and 2 to 14 for the case control. There were no signals within weeks 2 and 3 of vaccination. In the 1- to 21-day window, there was no statistically significant signal, which suggests that the risk is short-term and returns to baseline within 1 week of vaccination. For the Dose 2 analysis, there was no real signal within Week 1 of vaccination. After Week 2, there was a slight elevation with the case series (point estimate of 1.8 and a significant elevation at 2.1 in the odds ratio), but nothing in Week 3. There is a concern about potential risk of IS varying by age, but power is lost when this is done because vaccination happened on time; that is, most children were vaccinated by 14 weeks of age. In

Mexico, about 13% were vaccinated at older than 14 weeks of age, so this was compared. There was no statically significant interaction by age at vaccination. Children less than 14 weeks of age had a relative risk of 3.6 and those older than 14 weeks had a risk of 5.

With respect what the relative risk means in regard to absolute risk and in terms of excess cases in Brazil and Mexico, vaccine has been used in both countries for over 3 years. Thus, a fair amount of benefits data exist that can be assessed as well. Given that the vaccine has been used, real world vaccination coverage data, timeliness data from the demographic health survey, real world vaccine efficacy and effectiveness data from both settings, and pretty decent disease burden estimates from both settings prior to vaccination all went into the model.

In Brazil, in terms of the vaccination benefit versus risk scenario, assuming that Rotarix[®] coverage is the same as DTP3 coverage in Brazil and in Mexico, vaccination averted around 70,000 rotavirus events per year amongst children under 5 years of age and averted 640 deaths from rotavirus amongst children under 5 years of age per year. In contrast, using the risk estimates from the current study, there were 46 hospitalizations from IS per year among infants. With the 5% case fatality rate, approximately 2 deaths would be expected. There were 1500 hospitalizations and about 300 deaths. In Mexico, the burden estimates are lower than in Brazil so fewer admissions are averted per year, but this is still a substantial at 12,000 hospitalizations amongst children less than 5 years of age, and 700 deaths amongst children under 5 years per age. With the risk estimates from this study, about 43 IS hospitalizations would be expected per year that are attributable to vaccination and at least 2 deaths if using an assumption of the 5% case fatality from Brazil.

In terms of what is actually occurring in Mexico and Brazil, Vesta Richardson published in the *New England Journal of Medicine* with CDC's collaboration earlier this year and showed that there was a real world decline in childhood diarrhea deaths after rotavirus vaccination in Mexico. For the past 4 or 5 years prior to vaccine introduction, Mexico had approximately 1800 childhood deaths amongst children less than 5 years of age from diarrhea and 1800 deaths from diarrhea per year. Probably 30% to 40% percent of those are estimated to be from rotavirus. Each year before vaccination, there were substantial winter diarrhea deaths amongst children under 5 years of age. The peak correlates with the peak in rotavirus hospitalizations documented in Mexico.

As noted, vaccine was introduced in May 2007 nationally. In 2008, a reduction was observed in diarrhea deaths in the children under 1 year of age. There was little reduction in the second year of life because a few children had been vaccinated in that age group. In 2009, there was further reduction of deaths in the under 1 year of age group, and a reduction of death in the second year of life. With this study design, it is difficult to say whether this is really attributable to vaccination. Perhaps it had to do with increased breastfeeding rates, increased vitamin A supplementation, better hydration, and so forth. The data from 2010 make a stronger case that vaccine led to these reductions. This was observed in Mexico for 3 years after vaccination.

In summary, there is a short-term risk of IS after Dose 1 in Mexico. Two points strongly support a genuine effect: 1) the peak on day 4 and 5 after vaccination; and 2) the results were similar with the case series and the case control. It is possible that a detection bias or case identification bias could have led to the peak on Day 4 and 5. However, this should also be observed after Dose 2. Also unclear is why this was observed in Mexico but not in Brazil. This suggests that there is a real signal. The difference in risk after Dose 1 in Mexico, but not in Brazil was certainly perplexing. While the reason for this remains unclear, it is known that immune responses to rotavirus vaccines have been quite different by setting. It is unclear why

(e.g., differing maternal antibody levels, different breastfeeding rates prior to vaccination, co-infections that vary by setting, et cetera).

One additional factor is that Mexico uses the inactivated polio vaccine at 2 and 4 months of age. They switched to this in 2007 just prior to when surveillance was initiated; whereas, Brazil uses OPV. One study in South Africa assessed immune responses to Rotarix[®] when OPV is given concomitantly with Rotarix[®] versus separately. Rotarix[®] does nothing to OPV immune response, but Dose 1 of OPV reduces the Rotarix[®] response. After Dose 2, the immune responses to Rotarix seem to be similar in the vaccine and the placebo groups. Although highly speculative, it certainly is a difference between the two settings that warrants consideration.

In terms of next steps, studies will be conducted to try to better understand the reasons for the differences in risk. There is an on-going analysis of tissue samples from the Mexico sites. Immunogenicity is being assessed after Dose 1 in Mexico versus Brazil. There is an on-going benefit-risk analysis in Latin America for the 16 countries that are using Rotarix[®]. The findings also make a case for on-going IS surveillance in different settings to determine whether these results hold over time and in different locations.

Continued Surveillance for Intussusception (IS) Following RotaTeq[®] in VAERS and Vaccine Safety Datalink (VSD)

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

On behalf of himself and Penina Haber, Dr. Baggs presented on continued surveillance for IS following RotaTeq[®] in VAERS and VSD. For VAERS, since March 2006, approximately 33.5 million doses of the RotaTeq[®] vaccine have been distributed in the US. There have been 487 confirmed IS reports, of which 121 were within the first 7 days. A familiar peak has been reported previously to ACIP from VAERS data in the first 7 days after Dose 1, which seems to appear to some extent after Doses 2 and 3 as well. Approximately 2.8 million doses of Rotarix[®] vaccine have been distributed in the US since April 2008. There have been 22 confirmed IS reports, 9 of which were within the first 7 days following vaccine. For Rotarix[®], with only 22 cases, it is difficult to see any particular trends.

The VSD was established in 1990. It is a collaborative project between CDC and 8 managed care organizations, which allows for planned immunization safety studies as well as timely investigations. The VSD collects data from over 9 million members captured annually, or about 3% of the US population. In the past few years, the VSD has developed an active surveillance technique also known as RCA. In RCA, VSD data is updated weekly, particularly the vaccine and event data with ICD-9 codes. Using sequential analysis, the number of cases for about 5 to 10 pre-specified adverse events occurring after vaccine is compared each week to the expected number based on a comparison group. VSD conducted an RCA study for RotaTeq[®] vaccine from May 2006 to May 2008, the results of which have been published. There were 5 cases of IS identified within 30 days after RotaTeq[®] vaccine. Only 2 cases were validated after medical review, neither of which followed Dose 1. The 5 cases did not exceed the expected number of cases, and no cases were within 7 days of vaccination. This study included about 207,000 doses. The results provided no evidence that RotaTeq[®] was associated with increased risk of IS or the other pre-specified adverse events included in the study [Belongia EA, Irving SA, Shui IM, et al. Real-time surveillance to assess risk of intussusception and other adverse events after pentavalent, bovine-derived rotavirus vaccine. *Pediatr Infect Dis J.* 2010;29:1-5].

Because of the continued interest in this outcome and vaccine, subsequent analyses were conducted in VSD, which were reported to ACIP previously. Surveillance was conducted for IS using two windows: 30-day and 7-day. All 8 VSD sites participated. The exposed population was defined as children who received any dose of RotaTeq® with or without other vaccines from age 4 to 34 weeks. For the results reported during this session, the concurrent comparison group of children who received any immunization besides RotaTeq® from age 4 to 34 weeks was used, and the study included data from May 2006 to May 2010. In terms of the number of doses given by age / dose strata and the number of unexposed visits, 31 cases of IS were identified out of 850,000 RotaTeq® doses. In the comparison group, 19 cases were identified out of 405,000 comparison visits. Dr. Baggs emphasized that these results included unconfirmed cases at this point.

With the same number of doses limited to the 7-day window, only 2 cases followed Dose 1 out of 332,000 doses. For the comparison group, there were 4 cases total. Using that data with an exact Poisson regression model controlling for the age / dose strata, risk ratios were calculated for the 30-day and the 7-day window using all doses combined or focusing only on Dose 1. Of the 4 risk ratios, 3 were less than 1 and only 1 was greater than 1 (1.4), for the 30-day window for Dose 1. All the confidence intervals included 1, so there were no statistically significant results. However, when focused on Dose 1 for a 7-day window, the confidence interval was pretty wide.

To get a better idea of the statistical power of the VSD, some additional calculations were made. The additional calculations assumed that the identified 13 or fewer cases within the 30-day window were achieved after 332,974 doses. The VSD background rate was used for these first dose calculations. The assumption was made that there was a true risk in the 30-day window. A true risk of 8 times higher than the VSD background rate was assumed. If the true risk was 8 times higher, 59.1 cases would be expected. The probability that only 13 or fewer cases would be identified, given the expected 59.1, was very small (less than 0.0001). Assuming that the true risk was 3 times higher than the VSD background rate, 22 cases would have been expected and the probability that only 13 or fewer cases would be observed was 0.0258, which equates to an attributable risk of approximately 4.4. Similar calculations were made using the 7-day window. If the risk ratio was 4 times higher than the VSD background rate, approximately 7 cases would have been expected. The probability that 2 or fewer cases would be observed was 0.0321, which attributes to an excess risk of 1 to 2 cases per 100,000 doses. If true risk is assumed to be higher than 4, the probability would be pretty small of identifying only 2 cases following the 332,000 first doses.

There are some limitations to these analyses. The cases have not yet been chart-confirmed, although the results from chart confirmation were expected within 2 to 3 weeks following the ACIP meeting. Limiting cases identified in the ED / hospital, rather than all settings, did not alter the findings substantially. The preliminary analysis from the chart review suggests that the predictive positive value (PPV) for ED / hospital cases is about 80% percent. In addition, it is possible that the concurrent comparison group may not be as likely to utilize health care since they are not using all of their recommended vaccines. This would suggest an underestimate of the control rate and would not explain the findings. The investigators intend to do a historical comparison, but have identified potential temporal trends, especially in those cases that are not identified in the ED and hospital.. When this analysis is done, it is most likely that it will be limited to only those cases identified in the ED and hospital settings. With over 332,000 first doses monitored within the VSD, and given the observed rates of IS, there is limited power to

detect a very small risk ratio of less than 4 following RotaTeq®, especially within the 7-day window.

There are also certain strengths about these analyses. This is a large post-marketing study of IS following RotaTeq® which includes over 850,000 total doses. This is probably the largest active surveillance study of IS and RotaTeq® in the US. The study capitalizes on VSD strengths such as the high quality data sources. It has been shown in the past that the data quality for VSD studies is extremely high in that these data come from a single source in the VSD sites versus data from 4 or 5 different sources. The findings have been consistent within the VSD throughout the timeframe that rotavirus vaccines have been used, and elevated risks were not identified early on that have since declined, nor have increasingly elevated risks been identified. The VSD RCA is a proven methodology that avoids potential biases that may arise in other post-marketing surveillance systems. Several presentations have been given by VSD on its RCA, and the technique has been shown to identify potential adverse events following vaccine and reassure that those associations are not present.

In summary, the US post marketing experience in VSD provides no evidence that RotaTeq® is associated with an increased risk for IS in either the 30-day or 7-day window; however, there is limited power to detect a very small risk, especially within the 7-day window. Unfortunately, at this time, there are limited data available on Rotarix® in the VSD.

Post-Licensure Safety Study for RotaTeq® Review of Intussusception (IS) Data

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

Dr. Mast presented an overview of Merck's post-licensure safety study conducted in the US. These data were presented to ACIP members in October 2009, at which time there was no observed increase in risk of IS. This was an observational prospective cohort study that was conducted, like the VSD, in a large birth cohort of approximately 100,000 infants in the 2 years post-licensure. There were several comparison groups: a historical statistical monitoring boundary, and concurrent and historical controls who were not vaccinated with RotaTeq® but received other vaccines. Like the VSD, a large linked database was utilized. Within the same system, the investigators could link vaccination records with hospitalizations and emergency department (ED) visits. IS was evaluated within a 30-day period after any dose, and any other health outcomes were also assessed.

With regard to data review and validation of this study, case confirmation for IS was an important component. A broad case definition was used for ICD-9 codes to capture suspected cases, but there was also an independent external adjudication committee that used medical chart data that were blinded to vaccination status. This committee reviewed all of the charts to confirm whether they were IS. An independent safety monitoring committee reviewed these data and other study data on a quarterly basis to ensure that the statistical monitoring boundary was not crossed. The study was completed in 2009,; over 85,000 infants receiving over 210,000 doses total were evaluated. There were over 62,000 concurrent controls who did not receive RotaTeq® (but received other vaccines) and over 100,000 infants who were evaluated in the pre-licensure period to look for historical background rates. At the end of the study, the 6 chart confirmed adjudicated cases were about what would be expected, and were nowhere near the statistical monitoring boundary.

Risk of IS was also monitored using different control groups. Again, the overall conclusion was no increased risk. In the concurrent control groups, there was a 0.8 relative risk that overlapped 1. In the historical cohort in the 2004 and 2005 period, the relative risk was also close to 1 (0.9). Interestingly, when the entire historical cohort from 2001-2005 was used, the relative risk was not statistically significantly different than 1, but was higher than that from the 2004 and 2005 period. Interestingly, as licensure drew closer, the background rates of IS increased. This suggested that perhaps use of historical IS rates could generate different results than using concurrent background rates. Although the study was not designed to assess the 1- to 7-day period, an ad hoc analysis was done. When assessing the 1- to 7-day period after any dose, 4 cases were observed in the RotaTeq® group and 1 case in the DTaP for a non-statistically significant relative risk of 2.8. However, on further examination of those 4 cases in the vaccine group, only 1 was after Dose 1. For the concurrent controls, there were zero cases, so even that was not a statistically significant difference. However, the investigators could not calculate a relative risk.

With respect to vaccine impact, the same underlying population was used that was used to evaluate safety was assessed in order to determine how well the vaccine worked. In the two years after licensure in the same system, a 72% decrease was observed in rotavirus medical visits following vaccination.

In conclusion, this study is just one part of many studies. Contrary to what was presented earlier in this session, there is not a consistent association between RotaTeq® and IS. In clinical trials, the CDC VSD study, and the Merck study), over 1 million doses have been evaluated. None of these studies have shown a consistent association in the 1- to 7- or 30-day period after Dose 1. On the contrary, the remarkable impact of the vaccine that has been observed demonstrates its public health benefit.

RotaTeq® (Rotavirus Vaccine, Live, Oral, Pentavalent): Update on Porcine Circovirus (PCV)

**Colette Ranucci, PhD
Director, Merck Manufacturing Division**

Dr. Ranucci provided an update on porcine circovirus specific to RotaTeq®, Merck's rotavirus vaccine, reporting that at this point, a comprehensive investigation had been completed and Merck could report that infectious PCV is not present in RotaTeq®. She then reviewed the analytical methods and approach used to demonstrate this finding.

Given that a lot of the initial evaluations demonstrated RotaTeq® to either have very low levels of PCV DNA or no PCV DNA, the first step was to establish methods that were capable of differentiating between those two scenarios. From there, methodology was developed to systematically demonstrate the absence of infectious PCV. First, a quantitative PCR method was established that was capable of detecting short fragments of PCV1 and PCV2 DNA on the order of 100 base pairs. If short fragments of PCV DNA were detected, the investigators proceeded with the endpoint PCR method that was capable of detecting the presence of longer fragments of PCV1 and PCV2 DNA on the order of about 800 base pairs that could be associated with intact virus particles. If detected, they proceeded to the in vitro infectivity assay to evaluate for the presence of infectious PCV1 and PCV2 using a permissive cell line using quantitative PCR as the endpoint detection method. Dr. Ranucci emphasized that it was

important to establish the appropriate assay controls, conditions, and sensitivities to ensure the quality and the validity of the results generated by the analysis.

Each of these methods was applied to the evaluation to determine whether PCV was present in RotaTeq®. This was done by evaluating the final container and bulk lots using the methods described previously (e.g., quantitative PCR, endpoint PCR, and 28-day infectivity assay). Bulk lots are formulated to manufacture the final product. A number of RotaTeq® final container lots and rotavirus bulk lots from the commercial facility and the pilot facility were tested. Bulk lots manufactured at the pilot facility were the rotavirus clinical bulks associated with the Rotavirus Efficacy and Safety Trial (REST). This analysis demonstrated that low levels of PCV2 DNA were detected in the rotavirus bulk lots manufactured from the commercial facility. These samples were moved through the complete evaluation to demonstrate that while PCV2 DNA was detected, infectious PCV was not detected in any bulk lots tested. , PCV DNA was not detected in the clinical bulk lots associated with REST.

Having identified low levels of PCV2 DNA in the rotavirus bulk lots, the next step was to determine the source of the PCV DNA. This was done by an evaluation of process inputs. The process includes V cell expansion and rotavirus propagation to manufacture the vaccine bulk lots that are then formulated into the final RotaTeq® product. The key process inputs are the master and V working cell banks, the master virus seeds, the stock virus seeds, and irradiated trypsin. Trypsin is used in V cell expansion and rotavirus propagation and is the only porcine-derived raw material in the process.

The methodology described previously was used to evaluate the process inputs to determine the source of the PCV DNA (e.g., quantitative PCR, endpoint PCR, and infectivity testing) to assess the vero master cell bank, the working cell bank, the rotavirus master seeds, the rotavirus stock seed, and the irradiated trypsin. There are five individual master seeds and five individual stock seeds; because this is a pentavalent vaccine; all were tested. Through this analysis, it was demonstrated that the master and working cell banks were negative for PCV DNA, as were the master and stock seeds. The only positive result detected was for the irradiated trypsin for which PCV2 DNA was detected. This was then carried through the entire set of testing. It was demonstrated that while PCV2 DNA was detected, this sample was negative for infectious PCV.

Having established the low levels of PCV2 DNA in the product and having identified the source of that PCV as trypsin, the next step was to evaluate the clinical relevance of this finding. This was done by evaluating serum samples from vaccine recipients because it was determined that doing so would provide the greatest likelihood of detecting a clinical response, should there be one. All available serum samples were evaluated from vaccine recipients having received the clinical consistency lots. These were manufactured using bulk lots, which did contain low levels of PCV2 DNA. The analysis was performed using an enzyme-linked immunosorbent assay (ELISA), which demonstrated that all of the samples from the placebo and vaccine groups were negative for the PCV2 antibodies. Therefore, it was concluded that all of the serum samples were seronegative for PCV2.

In conclusion, PCV1 DNA fragments are below the limit of detection in bulk lots of RotaTeq®. Low levels of PCV2 DNA fragments were detected in bulk lots of RotaTeq® and the irradiated trypsin was confirmed to be the source of that PCV DNA. Infectious PCV has not been detected in any bulk lots of RotaTeq® or in the process inputs associated with the manufacture of RotaTeq®. PCV2 antibodies were not detected in serum samples of vaccine recipients who received clinical material that contained low levels of PCV2 DNA fragments. With that, all key

aspects of the PCV investigation of RotaTeq® have been completed and Merck is in the process of communicating these findings to regulatory agencies worldwide.

Post-Marketing Surveillance for Rotavirus Vaccines in Australia

Dr. Julie Bines

Dr. Jim Buttery

University of Melbourne, Australia

Dr. Buttery presented post-marketing surveillance data for rotavirus vaccines in Australia. Rotavirus vaccine was introduced into the Australian National Immunization Program (NIP) on July 1, 2007. Australia has a birth cohort of just over 250,000 births per year. Australia approved both rotavirus vaccines for implementation into the NIP at the same time. Within the first 18 months of the NIP, which this surveillance period covers, 87% of eligible infants received at least one dose before 4 months of age and 84% of eligible infants received a complete course of rotavirus vaccination. These vaccinations are recorded on the Australian Childhood Immunization Register (ACIR), which is the register of all NIP vaccines received up to the age of 7 years. Incentives are provided to healthcare providers and parents for registration, and it is estimated that 95% of vaccinations are registered in ACIR. In Australia, decisions pertaining to vaccines are made federally and then state government chooses one of the funded vaccines for that indication to implement. Approximately half of the states chose RotaTeq® (RV5) vaccine and half of the states chose Rotarix® or RV1. Of note, Western Australia initially implemented Rotarix®, but has been using RotaTeq® since 2009.

In terms of the impact of rotavirus vaccines in Australia, Queensland experienced peaks from 2000 to 2010 of traditional winter / spring seasons of gastroenteritis. Using the ACIR and state coding for admission, vaccine efficacy in Queensland has been calculated to be between 89% and 94% for rotavirus coded admissions. Even for non-rotavirus coded admissions, the vaccine efficacy is being estimated to be between 62% and 64% [Field et al *Pediatr* 2010]. With regard to the impact on the largest hospital in Victoria, which also implemented RV5 and where most admissions are admitted to the Short Stay Unit, from 2005 through 2009, total admissions to the Short Stay Unit remained stable, but the admissions due to gastroenteritis decreased from 15% of total admissions to 5% [Buttery et al *Pediatr Infect Dis J* 2011 (in press)].

Surveillance was established at the time of vaccine implementation from July 2007. Both of the complimentary surveillance systems were used for this analysis. The first was Australian Paediatric Surveillance Unit (APSU), which is a longstanding national surveillance method to facilitate active surveillance of uncommon childhood diseases, complications of common diseases, and adverse effects of treatment that was established in 1993. Each month, approximately 1250 clinicians on the APSU contact database are sent either a reply-paid report card or an e-mail card listing conditions currently being studied through the APSU. Clinicians are asked to report children newly diagnosed with any of the conditions listed (including IS). Investigators conducting a study are informed weekly of new cases reported by APSU contributors. The investigator then sends a questionnaire to the clinician requesting further de-identified information (e.g., date of birth, gender, clinical details, immunization status). Investigators are responsible for collation, analysis, and publication of this data, and report study findings annually through the APSU [<http://www.apsu.org.au>]. This particular study was de-identified and was not linked directly to the ACIR.

The second surveillance system, Pediatric Active Enhanced Disease Surveillance (PAEDS), was modeled upon the Canadian ImPACT system, and involved 4 sentinel sites involving each major pediatric hospital in 4 states (e.g., The Children's Hospital at Westmead Sydney, Royal Children's Hospital Melbourne, Women's and Children's Hospital Adelaide and Princess Margaret Hospital Perth). This includes two RotaTeq® states and two Rotarix® states. This system has nurse-based surveillance using multiple modalities to look for all presentations and admissions with IS. This study is conducted with informed consent, which enables full access to medical records, ACIR for those children, pathology / radiology records, and access to their general practitioner and pharmacy records.

In terms of the data analysis, unique patient data were combined from PAEDS and APSU to eliminate duplicates for each of the 4 states that conducted both studies, so this analysis only involved the 4 states exposed to transmission during the period 18 months from commencement of NIP vaccination (July 1, 2007 to December 31, 2008). Data are presented by vaccine, dose of vaccine, in 2 month age strata, and in 0-7 day and 0-21 day post-vaccination risk windows. Comparisons were made between the observed versus expected IS rates from 4 states, by vaccine used.

For background IS rates, national data were used on all hospital admissions of children less than 24 months by the Australian Institute of Health and Welfare in the period from 2000 to 2006. During that time period from 2000 through 2006, the rate of IS admissions was reduced. Information was obtained on age, region, epidemiology, and outcome of those IS cases. The background was estimated by the number of cases divided by the number of live births, obtained by the Australian Bureau of Statistics. Incidence rates were pooled for the expected rates by the 2 states administering RotaTeq® in NIP and the 2 states administering Rotarix® in NIP. The child-time at risk was estimated for the 4 states involved in both surveillance studies (APSU and PAEDS), incorporating data from ACIR calculated from the number of children who received each vaccine by dose number over that time period and calculating the time period at risk for each child following each dose of vaccine (7 or 21 days), which was assigned by month of age.

With regard to IS for RV5 involving the states of Victoria and South Australia, looking at the age, period of interest in 1 to less than 3 months of age, in the window period 1 to 7 days post-vaccine, 3 cases were observed with an expected case number of 0.57, an RR of 5.3, and a confidence interval of 1.1, 15.4. In the 1 to 21 day post-vaccine period, there were 6 cases observed compared with 1.7 cases expected, with a RR of 3.5 and the confidence intervals of 1.3, 7.6. No difference between expected and observed cases was seen following Dose 2 for either window period, and fewer cases were observed than expected for Dose 3 of RV5. Combining all of the exposure windows, there was no increase overall observed during the first 9 months of life. The same analysis was performed for Rotarix® vaccine. Only 2 doses were given at 2 and 4 months of age. In the 1 to less than 3 month age period, 3 cases were observed compared with the expected of 0.9, with a RR of 3.4 with the lower limit of the confidence interval of 0.71. For the 1 to 21 day period, 4 cases were observed compared with 2.6 expected cases, with a RR of 1.5. Again, the confidence interval is less than one. Similarly, there was no signal following Dose 2, and there was no increase overall for the first nine months of life based on the expected for either time period.

In conclusion, based on these data from the first 18 months following introduction of rotavirus vaccines into the NIP, the Australian program was highly successful for the uptake of vaccines, with 87% of children receiving at least one dose of vaccine and 84% completing a course of rotavirus vaccination. The benefit of rotavirus vaccine has been proven in Australia, but due to the unique state-based purchasing arrangements, they had the ability to compare safety and effectiveness of both vaccines within the NIP. Overall, they have observed no increase in risk of IS at 9 months of age with either vaccine. The relative risk of IS was increased within the 7 and 21 day post-vaccination risk window following Dose 1. These data are consistent with what was described earlier in this session in Mexico and Brazil. It is important to emphasize the need to continue to post-marketing surveillance for IS, particularly in regions with different baseline IS rates compared to US.

Estimates of Benefits and Potential Risks of Rotavirus Vaccination in the US

Margaret M. Cortese, MD
CAPT, USPHS
Centers for Disease Control and Prevention

Dr. Cortese reviewed the estimates of the benefits and potential risks of rotavirus vaccination in the US. She indicated that there has been a dramatic decrease in the number of rotavirus positive tests obtained from the NREVSS system of laboratories across the US. A usual winter peak was observed until the 2008 season, when there was good uptake of RotaTeq® vaccine, the vaccine available at that time in the US. Since then, there has been a marked decrease in the number of positive tests from across the country in this system. When these peaks are stacked on top of one another, the peak percentage positive can be observed that occurs around March, in the pre-vaccine and then comparing to the three post-vaccine seasons with good vaccine uptake. This line for percentage-positive was almost flat for the 2009 / 2010 season [Tate J et al PIDJ in press]. Aaron Curns examined the hospitalizations for gastroenteritis and rotavirus-coded gastroenteritis in 18 states from large discharge databases in children less than 5 years of age. Again, a similar pattern was observed with a dramatic reduction post-vaccine in the usual winter peak of gastroenteritis hospitalizations that was seen pre-vaccine. It was estimated that nationally, in 2008, over 40,000 hospitalizations for gastroenteritis were prevented [Curns A et al JID 2010].

CDC's "Cadillac" system, NVSN, involves active surveillance for rotavirus disease. This is led by Dr. Dan Payne at CDC with colleagues at the University of Rochester, Cincinnati Children's Hospital, and Vanderbilt. At these sites, all children aged 3 years and less who present with acute gastroenteritis during enrollment days (at least 4 days per week December through June) are consented. A stool sample is obtained from them, which is then tested for rotavirus. From the baseline season in 2006 (and in early 2007, which was still almost a baseline season since there was low vaccine uptake at that point), about half of the children hospitalized for acute gastroenteritis under 3 years of age were rotavirus-positive. Subsequently, there was an amazing reduction during the next 3 seasons. By the 2010 season, which ended in June 2010, at the three children's hospitals combined, only 4 hospitalized children were detected to have rotavirus gastroenteritis. Without a doubt, this vaccination program has quickly had a remarkable impact on rotavirus disease burden in the US [Payne D et al 2010].

Dr. Cortese then summarized the key findings from the post-marketing intussusception studies. Limited data are available on Rotarix® in the US, given that it was relatively recently introduced in the U.S.. Regarding the two studies in Mexico, the GSK study evaluated the 30-day period following Dose 1 and the PAHO-CDC studies evaluated smaller risk windows. In the data from

Brazil, a risk in Week 1 following Dose 1 was not detected. In terms of the data from Australia, the expected IS cases are based on historical rates. Data are available in the US on RotaTeq®. There are post-marketing IS studies from the VSD evaluation in which the controls are infants vaccinated with vaccines other than the rotavirus vaccine. No risk has been detected in this system. The Merck study includes data on concurrent DTaP recipients and with Doses 1, 2, and 3 data combined for analysis. The Australian data, provides an expected number of cases based on historical rates.

Regarding the benefits of rotavirus vaccination in US based on available data, Dr. Cortese acknowledged Dr. Martin Meltzer from CDC who developed a model with Dr. Marc Alain Widdowson and CDC colleagues that was presented to ACIP in 2006 and 2008. This model provided estimates of the cost-effectiveness of a rotavirus program in the US. For the update, rather than working from a cost perspective, disease burden with and without a vaccination program is the focus. Updated inputs for the model were offered, particularly in terms of vaccine effectiveness based on use of the vaccine in the US. Dr. Meltzer re-ran the model with these updated inputs. It is important to note that the results on impact of the vaccination program are extremely similar to the original results based on the original inputs that were published [Widdowson M, Meltzer M et al. Pediatrics 2007;119:684-97].

With regard to the model inputs, the 2009 US birth cohort was followed to age 5 years. If a cohort that size remained unvaccinated, rotavirus disease would cause approximately 33 deaths; 72,000 hospitalizations; over 200,000 ED visits; and about 400,000 clinic visits. For vaccine coverage, DTaP coverage estimates were used from the 2009 NIS, with some adjustments because there are maximum ages for rotavirus vaccine doses. The model results are based on reaching these levels of coverage with rotavirus vaccine by age 1 year. The estimate used for vaccine effectiveness using a 3-dose series was 88% for hospitalizations and deaths, 84% for ED visits, and 80% for clinic visits. Based on the model, the following table reflects the estimated of benefits of vaccination:

Rotavirus Events	Without vaccine	With vaccine	Number (%) prevented with vaccination
Deaths	33	17	16 (48%)
Hospitalizations	72,495	19,693	52,802 (73%)
ED visits	232,622	63,191	169,431 (73%)
Clinic visits	428,934	133,112	295,822 (69%)

The baseline incidence of IS in infants rises over approximately the first 7 months of life. Incidence by week of age was used based on population-based US data, using intussusception inpatient discharge diagnoses, from the years shortly before vaccine was introduced. There are data demonstrating that approximately 22% of infants with IS in the US are officially categorized as short-stay or ED patients. This is the billing category although the infants may remain in the hospital for up to 72 hours. They are not captured in inpatient discharge databases, so background rates were adjusted by this factor. Based on the literature, the estimated the proportion of all infants with IS who require surgery in the US is 37%. The proportion with a fatal outcome is less than 1%. Although a risk has not been documented in the US, for the estimate of potential risk, the point estimate results were used from the PAHO-CDC case series from Mexico, which showed an incidence rate ratio of 4.6 during Week 1 following Dose 1 in vaccinated infants. Vaccine coverage with Dose 1 varied by week of age.

The background rate of IS in US infants shows very low incidence in the first few months of life, with a peak at approximately 6 to 7 months of age. Adding on top of that distribution, we used the proportion of first doses of rotavirus vaccine given by age group, using data are from the 2009 NIS. Approximately 66% of first doses were given to infants aged 8 and 9 weeks and about 83% of first doses were given right on time in the second month of life, when the baseline IS rate is low. These data are from children born in 2007, but data are available from several thousand infants born in 2009 from the Immunization Information System Sentinel Sites in 8 states. These data show very similar results.. It is very reassuring that infants are receiving Dose 1 on time and within the recommended age window. Only about 2.5% to 6% are receiving Dose 1 after the recommended maximum age. Based on this, the number of infants who would receive Dose 1 in each one-week age period was calculated. The result was then applied to the baseline rate of IS. If there is a relative risk of 4.6 in Week 1 following Dose 1, an estimated 48 excess IS cases would occur in a birth cohort, with the background intussusception estimate of approximately 1,900 US infants who develop IS annually. This would be an approximately 2.5% increase in the number of infants with IS over baseline. The majority of excess cases would occur in 2-month old infants because that is when the first dose is given. With the relative risk of 4.6, it was estimated that, in one birth cohort, there would be 48 excess IS cases, 18 would require surgery, and there would be less than 1 fatality. Another way to present these estimates is to state that if there was a relative risk of 4.6 during Week 1 after Dose 1, the overall estimated attributable risk for infants vaccinated during the recommended age period would be 1 excess IS case per 97,000 vaccinated infants. This would be substantially lower than the attributable risk of intussusception estimated for the Rotashield[®] vaccine, which was about 1 IS case per 10,000 vaccinated infants [Peter G et al. Pediatrics 2002].

The benefits and potential risks for one vaccinated birth cohort followed to age 5 years are illustrated side-by-side in the following table:

Events	Rotavirus gastroenteritis sequelae prevented with vaccination	Excess intussusception cases and sequelae with vaccination	Rotavirus outcome prevented per 1 excess IS outcome
Hospitalization	52,802	48	1100 : 1
Emergency Department	169,431	---	
Clinic Visit	295,822	---	
Surgery	---	18	
Death	16	0.2	80 : 1

Discussion Points

Dr. Temte suggested that while a very good cost-effectiveness analysis was done prior to rotavirus vaccine use, it would be wonderful to use retrospective data to compare how well the original cost-effectiveness analyses compare to what has actually been realized.

Dr. Cortese responded that she believes people within and outside of CDC are currently examining the economic impact of the rotavirus vaccine program.

Dr. Baker said she suspected that they may see a trend toward the surprise observed with the introduction of the pneumococcal conjugate vaccine.

Dr. Marcy pointed out that if it really was 0 to 4 excess cases per 100,000, about 3 pediatricians could work a lifetime of 40 years each and only see 1 case of IS.

Dr. Meissner pointed out that the recommendation to administer the first dose before 15 weeks of age, based on suspicion of an increased risk if given after that time, results in a very tight timeframe. It is difficult for other countries to administer vaccine in that timeframe. He wondered whether this experience would reduce interest in trying to expand the ages at which the rotavirus vaccines might be administered.

Dr. Cortese replied that she did not know. Speaking from a personal perspective, it seemed like the potential risk of IS would require serious consideration. A notable finding, as seen in the PAHO Brazil data and from other countries is that remarkably, many countries are able to administer the great majority of first doses within the recommended window thus far.

Dr. Parashar reported that about 2 years ago, Dr. Patel conducted an exercise to model a hypothetical risk of magnitude of 6 with the first dose in the first week to determine the number of excess IS cases and the rotavirus mortality that would be prevented by expanding the age recommendations for vaccine administration. The figures overwhelmingly were still on the side of expanding the recommendations. This is clearly a discussion that needs to take place.

Dr. Baker indicated that Dr. Kathy Neuzil recently gave a lecture at the IDSA meeting in Vancouver in which she used rotavirus as a model in the developing world. It was interesting to Dr. Baker that many of the countries in Africa that are introducing rotavirus vaccines are packaging them with other fairly routine maternal infant efforts like vitamin supplementation, weight checks for the newborn, et cetera. Depending upon the infrastructure that is in place, this vaccine can be given on time.

Dr. Cieslak noted that there have been some suggestions from data of a nationally reduced incidence of IS over the whole time period. He inquired as to whether hospital discharge data over time had been assessed to determine trends now that there has been substantial uptake of the vaccine.

Dr. Cortese replied that this had been done. Drs. Jacqueline Tate and Catherine Yen have led an investigation to assess discharge database data from 18 states from 2000 to 2008 (5 pre- and 2-post vaccine years. Between 2000 and 2005, the overall IS rate in infants under 1, based on the hospitalization ICD-9 discharge diagnosis code, was generally stable. In 2007, there was an increase in the rate of IS detected in these databases. In 2008, it returned to baseline. It is not straightforward to interpret those data. When they further evaluated subgroups within the group under age 1 year,,, particularly the age group receiving the first dose of vaccine (those 6 to 14 weeks), there was an indication of an increase in 2007 and 2008 in the rate of IS in that small age group. However, by looking more closely with finer categories, there are small numbers of cases in each category. What has been observed overall in the age group 6 to 14 weeks was not a consistent finding by race / ethnicity group, and was observed in one of the groups. Overall, it is very important to examine these data in the best way possible. There are major limitations, but those are the preliminary data that are available.

Dr. Offit said he was trying to understand a phenomenon. In Mexico, for example, there was a temporal association between receipt of Rotarix® and development of IS. Rotarix® is an attenuated form of a natural virus in that P1G1 virus was isolated from a child in Cincinnati. If it is associated with IS, one would have to believe that to some extent, natural infection causes IS.

Vaccine-associated and wild type virus are rare causes of IS in the US. Although a bump occurs in rotavirus in the winter months, a bump in IS in the winter months does not occur. He thought if they had to pick which of the two would be more likely to cause IS, it would be the wild type virus. The data Dr. Cieslak requested are critical. The important question is: To what extent has the introduction of these two vaccines in the US increased the incidence of IS. He would predict that over time they would find that there is not an excess. It would be highly beneficial to those in the field to understand these findings in order to explain this phenomenon to the public. Provision of preliminary 2009 data would be very helpful. This was observed with Rotashield[®] and now Rotarix[®]. Although the data from Australia are smaller numbers, it seems that some level natural infection causes IS, albeit rarely. If natural infection causes IS and these vaccines prevent natural infection to some extent, he predicted that there would have to be a compensatory decrease in some of the IS.

Proposed Revised ACIP Recommendation Wording

Margaret M. Cortese, MD
CAPT, USPHS
Centers for Disease Control and Prevention

Dr. Cortese indicated that in light of all of the data, the working group evaluated the current recommendations for the use of rotavirus vaccine. There is currently a precaution for administration of rotavirus vaccine to infants with a previous history of IS. After reviewing the data and thinking all of this through, the working group proposed that the precaution wording be modified slightly. The precaution will remain, but some additional information will be provided for practitioners who are trying to weigh the benefits and potential risks. The revised statement would read as follows:

PRECAUTION

Previous History of Intussusception

Under usual circumstances in the United States, for infants with a history of intussusception, ACIP considers the possible increased risk of intussusception following rotavirus vaccine to outweigh the benefit of protection against severe rotavirus disease. (Note: Background information would be included here, but was eliminated during this presentation due to length)

Because specific data are not available on the risk of a subsequent episode of intussusception following rotavirus vaccine in infants with a history of intussusception, providers may administer rotavirus vaccine to an infant with a history of intussusception if, in a particular circumstance, they believe the benefit to outweigh the possible risk.

The working group felt that this provided additional guidance that would be valuable to providers.

Influenza Vaccine

Introduction

Wendy Keitel, MD, Chair ACIP Influenza Work Group

Dr. Keitel began by thanking Ms. Ehresmann for her moving tribute to Carol Friedman, whose passing was a great loss to her family, the community, and public health. Dr. Keitel was particularly looking forward to working with her on the Influenza Working Group.

She then acknowledged the leadership of Dr. Kathy Neuzil; Dr. Dale Morse, the former ACIP Chair; and Dr. Fiore, the CDC lead, as they navigated the Influenza Working Group through the 2009 pandemic. Now that that storm has passed, the working group is returning its attention to the pressing issues of inner-pandemic influenza control. Dr. Keitel assumed the workgroup lead in June 2010, and she thanked Dr. Tim Uyeki who graciously agreed and capably served as the acting CDC lead since July 2010 and she welcomed Dr. Lisa Grohskopf, the incoming CDC lead, and Dr. Jeff Duchin as an ACIP member of the working group. This is a large workgroup, which has a number of ACIP members and CDC and other liaisons representatives.

Dr. Keitel thanked the working group members for their continued activities during the summer and into the fall as they grappled with several issues, as well as the ACIP which was called upon several times to weigh in on various decisions. During that time, the *2010 Use of Influenza Vaccines* was published in the *MMWR* [August 6, 2010 / Vol. 59 / No. RR--8 / Pg. 1-62]. During the summer there was a recognized increase in the occurrence of febrile seizures and fever, particularly among young children in Australia and other countries. The Influenza Working Group reviewed information related to this occurrence and developed options for recommendations for the use of CSL Afluria® Vaccine in Children. An interim ACIP Meeting was convened on August 5, 2010 that resulted in a decision to restrict the use of this vaccine among children under the age of 9. *2010 Use of CSL Afluria® Vaccine in Children* was published in an *MMWR Policy Note* on August 13, 2010 [59(31);989-992]. In addition to these vaccine considerations, the working group touched up the antiviral treatment recommendations, which will be published later in 2010. The working group has also been considering several issues that have arisen regarding vaccine safety (e.g., narcolepsy, febrile seizures, and high dose influenza vaccine).

This session included discussion of influenza activity, influenza vaccine distribution and coverage, and vaccine safety.

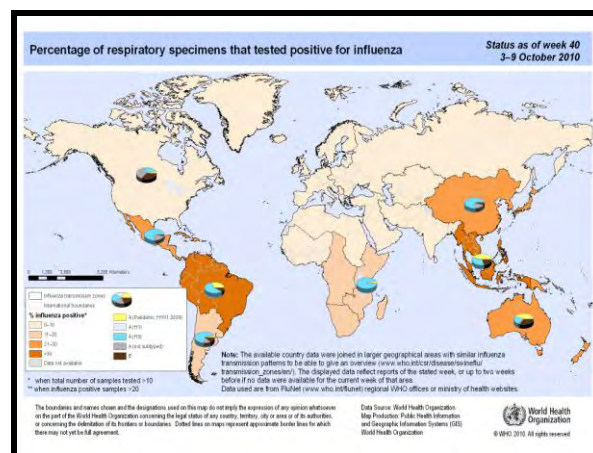
Update on Influenza Activity and Influenza Vaccination

Tim Uyeki MD, MPH, MPP

Influenza Division

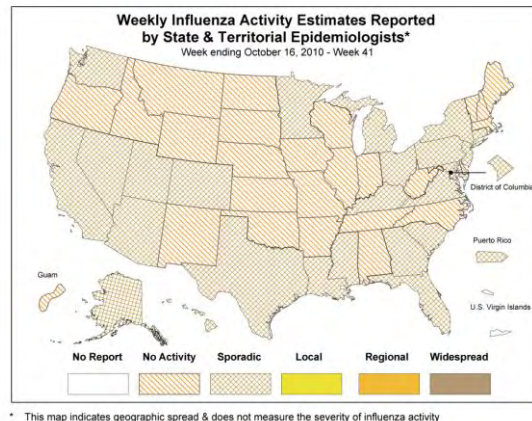
**National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Uyeki offered a brief update on current influenza activity and influenza vaccines. With regard to international influenza activity in the Southern Hemisphere temperate climate countries, influenza activity has peaked and is declining in most countries. There has been variable co-circulation of seasonal influenza A (H3N2), 2009 H1N1, and B virus strains. South Africa's season was predominated by influenza B virus, Australia's by 2009 H1N1 and B viruses, and new Zealand's by 2009 H1N1 virus. In several countries, H3N2 virus predominated. In tropical and subtropical countries there has been variable activity, which has been declining in some regions. Other regions (e.g., Southeast Asia, Central American, South America) have experienced moderate to increasing activity. There has been variable co-circulation of influenza A (H3N2), 2009 H1N1, and B virus strains. Many countries have greater H3N2 activity than 2009 H1N1. 2009 H1N1 virus predominated in India. There has been low activity in the Northern Hemisphere temperate countries, but there has been recent detection of H3N2, 2009 H1N1, and B viruses. The following WHO map reflects international influenza status as of Week 40:

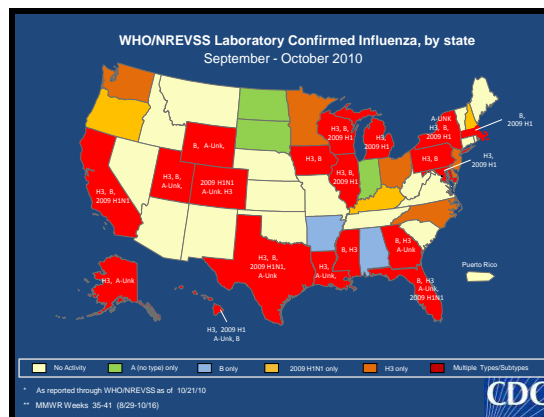


In terms of the characteristics of recent influenza viruses tested at CDC, 99% of the 2009 H1N1 viruses have been antigenically closely related to the A/California/7/2009 (H1N1) vaccine strain. These viruses are susceptible to neuraminidase inhibitors and resistant to adamantanes. The vast majority of H3N2 viruses have been antigenically closely related to A/Perth/16/2009. These are susceptible to neuraminidase inhibitors and resistant to adamantanes. The majority of the B viruses have been antigenically closely related to the B/Brisbane/60/2008 vaccine virus, which are susceptible to neuraminidase inhibitors.

The following map reflects low influenza activity as of Week 41, with some sporadic activity throughout the US:



The percentage of visits for influenza-like illness (ILI) reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), the weekly national summary reflected low though somewhat increasing activity from September 30, 2010 through October 16, 2010. Virological surveillance data from the US WHO / NREVSS Collaborating Laboratories for 2009 through 2010 also reflect low activity compared to last season. The following map shows the various strains that are circulating throughout the US, with red representing the states in which co-circulation of influenza A (H3N2), 2009 H1N1, and B virus strains has been detected:



The key points are that overall, influenza activity is low in the US. Influenza vaccination is recommended this season for all persons aged ≥ 6 months for 2010 through 2011. There has been recent global co-circulation of influenza A (H3N2), 2009 H1N1, and B viruses, including in the US. The good news is that recently circulating influenza viruses are well-matched by 2010-2011 influenza vaccine strains, and recently circulating influenza viruses are susceptible to neuraminidase inhibitors. Updated antiviral recommendations are to be issued.

Based on information provided by the Immunization Services Division (ISD) at CDC, total overall US vaccine projections for the 2010-2011 season are 160 to 165 million doses across all manufacturers and product types. In the US as of October 15, 2010, approximately 139 million doses (84-87% of projected total) have been distributed. This is the greatest number of seasonal influenza vaccine doses ever distributed in the US in a single season. Approximately 114 million doses were distributed during the 2009-2010 season.

Regarding influenza vaccination coverage through October 20, 2010, preliminary data reflect an estimated coverage for children aged 6 months through 17 years of age to be approximately 19% to 23% [National Immunization Survey (NIS) sample frame, parental interviews through October 23, 2010]. This is similar to seasonal vaccine coverage by the third week of October 2009. For children who were not yet vaccinated, parents were also asked whether they intended to obtain vaccination for children. Of the parents, 47% stated that their children already have or “definitely will” be vaccinated. This is similar to 2009-2010 seasonal coverage as of May (44%). Coverage estimates are higher in children 6 months through 23 months (59%) compared to adolescents (35% for 13-17 years of age) [National Immunization Survey (NIS) sample frame, parental interviews through October 23, 2010; SDI]. Provider office 2010-2011 influenza vaccination trends to date for persons aged \geq 6 months reflect slightly lower coverage than in 2009-2010, but higher coverage than in 2008-2009. This excludes vaccinations in workplace, pharmacies, public clinics and other settings not billed by provider offices [SDI].

Coverage data are not yet available for adults. BRFSS data will be used by CDC to provide monthly national and state level estimates for adults. The lag from the end of vaccination period to reporting of estimates will be approximately 6 to 8 weeks. Coverage estimates for children from the NIS sampling frame will be combined with adult estimates from BRFSS to estimate coverage in persons \geq 6 months.

Influenza Vaccine Safety Monitoring Update

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Division of Healthcare Quality Promotion,
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention (CDC)

Dr. Shimabukuro reported that the seasonal influenza vaccine for 2010-2011 is comprised of A/California/7/2009 (H1N1)-like virus strain, A/Perth/16/2009 (H3N2)-like virus strain, and B/Brisbane/60/2008-like virus strain. There is a universal recommendation for influenza vaccine for all people ages 6 months and older. High dose inactivated influenza vaccine has been approved for people aged 65 years and older. As of October 15, 2010, approximately 139 million doses of influenza vaccine have been distributed in the US.

CDC and FDA staff recently published a paper describing 2009 H1N1 influenza vaccine safety based on the VAERS monitoring system [Vellozzi C, Broder K, Haber et al. Vaccine. doi:10.1016/j.vaccine. 2010.09.021]. VAERS received approximately 10,000 reports after 2009 H1N1 vaccine for persons vaccinated during the first 4 months of the vaccination program. Of these reports, 93% were non-serious. The reporting rate was higher after 2009 H1N1 vaccines than 2009-2010 seasonal influenza vaccines, which may be due to stimulated reporting. Death, Guillain-Barré syndrome, and anaphylaxis reports after 2009 H1N1 vaccination were rare, with each no higher than 2 per million doses administered. The adverse event reporting profile after 2009 H1N1 vaccines was consistent with that of seasonal influenza vaccines [Vellozzi C, Broder K, Haber et al. Vaccine. doi:10.1016/j.vaccine. 2010.09.021].

With respect to the Vaccine Safety Risk Assessment Work Group summary of 2009 H1N1 vaccine safety, ACIP was briefed on the NVAC report on 2009 H1N1 vaccine safety risk assessment in June 2010. There was a weak signal for Guillain-Barré Syndrome (GBS) in the Emerging Infections Program (EIP) data. A weak signal was detected for Bell's Palsy in the

VSD and the Indian Health Service (IHS) database. The signal in the VSD has since been ruled out. There was a weak signal for TP / ITP in the Defense Medical Surveillance System (DMSS), Department of Veterans Affairs (DVA), and the IHS databases. Further work is on-going and the final end-of-season analysis for 2009-2010 will be presented to the NVAC's VSRAWG in November 2010 [Source: http://www.hhs.gov/nvpo/nvac/reports/vsrawg_repot_may2010.html].

With regard to vaccine safety monitoring for the 2010-2011 influenza season, the VSD currently has sufficient power to detect a relative risk of 5-10 for seizures.

CDC Monitoring systems include the following:

- Vaccine Adverse Event Reporting System (VAERS)
- Vaccine Safety Datalink (VSD)
- Real Time Immunization Monitoring System (RTIMS)
- Clinical Immunization Safety Assessment (CISA) Network
- Vaccine Analytic Unit (VAU)

High priority conditions, areas, and enhanced monitoring include GBS; seizures, especially in children aged < 9 years old; narcolepsy; and events associated with high dose influenza vaccine. The VAERS surveillance period for influenza vaccine began in September 2010. VSD rapid cycle analysis (RCA) is underway for influenza vaccine safety monitoring. As of October 10, 2010 there were 424,322 TIV doses and 45,843 LAIV doses in the VSD.

Events in Europe have raised concerns about a possible link between Pandemrix™ and narcolepsy. Pandemrix™ is a monovalent 2009 H1N1 influenza vaccine containing AS03 adjuvant, which has been used widely in Europe during 2009-2010. No adjuvanted influenza vaccines have been used in the US. The European Medicines Agency recently reviewed available data and concluded that the available evidence was insufficient to confirm a link and suggested that further studies would be necessary. The European Centre for Disease Prevention and Control (ECDC) is funding the VAESCO network, which is similar to the VSD project, to conduct further research to examine the possible link between Pandemrix™ and narcolepsy. The VAESCO network, coordinated by the Brighton Collaboration, is finalizing a case definition for narcolepsy along with partner researchers. The 2010-2011 seasonal influenza vaccines in Europe are unadjuvanted.

Comprehensive influenza vaccine safety monitoring in VAERS during the 2009-2010 influenza vaccination season yielded no signals for narcolepsy or cataplexy, which frequently accompanies narcolepsy and aids in its diagnosis. Enhanced monitoring was put in place in VAERS and VSD for the 2010-2011 influenza season. As of October 22, 2010, no reports of narcolepsy or cataplexy following 2010-2011 seasonal influenza vaccines had been submitted to VAERS.

Febrile seizures have not been associated with influenza vaccines in previous seasons. There have been no special concerns for the 2010-2011 influenza season, with the exception of CSL vaccine in children aged < 9 years. CDC implemented enhanced monitoring for seizure following receipt of 2010-2011 seasonal influenza vaccine in VAERS and VSD. The working hypothesis for CSL is that neuraminidase appears to be higher in the H1N1 strain used in the 2010 seasonal influenza vaccine used in the Southern Hemisphere (Australian Therapeutic Goods Administration, Oct 8, 2010). VAERS reports of febrile seizures for the 2010-2011 influenza season from July 1 through October 15, 2010 include 2421 total adverse event reports following influenza vaccine. Among these are 25 reports of possible seizure in children < 9

years of age, with 13 confirmed febrile seizures all in those < 5 years of age, none with CSL vaccine, 2 indeterminate, and 2 pending further review. The remainder were ruled out as febrile seizures. The take-home message thus far is that automated data review and clinical review of cases do not indicate a signal in VAERS for febrile seizures following receipt of influenza vaccine in children aged < 9 years. As of October 11, 2010 a total of 16,513 doses of TIV have been administered to children < 5 years of age, with 0 cases of seizures observed within 0-1 days of vaccine administration.

Moving to high dose Fluzone[®] pre-licensure data, the following is a table from the package insert reflecting a side-by-side comparison of injection site reactions and systemic adverse events for high dose Fluzone[®] versus regular Fluzone[®]:

Table 3: Frequency of Solicited Injection Site and Systemic Adverse Events within 7 Days

Post-Vaccination

	Fluzone High-Dose (N ^a = 2573) Percent	Fluzone (N ^a = 1260) Percent
Injection site reactions		
Pain	35.6	24.3
Erythema	14.9	10.8
Swelling	8.9	5.8
Systemic adverse events		
Myalgia	21.4	18.3
Malaise	18.0	14.0
Headache	16.8	14.4
Fever	3.6	2.3

^aN is the number of subjects in the Safety Analysis Set.

<http://www.fda.gov/downloads/biologicsbloodvaccines/ucm195479.pdf>

There is a slightly elevated risk for injection reactions and systemic adverse events for the high dose Fluzone[®]. As of October 15, 2010, VAERS had received 258 reports after high dose Fluzone[®], of which 94% were coded as non-serious. Adverse events reported in VAERS after high dose influenza vaccine were consistent with those that are clinically expected adverse events (e.g., fever and headaches). As of October 11, 2010, approximately 700 high dose Fluzone[®] doses had been administered in the VSD system, with 0 anaphylaxis cases observed. Early in the season, concern was expressed from a large vaccinator that they were observing some increase in anaphylaxis. Once those reports were submitted to VAERS and were analyzed, this concern was eliminated but continues to be monitored.

Discussion Points

With respect to vaccine safety, Dr. Katz (IDSA) asked what procedures were in place or are being planned to monitor vaccine safety in pregnant women.

Dr. Shimabukuro replied that for 2009 H1N1 vaccine, there was enhanced monitoring for vaccine adverse events in pregnant women who were considered to be a priority group. Reports of spontaneous abortion and stillbirths would be expected by change. CDC has a manuscript in clearance detailing these data, the bottom line of which is that there were roughly 344 reports, of which 149 were spontaneous abortion and 21 were stillbirths. The message is that a review of VAERS reports in pregnant women who received H1N1 vaccine revealed no unexpected patterns or unusual events. A paper was recently published by Dr. Pedro Moro that assessed adverse events in VAERS from 1990 through June 30, 2009 that found no patterns of adverse event reports in pregnant women [Moro PL, Broder K, Zheteyeva Y, et al. Adverse

events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990-2009. *Am J Obstet Gynecol* 2010;203:xx-xx]. VAERS continues to monitor for adverse events in pregnant women. There are currently VSD studies underway that are examining this issue as well.

Dr. Meissner requested that Dr. Uyeki make a statement about the current status of cell culture based influenza vaccine.

Dr. Uyeki responded that while there are tissue cell culture influenza vaccines approved for use in Europe, none are approved for use in the US. Some recent data have been published on this, and he asked that manufacturers add comments if they wished.

Dr. Lewin (Novartis) added that the Novartis cell culture vaccine is licensed in Europe and is undergoing Phase 3 trials in the US. Novartis expects to file for licensure in the first half of 2011.

Dr. Baker inquired as to whether these trials are based on serologic correlates or efficacy.

Dr. Lewin (Novartis) responded that some Phase 3 efficacy data compared to a comparator egg vaccine have been published in Europe, which was scheduled to be presented to the ACIP Influenza Vaccine Working Group the week follow this meeting.

Dr. Katz (IDSA) pointed out that each year they are told that vaccine expires by June after it has been distributed in the fall. He wondered whether there were any data to show that immunogenicity and potency have actually diminished during that timeframe.

Dr. Schuchat reminded everyone that there were several recalls for potency declines during the course of the last season, which is an example of things changing over time.

Dr. Keitel pointed out that the manufacturers should be prepared to address the issues of on-going potency. The supposition typically is that vaccine retains potency through that period, and likely contains adequate potency for periods after that timeframe. However, they expire because usually there is at least one antigen that changes in the vaccine from year to year. The potency would still have to be checked in an on-going fashion.

Dr. Baker noted that a common question from the public pertains to how long the vaccine will protect them if they are vaccinated in August. The serology suggests that it will.

Dr. Keitel responded that serum antibody titers decline over time. There is approximately a 50% decline after an inactivated vaccine over a season if not infected; however, higher than pre-vaccination levels are maintained at least through a year following vaccination.

Dr. Temte said he had heard rumors of a serological survey being conducted for 2009 H1N1, and wondered whether Dr. Uyeki could comment on this.

Dr. Uyeki replied that several serologic surveys are being conducted to assess the rates of 2009 H1N1 virus infection in various populations. The results of the surveys are not yet published. CDC's Influenza Division laboratory is continuing to work on the sera, but perhaps this information can be presented during the next ACIP meeting or during a subsequent working group meeting.

Dr. Schaffner (NFID) inquired as to whether Dr. Uyeki could tell them anything more than what appeared in the newspapers about the H1N1 drifted strain in Australia, New Zealand, and Singapore.

Dr. Uyeki clarified that influenza viruses are dynamic and continue to evolve. The antigenic changes are unpredictable. What was reported in *Eurosurveillance* the previous week was that the strains reported in Australia, New Zealand, and Singapore do not represent significant antigenic drift. The 2009 H1N1 virus that emerged as a pandemic virus has actually not significantly changed antigenically since the emergence. This is being monitored worldwide on an on-going basis. There is an expectation that at some point there will be significant antigenic drift, but genetic changes do not necessarily equal antigenic changes. The good news is that the 2009 H1N1 strain that is included the seasonal vaccine, which is the same as last season, is a good match with what is currently circulating.

Dr. Judson asked what was known about efficacy if the same strain circulated two years in a row, but someone was vaccinated the first year and not the second.

Dr. Keitel responded that clearly there is some protection if the same strain circulates two years in a row. The data she is familiar with involves university students who were vaccinated and followed for duration of protection. During a second season and even somewhat into a third season they still had some protection. She thought there were also some data published many years ago that showed protection in children for at least three years against an influenza B strain. There can be some, but it is low. There would be no reason to tell someone not to receive another dose of vaccine for the current influenza season because H1N1 that was provide last season was monovalent. All three viruses are circulating in the US this season.

Day 2 Public Comments

Dawn Bolyard, RN, MSN, CNS
Clinical Nurse Specialist
Mercy Children's Hospital

We know that the ACIP RSV workgroup is at work on new guidelines. Given the commitment being made to use evidence as a basis for guidelines development, it is our hope that all evidence will be included, such as the experiences I have had in both a professional capacity and as a mom of an RSV survivor. This is my son, Tyler. The demographics of my patient population include being located within an inner city. Our income levels are below the federal poverty level. We have a high teen pregnancy rate. It's the usual inner city population. In 2009, we studied the lived experience of our premature infants between 32 and 35 weeks gestation: 90% were below federal poverty level, 70% were male, 90% had siblings of varying ages, and they had many risk factors. Of the 32 to 35 week gestation infants who were denied prophylaxis, 53% got an RSV infection. Of those 53%, 66% were hospitalized, 56% had ER visits, 56% had doctors visits, and 67% continued to have wheezing or infections 5 months after the end of the season. A closer look at one particular case, Tyler's case, he was a 31 6/7 weeks gestation infant. A lot of risk factors. He went home at 34 weeks. He got his first RSV infection at 36 weeks. He was denied prophylaxis. He went home on oxygen after that first infection. He had a mild laryngotracheal bronchio malacia. At 48 weeks he got his second RSV infection because he was again denied RSV prophylaxis. The cost for his first year and a half of

care was \$1.5 million. On-going costs include speech therapy and all kinds of morbidities that were associated. On-going care is about \$4,000 per month. He was removed from the care of his family, so he lost his family.

Tyler Bolyard
RSV Survivor
Dawn Bolyard's Son

You can say that again. Hi. I am Tyler and RSV was bad for me. RSV has never really went away for me. It has made my life change. It has made everything hard for me. I cannot tell people what I think because the words don't come out right, and they do not understand what I am thinking. My friends don't understand what I am thinking. I am trying to tell them, and sometimes even Mom can't figure me out like when I tried to tell her something that has happened to me at school. It makes me mad, frustrated, and sometimes lonely. RSV makes it hard for me to be in large crowds or really noisy areas. It makes me confused and kind of scared. I cannot do physical things as well as other children either, like playing ball and swimming. I need special classes and I have to work harder than other children to learn because of RSV. Reading is hard for me because I do not understand the words like others can. I have to take medicine every night because RSV hurt my lungs. I go through a lot because of RSV. No other child should have to suffer like me.

Dr. Suzanne Staebler
Health Policy and Advocacy Committee Co-Chair
National Association of Neonatal Nurses and
National Association of Neonatal Nurse Practitioners

I do not have any conflicts of interest. This statement reflects not only our deep concern about the magnitude of the existing RSV problem for premature infants, but increasingly our concern that a greater number of infants may be more vulnerable in view of the recent immunoprophylaxis guideline revisions. As you know, RSV is a common virus that generally causes mild cold-like symptoms in adults and children. However, in preterm infants, because of their immature lungs and immune system, RSV can cause severe respiratory failure and has been associated with the development of childhood asthma. It remains the leading cause of hospitalization in infants less than one year of age. In 2009, the American Academy of Pediatrics Committee on Infectious Disease made revisions to the recommendations for immune-prophylaxis against RSV infection. We are concerned that these revisions have put approximately 145,000 high risk infants who would have received immune-prophylaxis in the past decade at risk as they will now be either denied care all together or be subjected to a sub-optimal regimen that has not been tested in a clinical trial. The Impact-RSV Study showed an incidence of RSV-related hospitalizations in the 32 to 35 week gestational age group to be 9.8% in the control group and 2% in the infants in the treatment group, representing an 80% decrease. We believe that the changes in the AAP guideline for immune-prophylaxis leave fragile infants vulnerable by reducing the number of doses they are eligible to receive during RSV season. We believe that denial of full seasonal coverage based on gestational age without consideration of other risk factors is discriminatory to a selected population of X-preterm infants and may put certain populations at even greater risk due to health disparities. I respectfully submit the signatures of 1031 of our members, as well as a letter from the National Association of Pediatric Nurse Practitioners supporting this position, and respectfully request that this advisory committee endorse the National Perinatal Association's 2010 RSV prevention guideline statement for immune-prophylaxis dosing criteria. Thank you.

**Deborah Discenza
PremieWorld, LLC**

I have no financial conflict of interest. I appreciate the committee's dedication to evidence-based practice in relation to the guidelines for RSV prophylaxis. In accordance with that, I am pleased to comment on this issue. I am the mother to a baby born at 30 weeks in 2003. In 2004 I founded and launched a national parenting magazine for parents of preemies called *Premie Magazine*. Earlier this year, I co-authored the *Premie Parents Guide to Survival in the NICU*. I serve on many national boards and committees that serve this community, and every day I am in contact with preemie parents who tell me their stories. My story is like so many out there, but yet it does have a very clear message. Over seven years ago, staring at my daughter in the NICU, I felt impotent to do anything for her. Doctors and nurses were taking care of her every need, and I sat by watching the circus of medical equipment and professionals attending each incubator. At one point in the NICU stay, the neonatologist started talking about discharge day and asked us if we knew what RSV was. My heart sank in fear. I knew all too well what this virus was. Many a friend's full-term baby had had it, had been hospitalized, and had all sorts of residual issues. Here I was with a medically fragile baby in the NICU preparing to go home on medical equipment. Other than home lock down, what else was there to help us? The tool: RSV prophylaxis. As the doctor continued on with her details, I found myself solely fixed on the tool itself. Why? Because I honestly believed that RSV prophylaxis was going to be the one thing that I could truly count on to help us keep Becky healthy during RSV season. No parent is 100% vigilant. It is impossible to expect any parent of a preemie to meet such unreasonable expectations. Everything was settling on us, but I assure you that we worked everything in our lives around those ingestions. My husband and I were never more grateful for this help. So I am here today to give a voice to the tiny babies from 22 weeks to 36 weeks that deserve the help that we would afford to anyone with cancer, anyone with diabetes, anyone with a life-threatening illness. To support the community's concern that we must do right by these babies, I am respectfully submitting the on-line signatures I have collected over the last two months of 920 parents, professionals, and concerned citizens of this country. As of a few minutes ago, this petition had moved up to 943 signatures. In this petition, I have a mother that cites a 34 weeker that was denied RSV prophylaxis, hospitalized with RSV, and then died of RSV. The signers of the petition, like me, view these babies as the future of our country and that we owe them the best chance in life just like everyone else. Thank you.

**Dr. Matthew Hunter
Hope for Autism**

I do not have any financial interests at all. This is my first time in this CDC building. I did go to school here in Atlanta I would say about 17 years ago. I did a few courses at Emory and my chiropractic degree at Life University. I am licensed in Canada, all of Europe, and 47 of the 50 United States. I am here on behalf of Hope for Autism. Unlike others, I want to say if you are going to sell Mercedes, you should definitely drive one. With that saying, I'm going to take it that everybody here is up on their shots, and everybody here has got their grandchildren up on their shots, and everybody in this room should also have their children on shots. If there are any of you that are not up to date, then I kind of question the utility of the whole reason of this meeting. I'm kind of finding that this industry is becoming more of a business than healthcare. Just like others, there is always going to be a bad one. Today I'm just going to have a quick thing about thimerosal. That's what I'm going to talk about today. July 7, 1999 a joint statement was issued by the US Public Health Service and AAP which called for immediate elimination of thimerosal from infant vaccines. What I am trying to say is that I am finding lots, and lots, and

lots of my patients are coming in with these heavy toxicities of metals, mercury being one of them. Back eleven years ago, they were saying they were going to remove that to prevent some of these problems, and to date they have not. I could go in and read the rest of this stuff, but I think it is in the science and it's public record, so you guys can look it up, so I'm really not telling you anything you don't know. In summary, the introduction of thimerosal into vaccines appears to have been based on single uncontrolled and poorly reported human study in the 1920s. However, this sole human study was not a true safety study and produced a faulty foundation upon which a robust vaccine program was built in which infants would receive multiple doses of ethyl mercury. Even today, 70 years after the introduction of thimerosal into infant vaccines, we still do not have adequate safety data with regard to the toxicity of thimerosal to support its continued use in vaccines. I guess what I am trying to say is it's been a pleasure to come here, but I do believe anytime you have 10 people out of 1000 that might have a problem, so we develop some sort of vaccine, and now we only have 4 people out of 1000 that get the problem, my point is when you have that 4, when you're that one person like this gentleman or that one person in my office that was healthy but now I see him declining because of a certain vaccine, it just kind of makes you wonder. But it doesn't matter. It's not a numbers game anymore. It's a more of a human race problem.

Dr. Renee Tocco Hope for Autism

I have no conflicts of interest. I am actually reading a brief statement today on behalf of the National Coalition of Organized Women (NCOW). They actually collected data on miscarriages and stillbirths in pregnant women that occurred after they were administered a 2009 A/H1N1 vaccine. Using the VAERS database as a second ascertainment source, capture / recapture statistical methods were used to estimate the true number of miscarriages and stillbirths following an H1N1 flu vaccination in the US. Typically, even so-called complete studies conducted by CDC have been shown to miss between 10% to 90% of actual cases because of under-reporting. The capture / recapture estimate, while not 100% accurate, is nonetheless a very cost-effective and rapid way to get a complete count of all cases when 2 or more ascertainment sources have failed to collect all of the existing cases. Overall, this approach shows that only approximately 15% of the occurrences of a miscarriage or stillbirth were actually reported. The ascertainment corrected estimate for the total number of 2009 A/H1N1 influenza-associated miscarriages and stillbirths during the 2009-2010 flu season is 1588 with a 95% goodness of fit confidence interval, meaning that the range probability of miscarriages and stillbirths following H1N1 vaccine is as low as 946 and as high as 3487. CDC ascertained that there were actually 56 maternal deaths from the H1N1 virus itself. It is assumed that the fetuses, of course, died with mothers. For a majority of these deaths, the actual cause of death was unconfirmed. In other words, despite the ability of CDC to confirm the H1N1 virus as the culprit, the confirming tests were not performed. NCOW has issued a request for the raw data in order to ascertain the co-morbidity factors. To date, that has not been received. Vaccine-related fetal death reports from VAERS increased 2440% from just 7 cases in the 2008-2009 flu season to 178 in the 2009-2010 season. 70 deaths reported from another source had 7 overlapping cases with VAERS, yielding 241 unique cases. According to federal data gathered over 15 years, only a mere 24 adverse events were reported for every million doses of annual flu vaccine amongst all people—men, women, and children. About 1 million pregnant women were vaccinated in 2009-2010. If the 24 adverse events that were reported for all demographics were assigned solely to the pregnant population, the actual 178 VAERS reports would still be nearly 8 times higher. Simplistically speaking, not vaccinating would have been at the low range 85 times safer for fetus than vaccinating and at a higher range of up to 192 times safer. It may be argued that ACIP and CDC willfully withheld information from vaccine providers that the

original maternal deaths were mostly unconfirmed and replete with co-morbidity factors. It may be argued that it was an act of gross negligence that ACIP and CDC failed to adequately track the adverse events in the pregnant population. It may be the case that CDC did track VAERS and willfully declined to inform their vaccine providers that there were numerous reports of suspected vaccine-related fetal demise. In fact, on two occasions Dr. Murray McCormick stated that there were no adverse events reported. Today I believe is the first time that acknowledgement was made of that. Considering the evidence of harm submitted by the NCOW, it could be argued that the current recommendation by the ACIP to vaccinate pregnant women with the seasonal flu shot containing H1N1, thimerosal, and two other viral components has now escalated to willful misconduct. We strongly request that during the 2010-2011 season, all vaccine providers are informed of last season's VAERS report of vaccines in pregnant women. In addition, every pregnant woman who is considering the flu vaccine should be given a CDC vaccine information statement that properly advises of the adverse events reported last year. Furthermore, the most responsible action would be for ACIP to withdraw its recommendation for pregnant women and strictly adhere to the FDA and manufacturers' warnings. After all, as we all know, the inserts for flu vaccines say that they should not be administered to pregnant women unless they are clearly needed. On one final note, on behalf of Hope for Autism and also on behalf of an ever growing thousands of parents and healthcare providers, we acknowledge that there is an abundance of evidence showing that our aggressive US vaccination policy is directly related not only to autism but many different chronic childhood illnesses. Despite government and pharmaceutical studies that claim otherwise, currently there are thousands of unvaccinated children in our country. It is an outrage that to date no study has ever been done on these to populations in showing the relative health outcomes. I believe that only when the results of those studies are shown to the public will everything be self-evident. Thank you.



Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the October 27-28, 2010 ACIP Meeting are accurate and complete.

Date

Dr. Carol Baker, Chair
Advisory Committee on
Immunization Practices (ACIP)

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2/4/2011
Date

Carol J. Baker

Dr. Carol Baker, Chair
Advisory Committee on
Immunization Practices (ACIP)

Attendees

Title	FirstName	LastName	Organization
Dr.	Remon	Abu-Elyazeed	GSK
Ms.	Pam	Alexa	Pfizer, Inc
Ms.	Chinyere	Alu	Public Health Prevention Fellow/CDC
Dr.	Karita	Ambrose	Novartis Vaccines and Diagnostics
Mrs.	Kris	Armstrong	Central Florida Family Health Centers
Ms.	Phyllis	Arthur	Biotechnology Industry Organization
Mr.	Don	Ashley	Pfizer Pharmaceuticals
Mrs.	Jennean	Atkins	GlaxoSmithKline
Dr.	Kevin	Ault	American College of Obstetricians and Gynecologists
	Carol J.	Baker	Baylor College of Medicine
Dr.	Allyn	Bandell	MedImmune
Ms.	Sandra	Bean	Oregon State University/Emory University
Dr.	Eric	Benning	sanofi pasteur
Dr.	Yabo	Beysolow	CDC
Dr.	Prakash	Bhuyan	Merck & Co., Inc.
Dr.	Theodora	Bibila	Merck & Co., Inc.
Mr.	Brant	Biehn	Dynavax Technologies
Dr.	Guthrie	Birkhead	New York State Department of Health
	Gary	Blalack	GlaxoSmithKline
Mrs.	Dawn	Bolyard	Mercy Children's Hosptial
Mr.	Tyler	Bolyard	Mercy Children's Hosptial
Mrs.	Amanda	Bouquin	Chautauqua Opportunities Inc.
Mrs.	Lynn	Bozof	National Meningitis Association, Inc.
Ms.	Kimberly	Bradley	Novartis
Dr.	Michael	Brady	Nationwide Children's Hospital
Dr.	Eddy	Bresnitz	Merck & Co., Inc
Ms.	Katherine	Brewer	American Nurses Association
Dr.	Dennis	Brooks	Pfizer Inc
Dr.	Lily	Brown	HEB Pharmacy
Dr.	Doug	Campos-Outcalt	American Academy of Family Physicians
Ms.	Patricia	Cannon	Allergan
	Donna	Cary	Sanofi Pasteur
	Jill	Castner	sanofi pasteur
Mr.	Mike	Chaney	Georgia Chapter, American Academy of Pediatrics
	Lance	Chilton	University of New Mexico
Dr.	Keith	Chun	Novartis Vaccines and Diagnostics

Dr.	Max	Ciarlet	Merck & Co., Inc.
Dr.	Paul	Cieslak	Oregon Health Authority
	Liana	Clark	Merck & Company, Inc.
	Richard	Clover	University of Louisville
Dr.	Kathleen	Coelingh	MedImmune
	Lisa	Coen	Novartis
Dr.	Romulo	COLINDRES	GLAXOSMITHKLINE BIOLOGICALS
Mrs.	Patricia	Colindres	None
	Chris	Colwell	Becton Dickinson
	Penny	Conner	Georgia Immunization Program
Mr.	Kevin	Connolly	Emergent BioSolutions
Mr.	Salvatore	Constantino	MedImmune
Dr.	Louis	Cooper	Columbia University
Dr.	Tamara	Coyne- Beasley	ACIP Member
Mr.	Mark	Cullison	Merck and Co., Inc.
Mr.	Donald "Dack"	Dalrymple	Dalrymple & Associates, LLC
Dr.	Adrian	Dana	Merck Sharp & Dohme Corp.
Ms.	Lisa	Davis	MedImmune
Ms.	Lucia Helena	de Oliveira	Pan American Health Organization
	Carolyn	Deal	National Institute of Allergy and Infectious Diseases
Dr.	Roberto	Debbag	SANOFI PASTEUR
Dr.	Michael	Decker	Sanofi Pasteur
	Daniel	DeNoon	WebMD
Mrs.	Michelle	Dickey	Cincinnati Children's Hospital Medical Center
Mr.	Richard	Dinovitz	RCDVaccine
Mrs.	Deborah	Discenza	PreemieWorld, LLC
Mr.	HARRY	DODOO	WORLD IN NEED BURKINA FASO
Dr.	Jeffrey	Duchin	ACIP Member
Mrs.	Sarah	Duggan Goldstein	American Medical Organization
Ms.	Theresa	Dulski	CDC Experience Fellow
Ms.	Kristen	Ehresmann	Minnesota Department of Health
Dr.	Joseph	Eiden	Pfizer Inc.
Dr.	Alexis	Elward	Washington University School of Medicine
Dr.	Janet	Englund	Seattle Children's Hospital/University of Washington
Dr.	Mark	Feinberg	Merck & Co., Inc.
	Jovelle	Fernandez	GlaxoSmithKline
	Brian	Filipski	Sanofi Pasteur
Dr.	JORGE	FLOREZ	IMMUNOPROTECTION
Ms.	Lynda	Flowers	AARP
Mrs.	Angela	Fortner	Northeast Georgia Medical Center

Dr.	Stephan	Foster	American Pharmacists Association
	Sylvia	Foster	GlaxoSmithKline
	Richard	Franka	CDC
Dr.	Leonard	Friedland	GSK
	sandra	fryhofer	ACP
Ms.	Diane	Gaffoglio	Nancy Lee & Associates
Miss	Melissa	Garcia	MedImmune
Dr.	Lisa	Gargano	Emory University
	Diana	Gaskins	retired
Dr.	Bruce	Gellin	National Vaccine Program Office
Dr.	Kathleen	Gensheimer	Sanofi Pasteur
	Tara	Gonzales	MedImmune LLC
Ms.	Deborah	Goodwin	Passport Health
Dr.	Philip	Gould	AFMSA
Dr.	Michelle	Goveia	Merck
Dr.	John	Grabenstein	Merck & Co., Inc
	David	Greenberg	sanofi pasteur
Dr.	Michael	Greenberg	CSL
Mr.	Joel	Greenspan	Attune, Inc.
	Joel	Greenspan	SDI Health
Dr.	Stanley	Grogg	AOA
Dr.	Jessie	Groothuis	MedImmune
Dr.	Angela	Guidry	Georgia Department of Community Health Division of Public Health
	Christine	Hahn	CSTE
Mr.	Ken	Hall	CDC
Dr.	Neal	Halsey	Johns Hopkins Bloomberg School of Public Health
	Erik	Halstrom	FFF Enterprises and VaxAmerica
Ms.	Claire	Hannan	Association of Immunization Managers
	Kathleen	Harriman	California Department of Public Health
Dr.	Richard	Haupt	Merck Research Labs
Dr.	Kimberley	Hazelwood	Georgia Division of Public Health
Dr.	Stephanie	Henry Wallace	Cambridge Communications & Training Institute / MTC
Dr.	William	Heyward	Dynavax Technologies Corp.
	Emma	Hitt	Hitt Medical Writing
Mr.	Phil	Hosbach	sanofi pasteur
Dr.	Barbara	Howe	GlaxoSmithKline
Dr.	Barbara	Howe	GlaxoSmithKline
Ms.	Kelly	Howell	Emory University
Dr.	Jim	Hughes	Emory University
Dr.	Harry	Hull	HF Hull & Associates

Ms.	Donelle	Humphrey Franklin	Georgia Division of Public Health, Office of Pharmacy
	Matthew	Hunter	Hope for Autism
Mr.	ADESEUN	ILORI	AIDS PREVENTIVE INITIATIVE IN NIGERIA(APIN)
	Juby	Jacob-Nara	GlaxoSmithKline
	Chuntiel	James	Georgia Immunization Program
Mr.	PETER	JAMES ANUEKATOA	WORLD IN NEED BURKINA FASO
Mr.	Rodney	Jamison	Aramark Healthcare
Dr.	Robert	Janssen	Dynavax Technologies
Dr.	Renee R.	Jenkins	ACIP Member
Dr.	David	Johnson	Sanofi Pasteur
Ms.	Erica	Johnson	APCO Worldwide
Mrs.	Amy	Johnson	Cambridge Communications
Dr.	Frank	Judson	University of Colorado School of Public Health
Dr.	Stephen	Kagan	Pfizer
Dr.	Niranjan	Kanesa-thasan	Novartis Vaccines and Diagnostics, Inc.
Dr.	Samuel	Katz	Duke Medical School & IDSA
Mr.	Richard	Keenan	North American center for Continuing Medical Education, LLC
Dr.	Wendy	Keitel	Baylor College of Medicine
	Harry	Keyserling	Society for Healthcare Epidemiology of America
Dr.	David	Kimberlin	American Academy of Pediatrics
Mr.	Chester	Kitchen	Merck & Company, Inc.
Ms.	Girishanthy	Krishnarajah	GlaxoSmithKline
Dr.	Barbara	Kuter	Merck
Ms.	Susan	Laird	CDC
	Sarah	Landry	National Vaccine Program Office
Dr.	Joanne	Langley	Dalhousie University
Dr.	Jody	Lawrence	Merck & Co., Inc.
Dr.	Herschel	Lawson	CDC Retired
Miss	Isobel	LeBlanc	daughter of liason member Joanne Langley
Dr.	susan	lett	Massachusetts Department of Public Health
Dr.	Clement	Lewin	Novartis Vaccines and Diagnostics
Mr.	simon	li	CHINA CDC
Ms.	Christina	Liu	Novartis
Mrs.	Lori	Lukus	sanofi pasteur
Dr.	Parthiv	Mahadevia	MedImmune
Dr.	Doris	Makari	MedImmune
	Melissa	Malhame	Dynavax Technologies
Dr.	Tyler	Martin	Dynavax
Dr.	Anthony	Masaquel	MedImmune

Dr.	T. Christopher	Mast	Merck Research Laboratories
	Jonathan	Matthews	Emory University, Rollins School of Public Health
Ms.	Michele	Mattioli	BioTest Pharmaceuticals
Dr.	Marie	Mazur	CSL Biotherapies
Mr.	Wayman	McAllister	Merck Vaccines
Ms.	Meshell	McCloud	GA Department of Community Health , Division of Public Health
Mr.	John	McKenna	CDC Foundation Experience Fellowship
Mr.	Jeffrey	Mclaughlin	Glaxosmithkline
Dr.	Bruce	Meade	Meade Biologics LLC
Mrs.	Wendy	Meigs	Meningitis Angels
Dr.	Cody	Meissner	Tufts Medical Center
Dr.	Amy	Middleman	Baylor College of Medicine
Mr.	ANTHONY	MIKE UNYIME	KOGI STATE GOVERNMENT
Dr.	Jacqueline	Miller	GlaxoSmithKline Biologicals
	Frankie	Milley	Meningitis Angels
Dr.	Derek	Misurski	GlaxoSmithKline
	Michaela	Mitchell	Meningitis Angels
	Jeremiah	Mitchell	Meningitis Angels
Mr.	Justin	Miyamoto	CDC
Dr.	Kelly	Moore	Tennessee Department of Health
Mr.	Ogwang	Moses	FICRD- Uganda
Dr.	Riyadh	Muhammad	SC Department of Health and Environmental Control
Dr.	Barbara	Mulach	National Institute of Allergy and Infectious Diseases, National Institutes of Health
Mr.	Naoki	Murata	Pfizer Japan Inc.
Mrs.	linda	murphy	Centers For Medicare & Medicaid Services
Ms.	(Ann) Terri	Murphy	Veterans Health Administration
Dr.	Martin	Myers	National Network for Immunization Information
Dr.	Tanya	Myers	Abbott Products Inc.
Dr.	Vasant	Narasimhan	Novartis Vaccines & Diagnostics
Mr.	Patrick	Neither	Merck & Co. Inc
	Stacey	Neloms	SRA International
Dr.	Mark	Netoskie	Americas Health Insurance Plans (AHIP)
Dr.	Kathleen	Neuzil	PATH
Dr.	Karen	O'Brien	American Academy of Family Physicians
Dr.	Paul	Offit	Children's Hospital of Philadelphia
	Saad	Omer	Emory University, Rollins School of Public Health
Mr.	Bill	Owen	MedImmune

Mr.	Christopher	Palma	CDC - EIS student - RDB
	Peter	Paradiso	Pfizer
Dr.	Nita	Patel	CDC
Dr.	Hemali	Patel	Novartis Vaccines
Dr.	Gonzalo	Perez	Merck & Company, Inc.
Dr.	Martin	Peters	Novartis Vaccines
	Diane	Peterson	Immunization Action Coalition
	Michael	Petrucelli	MedImmune
Ms.	Amy	Pisani	Every Child By Two
Dr.	Stanley	Plotkin	VaxConsult and Sanofi Pasteur
Dr.	Gregory	Poland	Mayo Clinic
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Mrs.	Jill B.	Roark	CDC National Center for Immunization and Respiratory Diseases (NCIRD)
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Miss	Kellie	Ryan	MedImmune
	Patricia	Saddier	Merck Research Laboratories
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Dr.	William	Schaffner	Vanderbilt University School of Medicine
Ms.	Stephanie	Schauer	Wisconsin Division of Public Health
Dr.	Florian	Schodel	Philimmune LLC
Mr.	Darin	Seehafer	Sanofi Pasteur
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	Elizabeth	Shawen	Moore Consulting Group

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Dr.	Judith	Shindman	Sanofi Pasteur Limited
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Dr.	Leonard	Silverstein	GlaxoSmithKline Vaccines
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Mr.	Eric	Skjeveland	Merck Vaccines
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	Susan	Smith	Medscape
Dr.	Alan	Spitzer	MEDNAX, Inc./ Pediatrix Medical Group
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	Nina	Steinberg	Ruder Finn
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Mr.	Mike	Stobbe	The Associated Press
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Dr.	David	Strutton	Pfizer
Mr.	Stacy	Stuerke	Merck Vaccine Division
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Mr.	Lonnie	Thomas	Henry Schein, Inc
Mr.	Brad	Thompson	Pfizer
	Renee	Tocco	Hope for Autism
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Mr.	John	Trizzino	Novavax, Inc.
Dr.	Andrew	Trofa	GlaxoSmithKline

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	Miriam E.	Tucker	Pediatric News
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Dr.	Christine	Vaupel	GlaxoSmithKline
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	Diane	Watson	Georgia Immunization Program
	Wayde	Weston	GlaxoSmithKline
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Dr.	Richard	Zimmerman	University of Pittsburgh
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