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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 23-24, 2010
Atlanta, Georgia

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia
June 23-24, 2010

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, June 23, 2010			
8:00	**Welcome & Introductions**		Dr. Carol Baker (Chair, ACIP) Dr. Larry Pickering (Executive Secretary, ACIP; CDC)
8:30	**Evidence Based Recommendations**		
	▪ Introduction: ACIP implementation of an explicit evidence-based recommendation format	Information	Dr. Jonathan Temte (ACIP, WG Chair)
	▪ Professional organization perspectives on development and endorsement of recommendations	&	AAFP: Dr. Doug Campos-Outcalt AAP: Dr. Joseph Bocchini
		Discussion	ACP: Dr. Gregory Poland
	▪ GRADE (Grading of Recommendations, Assessment, Development and Evaluation)	Information	Dr. Holger Schünemann (McMaster University, Canada)
	▪ WHO's Strategic Advisory Group of Experts (SAGE): approach to evidence-based recommendations	&	Dr. Arthur Reingold (UC Berkeley
	▪ Pilot of explicit evidence-based framework based on GRADE	Discussion	SPH, SAGE Member) Dr. Faruque Ahmed (CDC/NCIRD)
10 :45	*Break*		
11:15	**Meningococcal Vaccine**		
	▪ Introduction	Information	Dr. Cody Meissner (ACIP, WG Chair)
	▪ Guillain-Barré Syndrome (GBS) after receipt of Menactra	&	Dr. Priscilla Velentgas (Harvard Pilgrim)
	▪ Update on monitoring of GBS after receipt of meningococcal conjugate vaccines	Discussion	Mr. Eric Weintraub (CDC/NCEZID)
	▪ Meningococcal conjugate vaccines and GBS	Vote	Dr. Amanda Cohn (CDC/NCIRD)
	▪ Update on meningococcal vaccination program		Dr. Amanda Cohn (CDC/NCIRD)
12:30	*Lunch*		
1:30	**Human Papillomavirus (HPV) Vaccines**		
	▪ HPV vaccine update	Information & Discussion	Dr. Lauri Markowitz (CDC/NCHHSTP)
1:45	**Hepatitis Vaccines**		
	▪ Update on Hepatitis Vaccines Work Group	Information	Dr. Mark Sawyer (ACIP, WG Chair)
	▪ Trends in acute hepatitis B virus (HBV) disease		Dr. Ruth Jiles (CDC/NCHHSTP)
	▪ Hepatitis B risk among persons with and without diabetes mellitus	&	Dr. Dale Hu (CDC/NCHHSTP)
	▪ Hepatitis B vaccine safety and seroprotection rates among persons with diabetes mellitus	Discussion	Dr. Philip Spradling (CDC/NCHHSTP)
	▪ Preview of proposed recommendations; request for additional information		Dr. Trudy Murphy (CDC/NCHHSTP)

3:30	*Break*		
3:45	**Pertussis Vaccines**		
	▪ Update on Pertussis Vaccines Work Group activities	Information & Discussion	Dr. Mark Sawyer (ACIP, WG Chair)
	▪ Update on the Pertussis Vaccine Program		Dr. Jennifer Liang (CDC/NCIRD)
4:30	**13-Valent Pneumococcal Conjugate Vaccine (PCV13)**		
	▪ PCV13 VFC correction	VFC vote	Dr. Lance Rodewald (CDC/ NCIRD)
4:45	**Vaccine Supply**		
	▪ Update on vaccine supply	Information Discussion	Dr. Lance Rodewald (CDC/ NCIRD)
5:00	**Public Comment**		
5:15	**Adjourn**		

Thursday, June 24, 2010

8:00	**Agency Updates (CDC, CMS, DOD, DVA, FDA, HRSA, IHS, NIH, NVAC, NVPO)**	Information	ACIP *Ex Officio* Members
8:15	**Influenza Vaccines**		
	▪ Introduction Influenza season update and summary	Information & Discussion	Dr. Kathy Neuzil (ACIP, WG Chair) Dr. Tony Fiore (CDC/NCIRD)
	▪ Influenza vaccine effectiveness		Dr. David Shay (CDC/NCIRD)
	▪ Influenza Vaccine Work Group update		Dr. Anthony Fiore (CDC/NCIRD)
	▪ Vote on number of doses of seasonal vaccine required for children age <9 years who received no prior 2009 H1N1 monovalent vaccine	Information Discussion Vote	
	▪ VFC vote	VFC Vote	Dr. Lance Rodewald (CDC/NCIRD)
	▪ 2009 pandemic H1N1 monovalent vaccine safety studies	Information & Discussion	Dr. Frank DeStefano (ISO/NCEZID) Dr. Tracy Lieu (Harvard Pilgrim) Dr. Hector Izurieta (CBER/FDA)
10:45	*Break*		
11:00	**Respiratory Syncytial Virus (RSV) Immunoprophylaxis**		
	▪ Introduction	Information	Dr. Lance Chilton (ACIP, WG Chair)
	▪ Epidemiology of RSV infections	Information & Discussion	Dr. Gayle Fischer Langley (CDC/NCIRD)
	▪ History of RSV immunoprophylaxis		Dr. Cody Meissner (ACIP Member)
	▪ Summary		Dr. Lance Chilton (ACIP, WG Chair)
12:15	*Lunch*		
1:15	**Health Care Reform and its Implications for National Immunization Policy and Practice**	Information	Attorney Sara Rosenbaum (ACIP Member)
1:45	**Rotavirus Vaccines**		
	▪ Update on porcine circovirus in rotavirus vaccines	Information Discussion	Dr. Umesh Parashar (CDC/NCIRD) Dr. Margaret Cortese (CDC/NCIRD) Dr. Wellington Sun (FDA) Dr. Len Friedland (GSK) Ms. Kim Dezura (Merck)
3:15	**Public Comment**		

3:30 **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
AGREE	Appraisal of Guidelines Research and Evaluation
AIAB	Adult Immunization Advisory Board of ACP
AEs	Adverse Events
AHIP	America's Health Insurance Plans
AHRQ	Agency for Healthcare Research and Quality
AMA	American Medical Association
ANA	American Nurses Association
AOA	American Osteopathic Association
ARRA	American Recovery and Reinvestment Act
ASTHO	Association of State and Territorial Health Officials
BLA	Biologics License Application
BRFSS	Behavioral Risk Factor Surveillance System
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CEAS	Clinical Efficacy Assessment Subcommittee of ACP
CER	Comparative Effectiveness Research
CIDP	chronic inflammatory demyelinating polyneuropathy
CLL	childhood lymphoblastic leukemia
CMS	Centers for Medicare and Medicaid Services
COGS	Conference on Guideline Standardization
COI	Conflict of Interest
COID	Committee on Infectious Diseases of AAP
COPD	Chronic Obstructive Pulmonary Disease
CSAPH	Council on Science and Public Health of AMA
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DHQP	Division of Healthcare Quality Promotion
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
DVH	Division of Viral Hepatitis (of NCIRD)
EBV	Epstein-Barr Virus
EBRWG	Evidence Based Recommendations Work Group's
EIP	Emerging Infections Program
EMR	Electronic Medical Records
FDA	Food and Drug Administration
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

HGT	Horizontal gene transfer
HICPAC	Healthcare Infection Control Practices Advisory Committee
HepA	Hepatitis A
HepB	Hepatitis B
HHS	Department of Health and Human Services
Hib	*Haemophilus influenzae B*
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HTA	health technology assessments
ICD-9	International Classification of Diseases, Ninth Revision
ID	Influenza Division (of NCIRD)
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	Indian Health Services
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IPV	Inactivated Poliovirus-Containing Vaccine
ISO	Immunization Safety Office
IU	International Units
JAMA	Journal of the American Medical Association
maxSPRT	Maximized Sequential Probability Ratio Testing
MenACYW-CRM	Meningococcal Conjugate Vaccine
MCOs	Managed Care Organizations
MCV4	Quadrivalent Meningococcal Conjugate Vaccine
MMR	Measles, Mumps, Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MOE	maintenance of effort
MSM	Men Who Have Sex With Men
NACI	National Advisory Committee on Immunization
NCHHSTP	National Center for HIV, Hepatitis, STD, and TB Prevention (of CDC/CCID)
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NCZVED	National Center for Zoonotic, Vector-Borne, and Enteric Diseases
NHANES	National Health and Nutrition Examination Survey
NICU	Neonatal Intensive Care Unit
NIS	National Immunization Survey
NNDSS	National Notifiable Diseases Surveillance System
NNHS	National Nursing Home Survey
NREVSS	National Respiratory and Enteric Virus Surveillance System
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NVSN	National Vaccine Surveillance Network
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
QALY	Quality-Adjusted Life Year
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RoB	Risk of Bias
RSV	Respiratory Syncytial Virus Immunoprophylaxis
RTIMS	Real Time Immunization Monitoring System
SAEs	Serious Adverse Events

SAHM	Society for Adolescent Health and Medicine
SAM	Society for Adolescent Health and Medicine
SBA	Serum Bactericidal Antibody
sBLA	Supplemental Biologics License Application
SCOQIM	Steering Committee on Quality Improvement and Management
SES	Socioeconomic Status
SHEA	Society for Healthcare Epidemiology of America
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
VFC	Vaccines for Children
VIS	Vaccine Information Sheet
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
VSRAWG	Vaccine Safety Risk Assessment Working Group
VTrckS	Vaccine Tracking System
WG	Work Group
WHO	World Health Organization

June 23, 2010

Welcome and Introductions

Dr. Carol Baker
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

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

Dr. Pickering welcomed everyone to the June 2010 Advisory Committee on Immunization Practices (ACIP) meeting. As with the last three ACIP meetings, he indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web. He also welcomed those who could not attend the meeting in person. 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: Antonette Hill, Committee Management Specialist for ACIP, who was moving to another position within the agency following this meeting; Natalie Greene; Leola Mitchell; Tamara Miller, who was moving to North Carolina following this meeting; Tanya Lennon; and Suzette Law. He also recognized that the hard work of these individuals very much contributes to the success of each meeting, and stressed that Miss Hill and Miss Miller would be greatly missed as part of that team. Those with any questions were instructed to see him, any of these individuals, or Dr. Baker. He indicated that boxed lunches would be provided for a charge during the two days of the meeting in the hallway outside of the auditorium, and that coffee and tea would be available in the hallway for the duration of the meeting.

Handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented at this meeting will be posted on the ACIP website, generally within one to two weeks after the meeting concludes, while meeting minutes will be available on the website within 90 days of the termination of the meeting. Members of the press interested in conducting interviews with various ACIP members were instructed to contact Tom Skinner for assistance in arranging the interviews.

Ms. Alba Maria Ropero, Regional Advisor in the Comprehensive Family Immunization Project of the Pan American Health Organization (PAHO) office of the World Health Organization (WHO) in Washington, DC was in attendance as a guest observer of the ACIP meeting. Dr. Pickering indicated that Ms. Ropero is the focal point for influenza, yellow fever, and vaccination week in the Americas. He also welcomed to ACIP a new liaison organization, the American Nurses Association (ANA). Ms. Katie Brewer has been selected to represent ANA as its liaison representative to ACIP.

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

Liaison Representatives

- Dr. Greg Poland from the American College of Physicians (ACP) was present during the first day of the meeting; Dr. Sandra Fryhofer attended on his behalf on the second day
- Dr. Mark Netoskie from the America's Health Insurance Plans (AHIP); Dr. Richard Doskey attended on his behalf
- Dr. Jeffrey Duchin from the National Association of County and City Health Officials (NACCHO); Dr. Paul Etkind attended on his behalf
- Dr. Joanne Langley from the Canadian National Advisory Committee on Immunization (NACI)
- Dr. David Salisbury from the Department of Health, United Kingdom (UK)
- Dr. Norman Baylor from the Food and Drug Administration (FDA); Dr. Wellington Sun attended the second day of the meeting on his behalf

To avoid disruptions during the meeting, those present were instructed to turn off all cell phones or place them in the vibrate mode. Given that the meeting could not begin unless a quorum of members was present, all appointed members were asked to return from breaks and lunch in a timely manner to participate in the meeting.

Topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. In certain circumstances, a formal comment period may be scheduled during the deliberations of a specific agenda item rather than at the end of the day in order to be considered before a vote is taken. Those who planned to make public comments were instructed to visit the registration desk in the rear of the room to have Antonette Hill record their name and provide information on the process. Those who registered to make public comments prior to the meeting were instructed to see Ms. Hill to verify that their names were listed and to receive any additional information.

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

The following information was shared pertaining to ACIP:

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

Nominations: http://www.cdc.gov/vaccines/recs/acip/req-nominate.htm
The ACIP Secretariat solicits applications throughout the year for candidates to serve on ACIP. Detailed instructions for submissions of name of potential candidates may be found on the ACIP website. Applications may be submitted at any time of the year. Materials in support of the next cycle of applications for ACIP membership are due no later than November 15, 2010 for the term beginning July 2011. Interested parties were encouraged to complete an application and submit it by the deadline.

Next ACIP Meeting: October 27-28, 2010
Registration Deadlines: Non-U.S. Citizens 10/8/2010 – U.S. Citizens 10/15/2010

Vaccine Safety: http://www.cdc.gov/vaccinesafety/

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

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

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

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

Dr. Pickering indicated that Dr. Baker had requested an update on the status of ACIP provisional recommendations with regard to publications. There has been some delay in ACIP making recommendations and final acceptance by CDC of those recommendations (e.g., when Dr. Frieden accepts the recommendations and they are published in the *MMWR*). This is currently done in two ways. The first is via policy notes for which provisional recommendations are not generally posted, given that these are typically published within 1 to 2 months of the ACIP vote. The second is through recommendations and reports, which are longer documents for which provisional recommendations are posted as publication time for these documents ranges from 6 to 12 months. Work is being done to decrease this publication time.

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	*MWWR* Reference
JE Encephalitis	3/12/2010	Vol 59(RR01): 1-27
MCV4 (Menveo)	3/12/2010	Vol 59(09): 273
PCV13	3/12/2010	Vol 59(09): 253-257
Rabies	3/19/2010	Vol 59(RR02): 1-9
Measles, Mumps, Rubella & Varicella	5/7/2010	Vol 59(RR03): 1-12
HPV		
HPV4 in males	5/28/2010	Vol 59(20): 630-632
HPV2 in females	5/28/2010	Vol 59(20): 626-629
Rotavirus (SCID)	6/11/2010	Vol 59(22): 687-688
Anthrax Vaccine Adsorbed	6/25/2010	

Status of publication of ACIP recommendations:

Vaccine	*MMWR* Weekly (Policy Notes)	Recommendations and Reports
2010 Influenza Vaccines	N/A	Summer 2010
Yellow Fever Vaccine	N/A	July 16, 2010
General Recommendations (Combination Vaccines)	N/A	Summer / Fall 2010
Measles-Mumps-Rubella (HCP)	N/A	HCP document
Pneumococcal Vaccine (adults)	Pending	Pending

Dr. Baker noted that this was a bittersweet time, given that three ACIP members would be retiring. Each member was presented with a token of ACIP's appreciation. She first recognized Dr. Susan Lett, Medical Director in the Division of Immunization of the Massachusetts Department of Public Health in Jamaica Plain. Dr. Lett has more than two decades of policy and program planning experience that has aided ACIP's deliberations regarding number of issues. She has served on a number of national immunization advisory boards, and ACIP has been fortunate that she has been able to assist the committee with policy during her past four years on the committee. She has made numerous contributions to various ACIP work groups (e.g., Combination Vaccines, Influenza Vaccines, General Recommendations, Harmonized Schedules, Polio, Rabies, and Rotavirus). Her extensive public health and research and policy experience and skills have been a great asset to ACIP, and Dr. Baker stressed that she personally had sought Dr. Lett's guidance regarding potential barriers for what may have seemed to be easy implementation issues. Dr. Lett responded that this was a really sad time for her to leave ACIP, which had been the greatest honor of her professional career. She expressed her gratitude for having had the opportunity to serve on the committee, indicating that she looked forward to perhaps continuing to be involved in ACIP work groups.

Also retiring from ACIP was Dr. Kathy Neuzil, Senior Clinical Adviser for PATH in Seattle Washington. Dr. Neuzil is an adult infectious disease physician, who has extensive experience in epidemiologic studies and clinical trials. Having served previously as the Liaison Representative for the ACP, Dr. Neuzil came well-prepared in 2006 to join the ACIP. She chaired the Vaccines and Pregnancy Work Group during her first year, moving later to chair the Influenza Work Group. Dr. Baker stressed that Dr. Neuzil had done a marvelous job during the past three years, demonstrating tireless devotion, contagious enthusiasm, and uncommon wisdom as an ACIP leader. ACIP is grateful to Dr. Neuzil for her service, and as one who considers her a friend, Dr. Baker will greatly miss her. Dr. Neuzil replied that it had been a privilege and great joy to have been a part of ACIP, and to have worked with such competent and dedicated people, including fellow ACIP members, liaison representatives, and the CDC staff who support ACIP in so many ways. She thanked them all very sincerely for teaching her so much about vaccines, public health, and community service.

In addition, Dr. Cyro Sumaya, Founding Dean of the School of Rural Public Health and holder John and Maureen Cox Endowed Chair in Medicine at Texas A & M Health Science Center in College Station, was retiring from ACIP. Dr. Sumaya is a pediatric infectious disease physician with special expertise in Epstein-Barr virus (EBV) infections. His outstanding leadership skills, extensive experience in public health, and devotion to resolving ethnic disparities have been excellent resources to ACIP. Also, his warm manner and great smile have been encouraging to Dr. Baker and other committee members. During his 4-year term on ACIP, he has served as chair of the General Recommendations Work Group and been a member of the Meningococcal Work Group. It was Dr. Sumaya who made the historic motion to recommend universal administration of influenza vaccine annually during the February 2010 ACIP meeting. Dr. Baker said that she thought she was one of the more lucky members of ACIP because she and Dr. Sumaya would both be in Texas, so she hoped that perhaps their paths would cross again soon. Dr. Sumaya responded that it had been a distinct privilege to be part of ACIP and to work with distinguished colleagues, particularly given what ACIP stands for and the impact that it has for the American public and the global community. Immunizations can also affect many people, and is one of the primary cornerstones of public health principles and values for preventing disease and promoting health. He thanked everyone for what seemed like a quick four years, and wished them the best.

The following conflicts of interest were declared:

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

Evidence Based Recommendations Work Group

Introduction

Jonathon Temte, MD, PhD, Chair
Evidence Based Recommendations Work Group

Dr. Temte thanked the many and varied participants in the Evidence-Based Recommendations Work Group (EBRWG) for their thoughtful comments and participation in the telephone conferences convened, which allowed them to progress fairly rapidly. He reminded everyone that the EBRWG's charge is to develop a uniform approach to making explicit the evidence base for ACIP recommendations, and that this work group was reactivated in November 2007. The work group has convened monthly conference calls since January 2008, and has been working on guiding principles and reviewing several evidence-based systems for developing guidelines that are used by other organizations.

The work group's guiding principles are to focus on transparency; use evidence of varying strengths; consider individual and community health; adopt / adapt an existing system rather than re-creating something that may already exist; continually strive to improve the process; and first apply the proposed process to new vaccines and new indications or restrictions of existing vaccines. The components of evidence-based vaccine recommendations include key elements for consideration (e.g., safety, efficacy, and burden of illness); an assessment method for existing evidence; standardized format for recommendations; and a means for reporting of elements and evidence in a clear and transparent manner.

The work group has decided to adopt the Grades of Recommendation Assessment, Development and Evaluation (GRADE) framework for rating quality of evidence, and to adapt the GRADE system for moving from evidence to recommendations. Within this standardized system, the proposed evidence grades include A, B, C, and D, which basically reflect the level of confidence in an estimate of effect (e.g., causal relation) from a body of evidence. The proposed recommendation categories include: 1) Recommendation For and Recommendation Against, and 2) Optional Use. They wanted to move away from the terminology "permissive use," which is the reason for the "optional use" category. He then reviewed the agenda for this session, pointing out that the EBRWG discovered that the World Health Organization's Strategic Advisory Group of Experts is on a parallel path to the ACIP EBRWG in terms of applying GRADE for vaccine recommendations.

Professional Organization Perspectives: AAFP

Doug Campos-Outcalt, MD, MPA
American Academy of Family Physicians (AAFP)

Dr. Campos-Outcalt briefly described the American Academy of Family Physicians (AAFP) and its guideline development and endorsement process. AAFP has a total membership of 94,700 of whom 62,600 are active. The remainder is comprised of resident student and physicians in some level of retirement. Of the members, 20% have practices in rural areas.

Being a generalist physician organization, with most members involved in primary care, AAFP receives many requests to review, comment on, and endorse guidelines developed by external organizations. The following sample reflects the variety of groups who make such requests of AAFP:

- Government Agencies
  - → USPSTF (clinical prevention)
  - → CDC (public health, vaccines, prevention)
  - → CPSTF (community services)
  - → EGAPP (genomics)

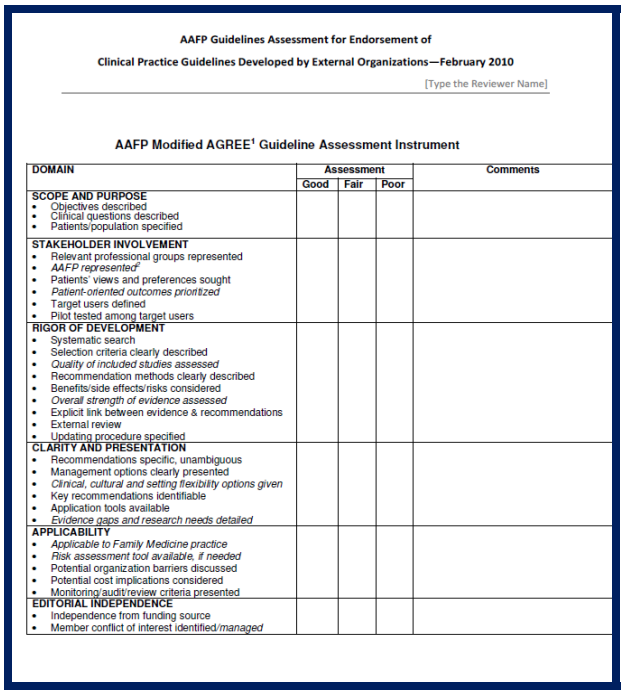
- Specialty Societies
  - → AAFP, ACP, AAP, ACOG, et cetera

- Specialty Interest Groups
  - → ACS, AHA, ATS, ALA, ADA, et cetera

- Agency for Healthcare Research and Quality (AHRQ)
  - → Does not develop guidelines, but does catalogue them

The AAFP's Commission on the Health of the Public and Science selects topics that are important to its members. AAFP will petition AHRQ evidence reports, for which there is a process. This is often done in collaboration with other specialty groups. AAFP attempts to work with inter specialty panels when possible, and uses the GRADE system when developing its own guidelines. The staff in the Scientific Activities Division of AAFP staffs the guideline panels.

The Commission on the Health of the Public and Science is also the responsible group when AAFP receives requests from outside organizations to consider, comment upon, and potential endorse their guidelines. The Commission on the Health of the Public and Science makes recommendations to AAFP's Board of Directors, which is ultimately responsible for approval. This process has evolved over time, and now includes a tool with specific procedures. The following example illustrates the tool that AAFP uses:



AAFP Guidelines Assessment for Endorsement of

Clinical Practice Guidelines Developed by External Organizations—February 2010

[Type the Reviewer Name]

AAFP Modified AGREE[1] Guideline Assessment Instrument

DOMAIN	Assessment			Comments
	Good	Fair	Poor	
SCOPE AND PURPOSE • Objectives described • Clinical questions described • Patients/population specified				
STAKEHOLDER INVOLVEMENT • Relevant professional groups represented • *AAFP represented*[2] • Patients' views and preferences sought • *Patient-oriented outcomes prioritized* • Target users defined • Pilot tested among target users				
RIGOR OF DEVELOPMENT • Systematic search • Selection criteria clearly described • *Quality of included studies assessed* • Recommendation methods clearly described • Benefits/side effects/risks considered • *Overall strength of evidence assessed* • Explicit link between evidence & recommendations • External review • Updating procedure specified				
CLARITY AND PRESENTATION • Recommendations specific, unambiguous • Management options clearly presented • *Clinical, cultural and setting flexibility options given* • Key recommendations identifiable • Application tools available • *Evidence gaps and research needs detailed*				
APPLICABILITY • *Applicable to Family Medicine practice* • *Risk assessment tool available, if needed* • Potential organization barriers discussed • Potential cost implications considered • Monitoring/audit/review criteria presented				
EDITORIAL INDEPENDENCE • Independence from funding source • Member conflict of interest identified/*managed*				

Typically, three to four members review a guideline and evaluate several of its aspects, including the scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability to family physicians, and editorial independence. For the rigor or development, consideration is given to whether a systematic search was conducted, whether the selection criteria clearly described, whether the quality of the included studies is assessed, whether recommendation methods are clearly described, whether benefits / side effects / risks are considered, whether the overall strength of evidence assessed, and whether there is an explicit link between the evidence and the recommendations. AAFP likes for guidelines to have been disseminated for external review and comments, and specifies an updating procedure.

AAFP basically places guidelines into three categories: Endorsement, Endorsement with Reservations, or Not Endorsed. To be endorsed, guidelines should include the following characteristics:

- ❑ Specific, clear, and unambiguous recommendations that are applicable to family medicine settings
- ❑ Overall quality ranked as good, or ranked as fair (with rationale for endorsement)
- ❑ Based on an evidence report or systematic review conducted with sound methodology
- ❑ Strong, key recommendations are supported by good quality evidence
- ❑ Guideline development process is editorially independent from funding sources
- ❑ Should include a conflict of interest policy that minimizes the effects of potential conflicts on the guideline development process

All of AAFP's guidelines and endorsements can be found on the AAFP web site:

http://www.aafp.org/online/en/home/clinical/clinicalrecs.html?navid=clinical+recommendations

The AAFP is very supportive of the ACIP adopting a standardized evidence-based process to arrive at ACIP recommendations for vaccines.

Professional Organization Perspectives: AAP

Joseph A. Bocchini, Jr. MD
Department of Pediatrics
Louisiana State University Health Sciences Center – Shreveport
Chairperson, American Academy of Pediatrics
Committee on Infectious Diseases

Dr. Bocchini reported that the American Academy of Pediatrics (AAP) was founded in 1930 and currently has approximately 60,000 members worldwide comprised of general pediatricians and pediatric medical and surgical subspecialists. AAP's mission is to attain optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults.

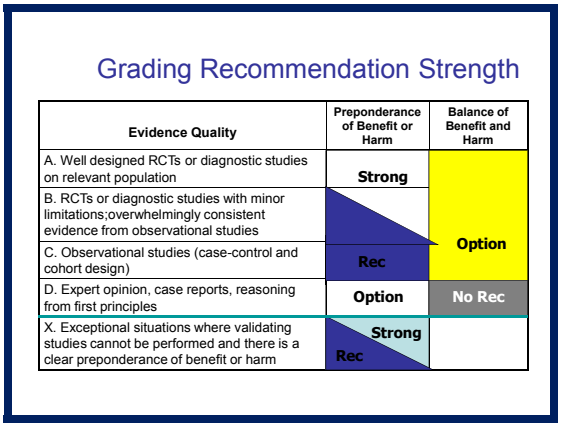
Because it recognized the need for a transparent evidence-based approach for its policies and endorsement, AAP established a Steering Committee on Quality Improvement and Management (SCOQIM) in 2001. This committee was charged with the responsibility for oversight of development of clinical practice guidelines within AAP and the AAP endorsement process. SCOQIM members include individuals with expertise in practice, technology, and evidence-based medicine. Liaisons are included from AHRQ and the National Association for Children's Hospitals and Related Institutions.

SCOQIM issued their first Policy for Classifying Recommendations for Clinical Practice Guidelines in 2004. This Policy established a very clear evidence quality appraisal format with assessment of benefit versus harm for recommendations. These guidelines are currently under revision [Pediatrics 2004;114:874-877]. AAP is currently considering GRADE or a modification of GRADE as one of the options to revise this protocol. AAP currently recommends greater transparency and application of evidence grading to all clinical policies [Pediatrics 2008;121:643-646].

In addition to establishment of new rules for evidence review, SCOQIM is also assessing AAP's internal policy categories to determine whether they need modification as well. AAP's internal policy categories include the following:

- Policy Statement: Statement of advocacy, direction, or a public health position of concern to AAP, including recommendations
- Clinical Report: Offers guidance for the pediatrician in the clinical setting, addressing best practices and state of the art medicine without formal recommendations
- Clinical Practice Guideline: Based on a comprehensive literature review and data analyses with formal rules of evidence in support of each recommendation made
- Technical Report: Based on a literature review and data analyses but does not contain recommendations

The following illustrates the current AAP grading system for clinical guidelines:



The Committee on Infectious Diseases (COID) felt that there were some components of the current AAP grading system that are not applicable to vaccine-related statements; therefore, AAP has chosen not to use this grading system. The COID differs somewhat from other organizations in that AAP develops its own policies for vaccine recommendations, and COID is responsible for development of vaccine policy. The COID consists of 12 members along with liaisons from CDC, CPS, FDA, NIAID, NICHD, NVPO, and PIDS. The COID has established a strong relationship with ACIP. Members serve as liaisons on relevant ACIP working groups. Through liaisons, the COID provides input into work group deliberations. The committee conducts independent reviews of data, with a goal to reach harmonized recommendations. COID develops vaccine-related policy statements for AAP Members, and has used IDSA / USPHS guidelines for evidence rating. Statements become AAP Policy following approval by the AAP Board of Directors and publication in *Pediatrics.*

Because AAP agreed that greater transparency and a guide for examining evidence were needed, COID has used the current *US Public Health Services Grading System for Ranking Recommendations and Clinical Guidelines* for vaccine recommendations, shown in the following illustration:

APPENDIX 1 **Infectious Diseases Society of America-US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines**

Category, Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Adapted from Canadian Task Force on the Periodic Health Examination. *Can Med Assoc J.* 1979;121(9):1193–1254.

[From: Prevention of Rotavirus Disease: Updated Guidelines for Use of Rotavirus Vaccine. Committee on Infectious Diseases. *Pediatrics* 2009;123:1412-20]

With regard to AAP endorsement of externally developed clinical guidelines, SCOQIM uses the Conference on Guideline Standardization (COGS) checklist to assess quality [held in New Haven, Connecticut on April 26, 2002: http://gem.med.yale.edu/cogs/]. This statement was developed to be used prospectively as guidelines were developed; however, SCOQIM also uses them to evaluate any guideline sent to AAP for its approval. COGS statements include 18 items critical for understanding a guideline, similar to those used by AAFP. This includes an evaluation of the systematic evidence review and evidence grading, including the criteria used to rate quality of evidence, how evidence was used to create recommendations, and the system describing strength of recommendations. COGS statements are submitted to Board and Executive Committee of AAP for approval. AAP can choose to endorse, not endorse, or affirm. If data are thought to be beneficial to pediatricians, but are not of the quality that would permit endorsement, a statement can be affirmed to make practitioners aware of the data.

In conclusion, AAP would support a transparent, evidence-based process to arrive at ACIP recommendations for vaccines.

Professional Organization Perspectives: ACP

Gregory A. Poland, MD, MACP
American College of Physicians

Dr. Poland first announced that in July 2010 a new international learned society for vaccinologists would be officially launched called the Edward Jenner Society, about which further information may be obtained at http://www.edwardjennersociety.org

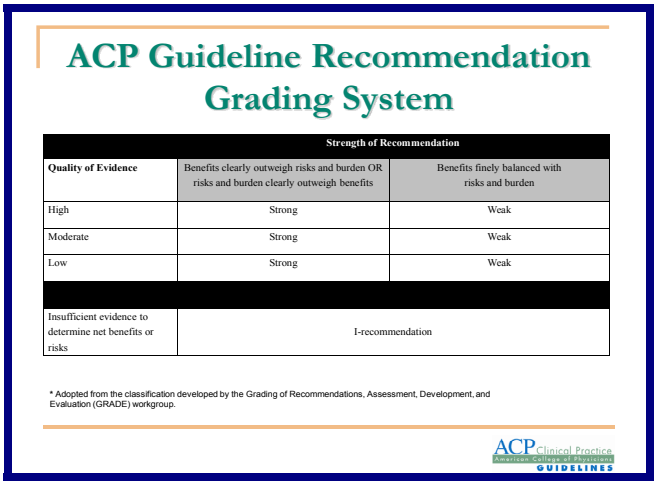
He then explained that the American College of Physicians (ACP) is the United States (US) largest medical specialty organization. ACP has 129,000 members representing internists, sub-specialists in internal medicine, residents and fellows in training, and medical students. The ACP headquarters is in Philadelphia and there is an office in Washington, D.C.

With regard to background, ACP's Clinical Efficacy Assessment Subcommittee (CEAS) was established in 1981. Members are all internists / subspecialists and methodologists, and are full time practitioners. There is stable membership on CEAS, with members serving up to 5 years and the chair serving up to 4 years. No external funding is accepted for CEAS; it is funded by ACP. There is conflict of Interest vetting of each member. CEAS does not endorse consensus statements or other groups' guidelines. Instead, CEAS delivers two products: 1) Clinical Guidelines, which involves a systematic review of available evidence and a guideline statement with recommendations; and 2) Clinical Guidance Statements, which involves review of available guidelines and summary recommendations.

Guideline topics are selected based on the prevalence of the disorder or the issue, potential impact on mortality and morbidity, effective health care / intervention available, areas of uncertainty and evidence that current performance is deficient, cost, likelihood of availability of strong evidence, and relevance to internal medicine. Systematic evidence reviews for clinical guidelines are ACP sponsored. These used to be done internally, but now usually are done by AHRQ. The process of a good systematic review is incredibly intense and generally cost about $200,000. ACP nominates topics to the AHRQ's Evidence-based Practice Centers for systematic review and evidence report. ACP collaborates with other societies after extensive negotiations regarding what the evidence review would involve and evidence levels.

Medline, NGC (national guidelines clearinghouse) search, and experts in the field are all polled for information. The Appraisal of Guidelines Research and Evaluation (AGREE) instrument is used to rate guidelines [http://www.agreetrust.org]. ACP also summarizes other guidelines and recommendations and offer sometimes offer summary recommendation based on other's guidelines.

The guideline development process involves formulating questions for the evidence review; a systematic evidence review, with a background evidence-review paper and a guideline paper that offer the actual recommendations; CEAS meetings and conference calls; CEAS Guideline Sub-Panel conference calls; and extensive internal ACP review by approximately 60 people; and external review by specialty societies, *Annals of Internal Medicine*, and others. The development process takes approximately 18 to 24 months on average. It is approved by the sub-panel, CEAS, the ACP Education Committee, and the Board of Regents. Guideline and background papers are then typically submitted to the *Annals of Internal Medicine* where they undergo independent peer-review. The shelf life of ACP guidelines is anticipated to be on average about 5 years. The following is an example of the grading system ACP uses:



ACP Guideline Recommendation Grading System

	Strength of Recommendation	
Quality of Evidence	Benefits clearly outweigh risks and burden OR risks and burden clearly outweigh benefits	Benefits finely balanced with risks and burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks	I-recommendation	

* Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

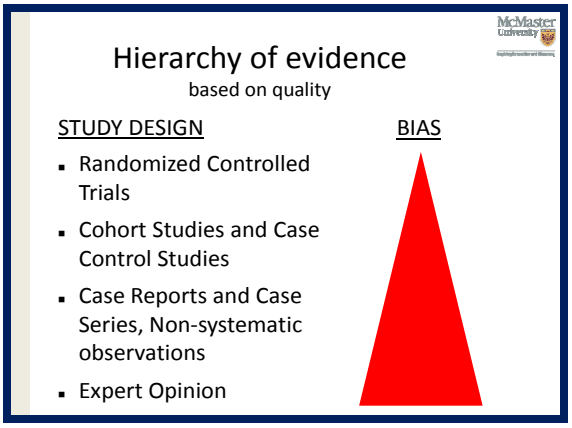
ACP Clinical Practice GUIDELINES

For years, the ACIP recommendations were not endorsed by the ACP guidelines committee because they were not evidence-based. Instead, they were endorsed by the ACP Adult Immunization Advisory Board (AIAB), then by the Education Committee, and then by the Board of Regents. The ACP AIAB was able to convince the ACP leadership that it was important to sign on to the ACIP schedule even though it did not meet ACP evidence-based criteria. The efforts of the ACIP EBRWG have been monumental and were started largely due to input / pressure from the ACP and other societies. The ACP appreciates this effort and strongly supports a standardized evidence-based approach for developing the ACIP recommendations on vaccine policy.

GRADE

Holger Schünemann, MD, PhD
Chair, Department of Clinical Epidemiology & Biostatistics
Michael Gent Chair in Healthcare Research
McMaster University, Hamilton, Canada

Dr. Schünemann explained that the GRADE framework in general is based upon the framework for evidence-based healthcare decisions, which results from the integration of clinical state and circumstances, population values and preferences, and best research evidence. Expertise is required to do this. There is a need to assess whether evidence is actually available. Some would propose that there always is evidence and that when there is a question there is evidence. The evidence may not be complete and it may only be relevant for certain aspects of the question, but typically when there is a question, some form of evidence exists. It also means that when there is better research, there will be greater confidence in the evidence and the decisions that follow from this evidence. Better research means that there must be some form of hierarchy. Shown in the following illustration is a typical hierarchy for evidence that is from the Canadian Task Force for Preventive Services from about 30 years ago:



Typical hierarchies of evidence have expert opinion at the bottom, which does not bode particularly well for the experts, and randomized controlled trials (RCTs) at the top. All of this is based on the assumption that expert opinion is associated with the greatest bias and RCTs are associated with the least amount of bias. Dr. Schünemann proposed that this hierarchy was entirely too simplistic, quoting Albert Einstein who said, "Everything should be made as simple as possible but not simpler." He asked the audience whether they would feel comfortable explaining the following concepts, which all more or less have to do with whether an estimate of effect for a certain population for whom guidelines are likely to be applied is actually correct:

- ❑ Confounding, effect modification, and external validity
- ❑ Concealment of randomization
- ❑ Blinding (who is blinded in a double blinded study?)
- ❑ Intention to treat analysis and its correct application

- P-values and confidence intervals

He posited that few people would feel comfortable with this because special training is required to assess evidence. Dr. Schünemann referred to a publication in the *British Medical Journal* in 2003 in which investigators made fun of themselves and RCTs titled, "Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials" [Gordon CS smith, Jill P Pell]. Lo and behold, the investigators did not find any RCTs. If Dr. Schünemann were to pose the question, "Why do you believe that parachutes actually prevent death and injury when jumping from an airplane?" after some deliberation, people would say that it is because the effects are so large. It is based on many observations that parachutes actually do prevent deaths. RCTs are not needed when effects are very large. In fact, the evidence from the US Parachutte Association reported 821 injuries and 18 deaths out of 2.2 million jumps in 2007. The risk estimates can be calculated, with the relative risk reduction being > 99.9 % (1/100,000). At the same time, if assessing the first parachutes, theory alone and gravitational theory would not help to make decisions because the first parachutes did not work.

In health care, there are very few such large effects. Nevertheless, when dealing with large effects, RCTs are not needed. However, the evidence hierarchy shown is far too simplistic. Dr. Schünemann stressed that expert opinion is not a form of evidence and should not be at the bottom of the hierarchy—it actually should be required to evaluate various forms of evidence. Clearly, many things can go wrong with RCTs and many things can be good about observational studies, such as large effects that increase the confidence that an estimate of effect is actually correct.

There is another issue with evidence hierarchies. In what should be a simple recommendation for the use of oral anticoagulation in patients with atrial fibrillation and rheumatic mitral valve disease, the following table represents the evidence and recommendations of three organizations:

Evidence	Recommendation	Organization
B	Class I	AHA
A	1	ACCP
IV	C	SIGN

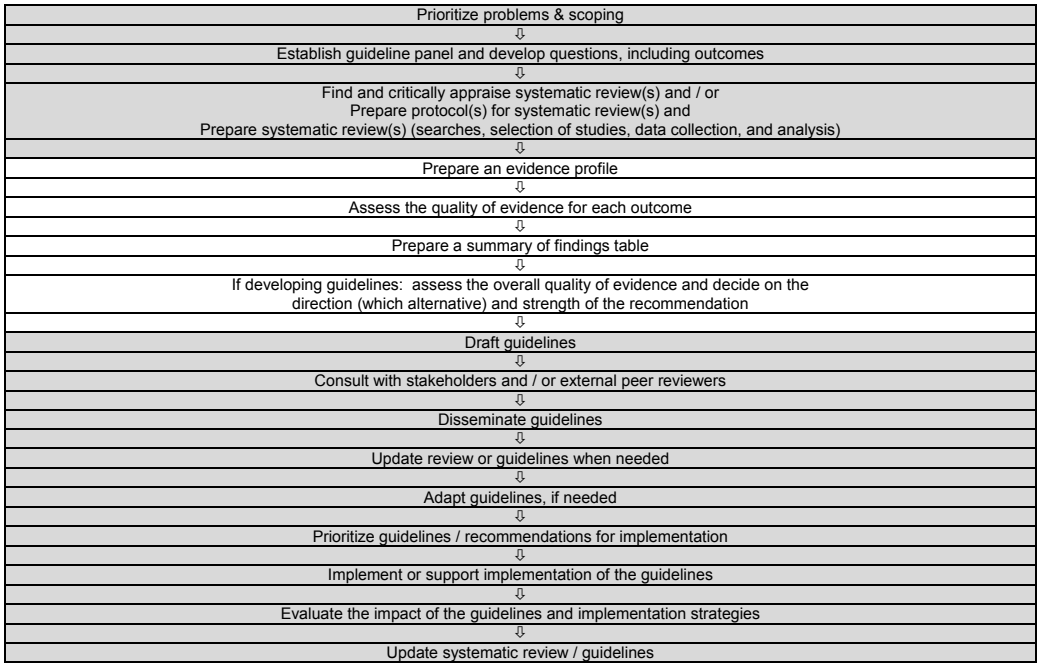
A practitioner looking at this evidence would likely have been very confused, particularly given that the three organizations reviewed exactly the same five RCTs. While not concerned about the different judgments, Dr. Schünemann was concerned that at the time, there was little information regarding why these evidence ratings were categorized as they were. The transparency related to making the assessment about the evidence and development of these recommendations can be improved.

This is part of the rationale for forming the GRADE Working Group. The aim of the GRADE Working Group is to develop a common, transparent, and sensible system for grading the quality of evidence and the strength of recommendations. This is an international group of guideline developers, methodologists, and clinicians from throughout the world (>100 contributors) since 2000. Groups include ACCP, AHRQ, Australian NMRC, BMJ Clinical Evidence, CC, CDC, McMaster, NICE, Oxford CEBM, SIGN, UpToDate, USPSTF, and WHO.

The GRADE systems has experienced wide uptake by the following:

- World Health Organization
- Allergic Rhinitis in Asthma Guidelines (ARIA)
- American Thoracic Society
- American College of Physicians
- European Respiratory Society
- European Society of Thoracic Surgeons
- British Medical Journal
- Infectious Disease Society of America
- American College of Chest Physicians
- UpToDate®
- National Institutes of Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- Cochrane Collaboration
- Infectious Disease Society of America
- Clinical Evidence
- Agency for Health Care Research and Quality (AHRQ)
- Partner of GIN
- Over 40 major organizations

Much of this is work has been published in a series of 16 articles that were developed for WHO beginning in 2005 for the Advisory Committee for Health Research, which reviewed WHO's and other organizations' guideline development, and formulating a recommendation for WHO regarding how the process could be improved. A very complete process was laid out for guideline development that ranged from prioritizing problems and scoping of questions to developing recommendations and evaluating the impact of guidelines, as reflected in the following illustration:



Dr. Schünemann presented a brief case scenario to illustrate how the GRADE system was applied at WHO. A 13-year-old girl who lived in rural Indonesia presented with influenza symptoms and developed severe respiratory distress over the course of the 2 previous days. She required intubation. The history reveals that she shared her living quarters with her parents and her three siblings. At night, the family's chicken stock also shared this room, and several chickens had died unexpectedly a few days before the girl fell sick. The way avian influenza is approached is by considering the potential interventions (e.g., antivirals, such as neuraminidase inhibitors, oseltamivir and zanamivir). They followed a structured approach for developing questions. Guidelines should deal with actionable items, and often background questions are addressed in guidelines. However, background questions usually do not lead to recommendations. They usually include questions such as: What is Avian Influenza? What is the mechanism of action of oseltamivir? Foreground questions lead to actionable items and recommendations, and usually deal with issues that assess whether benefit outweighs potential harm: In patients with avian influenza, does oseltamivir therapy improve survival?

Framing a foreground question is extremely important for developing clinical practice guidelines, and involves specifying the population, intervention, comparison, and outcomes. For example:

Population: Avian Flu / influenza A (H5N1) patients
Intervention: Oseltamivir
Comparison: No pharmacological intervention
Outcomes: Mortality, hospitalizations, resource use, adverse outcomes, antimicrobial resistance

A framework for developing recommendations and clinical questions should consider all important outcomes that are relevant for clinical questions. Frequently, recommendations that focus on single and particular outcomes were evaluated in studies rather than beginning with the clinical question and then evaluating the evidence. Choosing outcomes mean that there must be clarity about the following:

- Desirable outcomes
  - → lower mortality
  - → reduced hospital stay
  - → reduced duration of disease
  - → reduced resource expenditure

- Undesirable outcomes
  - → adverse reactions
  - → the development of resistance
  - → costs of treatment

- Every decision comes with desirable and undesirable consequences
  - → Developing recommendations must include a consideration of desirable and undesirable outcomes

It is also important for decision makers and guideline authors to consider the relative importance of outcomes when balancing these outcomes to make a recommendation. One way to do this is to decide which outcomes are critical for decision making; which are important, but not critical for decision making; and which are of low importance. Moreover, relative importance may vary across populations and across patient groups within the same population. Once a guideline panel decides that an outcome is critical, the quality of the evidence and effects associated with it should then be evaluated in order to make the most informed decisions.

GRADE separates two issues in terms of the quality of the recommendation:

1) Two Recommendation Grades: Weak / conditional / optional or strong (for or against an intervention)

    → Balance of benefits and downsides, values and preferences, resource use and quality of evidence influence the strength of a recommendation

2) 4 Categories of Quality of Evidence: Recognizing that this is a continuum, these categories are used to improve communication: ⊕⊕⊕⊕ (High), ⊕⊕⊕◯(Moderate), ⊕⊕◯◯(Low), ⊕◯◯◯(Very low). These are just labels. The importance is the conceptual underpinnings:

    → methodological quality of evidence
    → likelihood of bias
    → by outcome and across outcomes

In the context of making recommendations, the quality of evidence reflects the extent of confidence that the estimates of an effect are adequate to support a particular decision or recommendation. To illustrate, Dr. Schünemann shared a cartoon of two weathermen, one of whom says, "I think that there is a 40% chance of showers and, a 10% chance we know what we're talking about." This expresses the likelihood of and the confidence in an outcome. The effect estimate in this illustration is 40% and the confidence that these two meteorologists are reporting the truth is 10%. That is due to the fact that they may have used poor models for prediction, or the evidence for creating these models may be poor. The same is true in health care. There are sometimes confidence intervals that are very narrow, but nevertheless the evidence supporting these confidence estimates and the point estimate are very low.

The definition provided for the grades of evidence include:

- ⊕⊕⊕⊕/A/High: Further research is very unlikely to change confidence in the estimate of effect.
-
- ⊕⊕⊕◯/B/Moderate**:** Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

- ⊕⊕◯◯/C/Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

- ⊕◯◯◯/D/Very low: Any estimate of effect is very uncertain.

With respect to determinants of quality, randomization results in greater confidence in estimates of effect so RCTs are of high quality (⊕⊕⊕⊕), while observational studies are of low quality (⊕⊕◯◯); however, many factors can lead to bias and many things can go wrong in RCTs.

Factors that can lower confidence in estimates of effects include:

- Limitations in detailed design and execution *(risk of bias criteria)*
- Inconsistency *(or heterogeneity)*
- Indirectness *(PICO and applicability)*
- Imprecision *(number of events and confidence intervals)*
- Publication bias

Factors that can increase confidence in estimates of effects include:

- Large magnitude of effect
- All plausible residual confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed
- Dose-response gradient

Examples of design and execution / risk of bias include:

- Inappropriate selection of exposed and unexposed groups, failure to adequately measure / control for confounding
- Selective outcome reporting
- Failure to blind (e.g., outcome assessors)
- High loss to follow-up
- Lack of concealment in RCTs
- Intention to treat principle violated

The Risk of Bias (RoB) Table is a tool used by the Cochrane Collaboration. Dr. Schünemann shared an example in which the authors examined 30 RCTs that fulfilled their inclusion criteria for adverse effects as a result of using formoterol for asthma [From Cates, CDSR 2008]. To assess the trials, the investigators used three key methodological criteria: concealment of randomization, blinding, and whether there was selective outcome reporting. About half of the studies did not report on adverse events, although they had the data. The RoB table is too complicated for clinicians who have to deal with more important problems, but this can be utilized by adequately trained individuals. It also means that an overall judgment of the underlying quality of the evidence is required. In this case, given that about half of the studies did not report on adverse events, any estimate of effect in relation to adverse events would probably be met by less certainty than if these studies had reported on adverse events. Thus, there is a reason to lower the quality of evidence for RCTs. Another example shared by Dr. Schünemann pertained to anticoagulation and reduction in mortality in patients with cancer for which the trials were of much better quality, with few things done wrong. The guideline panel rightly decided not to lower the quality of evidence because the RCTs were done well [Akl E, Barba M, Rohilla S, Terrenato I, Sperati F, Schünemann HJ. "*Anticoagulation for the long term treatment of venous thromboembolism in patients with cancer*". Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006650].

If there is inconsistency of results between RCTs or observational studies, an explanation should be sought in terms of whether there are differences in the patients, intervention, comparator, and outcomes that explain differences in results between studies. If this remains

unexplained, confidence may be lowered in the overall estimate of effect across studies. Dr. Schünemann shared an example of a Cochrane review from the immunization literature pertaining to how reminders can increase the uptake of immunizations [Jacobson Vann JC, Szilagyi P. Patient reminder and recall systems to improve immunization rates. Cochrane Database of Systematic Reviews 2005, Issue 3, Art. No.: CD003941. DOI: 101002/14651858. CD003941.pub2.] In this example, five studies all showed similar effects and appeared to vary due to random influences. The overall estimate of effect was that there is an increase in the odds ratio of 1.58 (1.26, 1.99) for an uptake of immunization across these five studies. There is not a lot of reason to believe that these five studies measured anything differently.

An alternative example from the same type of review involves a different intervention of patient reminders in a subgroup that dealt with preschool children. The intervention in the two studies was highly efficacious; however, the odds ratio differed greatly between them at 6.77 (4.57, 10.02) and 1.92 (1.51, 2.43), so confidence in the overall estimate of effect would be lowered by the inconsistency between the two studies despite the fact that both show efficacy. These are important considerations, especially given that sometimes a threshold must be used for when an intervention really becomes efficacious.

Directness of evidence is related to the concept of generalizability, transferability, and applicability though it is slightly different in that it goes beyond these concepts. The interest is in the differences in populations / patients (e.g., have information on children and are interested in making recommendations about neonates; have information on women in general and are interested in making recommendations about pregnant women); interventions (e.g., interested in making recommendations for a vaccine when information comes from older vaccines); comparator appropriateness (e.g., comparator included in the evidence should relate to the question of interest); and outcomes (e.g., does seroconversion actually mean cases prevented). Another concept pertains to indirect comparisons, particularly in the context of comparative effectiveness research. For example, perhaps there is an interest in comparing Vaccine A to Vaccine B but the only comparison possible is an indirect comparison between A versus C and B versus C or Vaccine A versus a Placebo and Vaccine B versus a Placebo. Relative estimates of effect can be calculated, but the certainty would be lower.

The fourth criterion is publication bias, which should always be suspected with research not being published in particular with small “negative” trials, when there are only a few small “positive” trials, and when there is a lot of for profit interest. There are various methods to evaluate whether there are publication biases, though none of these is perfect. The fifth criterion of imprecision pertains to small sample size. When there are a small number of events or very small studies, there are usually wide confidence intervals, which results in uncertainty about the magnitude of effect. This can be interpreted as the extent to which confidence in estimate of effect is adequate to support a decision.

With regard to what can raise quality, a large magnitude in effect (RRR 50%/RR 2). When there is a very large effect, quality may be raised by two levels (RRR 80%/RR 5). The common criteria would be that everyone used to do badly before the intervention, but following the intervention almost everyone does well (e.g., parachutes to prevent death when jumping from airplanes). There are also examples from health care. In an intervention to increase the uptake of immunizations in which telephone reminders were used, three observational studies were found by the systematic reviewers. There was a large number of participants and the effect across these studies comes with a relative risk (RR) >2, which would increase the confidence that this particular intervention worked in this context. Dose response relationships can also raise confidence. A common example is that the more a patient’s blood is thinned, the higher

the risk of bleeding. There is a good example from the observational study literature, not related to immunization, on children diagnosed with childhood lymphoblastic leukemia (CLL). Physicians frequently use prophylactic CNS radiation to reduce the risk of CLL recurring. However, this radiation comes with the risk of secondary CNS malignancies 15 years after cranial irradiation. When investigators assessed the evidence related to this, they found that children who received no radiation had about a 1% (95% CI 0% to 2.1%) incidence of CNS malignancies, a 12 Gy radiation dose led to a 1.6% (95% CI 0% to 3.4%) incidence, and 18 Gy to a 3.3% (95% CI 0.9% to 5.6%) incidence.

The third criterion pertains to whether all plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed. In terms of whether all plausible residual confounding would result in an overestimate of effect, Dr. Schünemann shared an example from the general medical literature. A drug that was used for the treatment of diabetes, phenformin, was highly suspected of causing the devastating complication of lactic acidosis. The related agent, metformin, is under suspicion for the same toxicity. This was widely publicized. Large observational studies have failed to demonstrate an association despite the over-reporting as a possible residual confounding of this association. This type of observations would increase the confidence in the estimate of effect. There are parallels in the vaccine literature. Suspicion that adverse effects may exist may be refuted by observational studies that assess all patients immunized that do not find these associations. Under these circumstances, the quality of the evidence for the existence of no association may be increased.

To summarize the quality of evidence assessment, the body of evidence would be examined as illustrated by the following table:

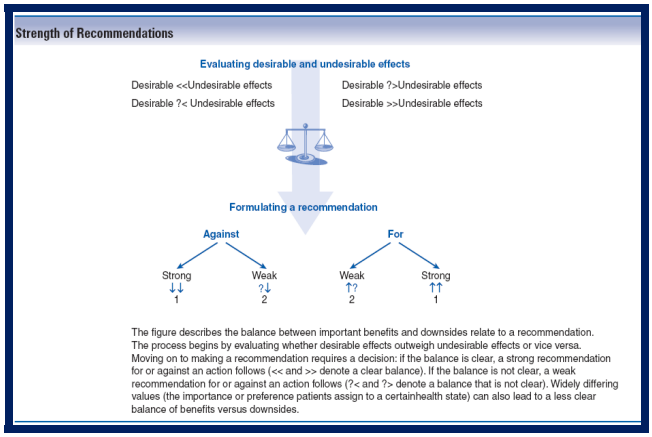
Study design	**Initial quality of a body of evidence**	**Lower if**	**Higher if**	**Quality of a body of evidence**
Randomised trials	**High**	**Risk of Bias** - 1 Serious -2 Very serious **Inconsistency** - 1 Serious -2 Very serious **Indirectness** - 1 Serious -2 Very serious **Imprecision** - 1 Serious -2 Very serious **Publication bias** - 1 Likely -2 Very likely	**Large effect** + 1 Large +2 Very large **Dose response** +1 Evidence of a gradient **All plausible residual confounding** +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed	**A/High** (four plus: ⊕⊕⊕⊕)
				B/Moderate (three plus: ⊕⊕⊕◯)
Observational studies	**Low**			**C/Low** (two plus: ⊕⊕◯◯)
				D/Very low (one plus: ⊕◯◯◯)

Comprehensive evidence summaries are ultimately produced to ensure that everyone on a guideline panel is looking at the same type of evidence. A quality assessment is conducted for outcomes that are critical for a clinical question that examines the number of studies, design, limitations, inconsistency, indirectness, imprecision, and other considerations. The numerical results are presented to a guideline panel. Importantly, all of this information will be made available for those interested in exploring the recommendations (e.g., transparency).

With regard to moving to recommendations, the strength of a recommendation is defined as follows, "The strength of a recommendation reflects the extent to which we can, across the range of patients for whom the recommendations are intended, be confident that desirable effects of a management strategy outweigh undesirable effects." Regarding the determinants of the strength of a recommendation, the factors that can strengthen a recommendation include the following:

- Quality of the evidence: The higher the quality of evidence, the more likely is a strong recommendation.
- Balance between desirable and undesirable effects: The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely a weak recommendation is warranted.
- Values and preferences: The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely a weak recommendation is warranted.
- Costs (resource allocation): The higher the costs of an intervention (e.g., the more resources consumed), the less likely is a strong recommendation warranted.

This framework is then applied as reflected in the following illustration, which demonstrates the continuum from desirable effects clearly outweighing the undesirable effects to the undesirable effects clearly outweighing the desirable effects:



It is imperative to use categories in order to improve communication. In this system, strong recommendations are made when the balance is clear and weak or optional recommendations are made when the balance is less clear in favor of an intervention. When the undesirable effects are likely larger than the desirable effects, weak recommendations are made if the balance is not as clear or strong recommendations if the balance is very clear.

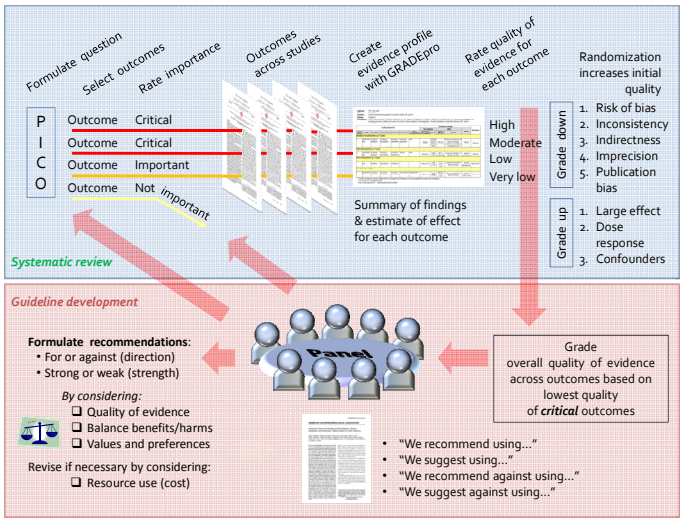
Returning to the avian influenza case scenario example and what was done with WHO, a standard guideline development process was utilized based on the 16 cases. Group composition included a panel of 13 voting members of clinicians who treated influenza A(H5N1) patients, infectious disease experts, basic scientists, public health officers, and methodologists. Independent scientific reviewers identified systematic reviews, recent RCTs, case series, and animal studies related to H5N1 infection. There were five studies, none of which directly dealt with avian influenza patients. There were no clinical trials of oseltamivir for treatment of H5N1 patients. However, there was a body of indirect evidence from cases with seasonal influenza infection that included four systematic reviews and health technology assessments (HTA) reporting on five studies of oseltamivir in seasonal influenza. The findings were that for hospitalizations the odds ratio was 0.22 (0.02 – 2.16), and for pneumonia the odds ratio was 0.15 (0.03 - 0.69). This was a large effect, but it was based on very few events. For non-pandemic conditions, the cost per treatment course was approximately $40. The panel then assessed the strength of the evidence and made several judgments that were made transparent. They found that there was a very low quality of evidence. The balance between desirable and undesirable effects was uncertain, but the small reduction in relative risk led to a large absolute effect. Values and preferences were clear and there was little variability, and the cost was low in this non-pandemic setting.

Dr. Schünemann pointed out that he presented this example because it was an exception to the rule in that very low quality evidence led to a strong recommendation that was formulated very clearly: “In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians should administer oseltamivir treatment as soon as possible (strong recommendation based on very low quality evidence).” This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places relatively low values on adverse reactions, the development of resistance, and costs of treatment.

It is important to provide users of the recommendation with information regarding what these strong recommendations really mean. For patients, most people in this situation would want the recommended course of action and only a small proportion would not. For clinicians, it means that most patients should receive the recommended course of action. For policy makers, the recommendation can be adapted as a policy in most situations. In terms of the iimplications of a conditional / weak recommendation, the majority of people in this situation would want the recommended course of action, but many would not. Clinicians will be more prepared to help patients to make a decision that is consistent with their own values / decision aids and shared decision making (e.g., pregnant women). For policy makers, there is a need for substantial debate and involvement of stakeholders.

Dr. Schünemann reiterated that guideline development needs to take place in interaction with systematic, complete and transparent evaluation of the evidence. This begins with development of a clinical question, which should not debate only on what the evidence reviewers put together, but should also be informed by and take place in close interaction with the guideline in question. A guideline panel must decide what outcomes are relevant for the specific clinical

question, and must decide which are critical and which are not as important. Outcomes must be evaluated across studies. Critical and important outcomes must be assessed for their quality, and it may not be necessary to spend much time on non-important outcomes. Systematic and transparent summaries should be prepared, and quality ratings should be taking place based on the factors that increase or decrease the quality of the evidence. An overall assessment for all critical outcomes should be completed. The guideline panel must then integrate this evidence and formulate recommendations either for or against an intervention. These can be strong or weak or conditional / optional. This takes place after weighing the quality of evidence across outcomes based against the balance of benefits and harms, values and preferences, and resource use. This should result in clearly formulated recommendations. This process is reflected in the following illustration:



There are some specific issues related to guideline development for immunization. Dr. Schünemann said he wanted to stimulate some thoughts about whether demonstrating causation is closely related to efficacy of interventions. He believes that causation is not equivalent to efficacy of interventions. The Bradford Hill criteria are extremely important, but they are nearly half a century old. The question regards whether they should be taken as a "tablet from the mountain" or whether health research methodology has changed over the past 50 years. The situation of causation is very much reflected in harms caused by medications. There is an assumption that not administering an immunization would lead to no exposure, which would lead to no adverse effects based on the strong associations observed. Another question regards whether to stop exposure, such as implementing policies to no longer administer a drug, which directly relates to stopping the outcome from occurring. An assessment is needed between the strength of an association and causation in relation to how an intervention may actually affect the exposure-outcome relation. That is, an assessment must be made of how confident one can be that removal of the exposure is effective in preventing disease. This is true whether it is drugs or environmental factors, and will depend on the intervention to remove exposure.

Four considerations pertaining to GRADE and immunizations include the following:

- ❑ Can herd immunity following immunization and indirect effects on the co-circulation of other pathogens typically be ascertained only through the use of observational epidemiological

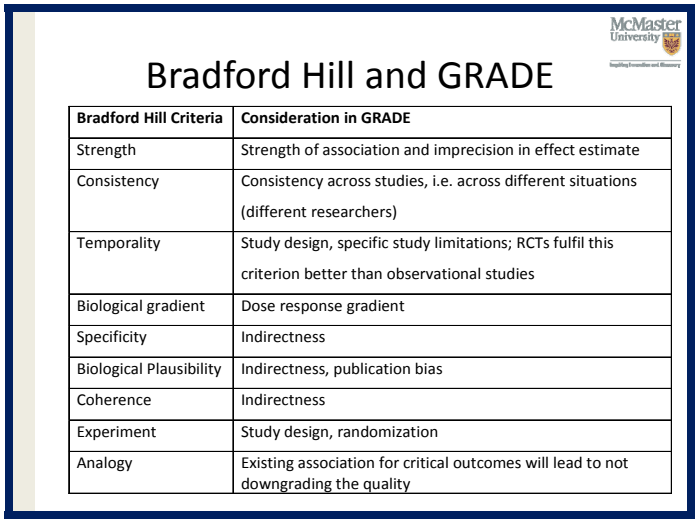
methods? Innovative randomized controlled trials (RCTs) using cluster-randomization are increasingly being conducted to provide this evidence.

- A 94% protective effect of a live, monovalent vaccine against measles is classified as "moderate level of scientific evidence." GRADE's strength of association criteria may be applied to increase the grade by 2 levels from "low" to "high" in this situation.

- GRADE ratings do not give credit to "gradient of effects with scale of population level impact compatible with degree of coverage." GRADE's dose-response criterion would apply to such gradients.

- Might anti-vaccination lobby groups abuse the ratings? Abuse of any system is possible. It is equally likely that increased transparency provided by the GRADE framework can strengthen, rather than undermine, the trust in vaccines and other interventions.

In conclusion, Dr. Schünemann said he would agree with modifying the GRADE criteria if Bradford Hill criteria were not already considered, but they are. The emphasis in GRADE is on the strength of a recommendation, and the quality of evidence is only one factor. GRADE considers the Bradford Hill criteria to some degree, as reflected in the following table:



WHO's Strategic Advisory Group of Experts (SAGE): Approach to Evidence-Based Recommendations

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Dr. Reingold reported that WHO's Strategic Advisory Group of Experts (SAGE) was established in 1984 to serve as the principal advisory group to WHO for development of policy related to vaccines and immunization. Since 2005, the SAGE chair reports directly to the Director General of WHO. SAGE currently includes 15 members who represent a broad range of disciplines relating to vaccines and immunizations, with a strong emphasis on geographic representativeness throughout the world. Currently, there are two Americans on the committee (e.g., himself and Jon Abramson). SAGE currently meets twice per year in April and November, and meetings are three days in length. In addition, four conference calls are convened annually. In the past three years, SAGE has dramatically increased its activities, somewhat attempting to parallel the way ACIP operates, but with far fewer resources. SAGE has benefitted in recent years from funding from the Gates Foundation to increase its number of meetings and activities. As of July 2010, working groups include: Measles; Inactivated Polio; H5N1 Influenza; Influenza; Pertussis; Meningococcal Meningitis; Rubella; and Hepatitis A. Much of the work of SAGE is conducted through these working groups, which develop position papers that are subsequently discussed and approved by the entire SAGE committee. Staff support is provided by P. DuClos, who serves the same purpose that CDC serves for ACIP, except that he is a one-man show. He is an extraordinarily important person in helping SAGE with its work.

SAGE is primarily intended to discuss and develop position papers for WHO to use to promulgate to regional offices and to countries which rely on WHO. SAGE develops position papers pertaining to new vaccines and revises and develops position papers regarding old vaccines and immunization schedules. The primary target audiences for these position papers are poor and middle income countries that do not typically have an ACIP or comparable organization to conduct this type of review and develop these types of papers for them. SAGE is particularly concerned about what occurs at the group level across large populations, and their work involves SAGE and outside members, and a working group typically includes two SAGE members and four to six subject matters experts from throughout the world who participate in the process. SAGE's position papers are published in the Weekly Epidemiological Record and on the WHO website. The development of position papers began in 1998. SAGE has developed position papers for each vaccine-preventable disease, which have to be published in all of the WHO languages.

In 2003, WHO decided to adopt GRADE as its approach to evaluate evidence. All of WHO's advisory committees, including SAGE, are obliged to use the GRADE approach in one fashion or another. In 2006, WHO began to use GRADE for a series of 16 reviews. In 2007, WHO formed a Guideline Review Committee to implement the use of GRADE across all of WHO's guidelines in vaccines and other areas. In 2008, WHO introduced the use of GRADE tables in its vaccine position papers. GRADE can be used to examine the quality of evidence in support of a decision and to assess the strength of the recommendation itself. Currently, GRADE is

used by SAGE to assess the quality of evidence in support of a vaccine, but SAGE does not use this approach in terms of making a decision about the strength of a recommendation being made. In 2009, a SAGE discussion group was formed concerning the use of GRADE to determine whether they may wish to modify the GRADE framework in some ways and to address challenges in applying GRADE to vaccines. This committee is currently comprised of Professor David Durrheim (Australia); Professor Zulfiqar Ahmed Bhutta (Pakistan); Helen Rees (South Africa; SAGE Chair); himself (US); P. DuClos (WHO Secretariat). Their business is conducted primarily by emails and conference calls. The objectives of SAGE's GRADE Discussion Group are to develop a communication strategy concerning SAGE's use of GRADE in its position papers; discuss possible "adjustments" to the GRADE approach; and discuss possible alternatives to the GRADE approach. To be perfectly honest, Dr. Reingold thought that the possibility of alternatives to the GRADE approach was not really "on the table" currently given WHO policies.

SAGE position papers revised or created using the GRADE approach include the following:

New Vaccines	Existing Vaccines
HPV vaccine	Pneumococcal Polysaccharide Vaccine
	Typhoid vaccine
	Measles vaccine
	Hepatitis B vaccine
	Cholera vaccine

When SAGE publishes a position paper, they make recommendations about the use of a vaccine. These recommendations have now become absolutely vital in terms of funding of vaccines for poor countries. For example, the Global Alliance for Vaccines and Immunisation (GAVI) Board, in deciding whether to utilize GAVI money to fund vaccines (e.g., pneumococcal conjugate, HPV, rotavirus, etc) will not do so until SAGE issues a position paper.

SAGE's HPV vaccine position paper states that "WHO. . . recommends that routine HPV vaccination should be included in national immunization programmes, . . . the primary target population is likely to be girls within the age range of 9 or 10 years through to 13 years" [WER 15; 10 April 2009]. This represents the challenging fact that WHO is dealing with many countries in many cultural settings, so they try to be broader in the writing of position papers than a single country might be. The footnote in this position paper reads, "Moderate quality of scientific evidence to support HPV vaccination of young adolescent girls to prevent cervical cancer later in life" [WER 15; 10 April 2009]. Because of the use of the GRADE approach and the desire for transparency, the tables are presented.

The theory is that anyone using GRADE to review this same set of papers would develop this identical table. The position paper then continues, stating that "Although the immunogenicity and efficacy of HPV vaccines may be reduced in HIV-infected females, the potential benefit of

vaccination in this group is particularly great. . . HIV testing should not be a prerequisite before routine HPV immunization." Another footnote is included that states, "Very low quality of scientific evidence to support vaccination of HIV-infected young adolescent girls to prevent cervical cancer later in life." Another table is then included to explain the grading of scientific evidence in terms of HPV and to show that only one study that has relevant data on this subject. That is an example with a new vaccine. It is generally easier to use the GRADE system for newer vaccine for which there are generally well done studies. It is somewhat more challenging to apply the system to older studies and older vaccines.

SAGE's pneumococcal polysaccharide vaccine 23 (PPV23) position paper includes a revised statement reading, "RCTs have failed to demonstrate efficacy against IPD or all-cause pneumonia in individuals with immune compromising conditions, regardless of age. Most observational studies suggest an effectiveness as high as 50 to 80% against IPD in healthy adults, and similar results have been reported in some high-risk populations" WER 42; 17 October 2008. The footnote states that, "Low-quality evidence of a lack of effectiveness of PPV23 against IPD in high-risk groups, acknowledging the variability of high-risk groups and of effectiveness in these groups." This is followed by a table showing the various studies. While there are people who believe that PPV23 is a great vaccine, SAGE's assessment using the GRADE criteria is that the evidence is of low quality. Again, the theory is that anyone using GRADE to review the papers for this topic would develop this identical table.

There are a number of perceived challenges to using GRADE when assessing vaccines, which include the following:

- Poor quality of many early studies of existing vaccines (e.g., tetanus toxoid)
- Ethical inhibitions to conducting additional RCTs
- Lack of consistency of the biological products used (e.g., BCG)
- Inability to examine safety vis–à–vis rare AEFIs in RCTs and reliance on post-marketing surveillance
- Difficulty of factoring in indirect effects (e.g., herd immunity)
- Difficulty of factoring in effects on ecologic niches (e.g., serotype replacement)
- Different measures of effect (immunogenicity with / without surrogates of protection; various clinical endpoints)
- Duration of protection
- Differences in age at vaccination / optimal age for immunization
- Effects of "natural boosting" (e.g., *B. pertussis*)

In conclusion, SAGE is using the GRADE approach to rate the quality of the evidence. There are concerns that low ratings of the quality of evidence will be misconstrued or misused. Possible modifications to the GRADE approach, tailored to the assessment of vaccines, are being considered.

Pilot of Explicit Evidence-Based Framework Based on GRADE

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Centers for Disease Control and Prevention

Dr. Ahmed reiterated that the EBRWG was proposing that ACIP adopt an explicit evidence-based framework based on the GRADE approach for new vaccines and for changes in recommendations for existing vaccines.

GRADE has two components, the first of which is to assess the evidence grade for a body of evidence. The evidence grades are classified as high, moderate, low, or very low. The second component is grading a recommendation's strength as strong or weak (for or against). Evidence grade is only one factor in determining the strength of a recommendation. Other factors include the balance of benefits and downsides, values and preferences, and resource use. Rather than the terms high, moderate, low, and very low quality EBRWG proposes to use the following letting system for ACIP evidence grades:

A: Further research is unlikely to change the estimate of effect
B: Further research may change the estimate of effect
C: Further research is likely to change the estimate of effect
D: Estimates of effect are uncertain

EBRWG feels that the terms high or low quality may be misinterpreted or misused by persons who are not familiar with the GRADE method. The grades A, B, C, and D reflect the confidence in an estimate of effect from a body of evidence. A and B are often considered to be a good level of evidence.

The GRADE approach of rating evidence begins with a study design. RCTs are initially rated as Grade A and observational studies as Grade B. Five factors can lower the grade: study limitations, inconsistency, indirectness, imprecision, and publication bias. Three factors can increase the grade: strength of association, dose-response, and confounding. If the relative risk is 2 from at least two observational studies with no possible confounders, the grade can be increased by one level from C to B. If the relative risk is 5 based on direct evidence with no major threats to validity, the grade can be increased by two levels from C to A. Expert opinion is graded as D, unless evidence informing opinion is graded (e.g., indirect evidence from other populations, vaccines, or diseases).

Categorizing recommendations as strong or weak may not be most appropriate for vaccine recommendations. Therefore, the EBRWG proposed the following categories for ACIP:

- Category I: Recommendations for or against, which apply to all persons in an age group - universal recommendations - or all persons in a specified high-risk group.

- Category II: Optional use recommendations mean that clinicians should help each patient arrive at a decision that is consistent with their values and preferences. The optional use recommendation is similar to what is currently referred to as a permissive recommendation. It is also possible that the ACIP may decide not to make a recommendation.

The key elements for any ACIP recommendation include direct evidence assessment for vaccine safety and vaccine efficacy and indirect evidence assessment of burden of illness. Evidence grading would be applied to the data on vaccine safety and vaccine efficacy. Burden of illness information from research studies or from surveillance systems is used for calculating estimates of numbers needed to treat (NNT) or numbers needed to harm (NNH). Considerations that may result in an ACIP optional use recommendation include lower evidence grade, smaller net benefit, uncertainty or variability in values and preferences, or uncertainty about whether the net benefits are worth the costs (e.g., cost-effectiveness). For example, the ACIP recommendation for use of HPV vaccine in males is a permissive or optional use recommendation because of cost-effectiveness, burden of illness, and other factors.

A pilot was conducted of the GRADE framework on a new vaccine, human-bovine reassortant pentavalent rotavirus vaccine (RotaTeq). Studies were used that were available at the time of the 2006 ACIP recommendation. This included Phase 3 studies of the pentavalent vaccine. Phase 1 and 2 studies that used a different vaccine formulation were excluded. Studies of rotavirus vaccines using other rotavirus strains (e.g., human-rhesus, human, lamb, bovine) were also excluded. Based upon the review of the studies, in terms of benefits and safety, an evidence grade of A was assigned for all outcomes shown, given that there were no serious study limitations, inconsistencies, indirectness, or imprecision. With respect to the balance between desirable and undesirable effects, the benefits were large compared to potential harms. In terms of values and preferences, parents are likely to place high value on preventing severe rotavirus gastroenteritis. While the vaccine is likely to be cost-saving from the societal perspective if the vaccine cost was $42 per dose, the vaccine price was not known at the time ACIP was making the recommendation. ACIP recommended universal vaccination of US infants with three doses of rotavirus vaccine administered orally at ages 2, 4, and 6 months (Recommendation Category: I, Evidence Grade: A). The key considerations behind the consideration are included in the remarks section of the recommendation and read as follows in this example, “Nearly every child in the US 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. Randomized controlled trials show that vaccination reduces severe rotavirus diarrhea by 97%. No increased risk of intussusception was observed.”

Dr. Ahmed then presented evidence grades for post-licensure safety studies for Rhesus-based tetravalent rotavirus vaccine (Rotashield) and the combination measles, mumps, rubella, and varicella vaccine (MMRV). Rotashield was withdrawn from the US market because of a reported association with intussusception. For grading the evidence for intussusception associated with Rotashield vaccine, two cohort and case-control studies were included that were available at the time ACIP withdrew its recommendation for using the vaccine. Ecological studies were excluded. The initial grade was C because studies were observational. The initial grade was upgraded by two levels to an A because the relative risk of intussusception for vaccinated compared to unvaccinated infants is greater than 5. This upgrade is based on GRADE’s strength of association criterion. Regarding MMRV vaccination and febrile seizures after Dose 1, MMRV was compared to MMR+V vaccination for children ages 12-23 months. The initial grade for increased risk 5-12 days after vaccination was upgraded by one level because relative risk is ~2 based on consistent evidence from two studies. Other data support this finding. For decreased risk 13-30 days after vaccination, the initial grade was downgraded by one level because of imprecision. One study indicated a decrease, but it was not significant, and one study found no association.

In summary, the GRADE framework has two components: criteria for evidence grading and consideration from moving from evidence to recommendations. The framework increases transparency. There will usually be a high evidence grade for the primary target population for a new vaccine, given that the FDA requires RCTs for licensure. The evidence grade may vary for post-marketing observational studies. The EBRWG is proposing to use the evidence framework for new vaccines, and for changes in recommendations for existing vaccines.

Discussion Points

Dr. Baker indicated that Dr. Ahmed's slides had been modified from the version originally distributed and that the revised slides would be disseminated to those present.

Carrying Dr. Schünemann's metaphor a little further regarding Bradford Hill, Dr. Marcy pointed out regarding his colleagues and their role in the hierarchy of evidence for expert opinion, the Ten Commandments were based solely on expert opinion. So, it depends upon the authority and experience of the expert. He pointed out to Dr. Poland that the Edward Jenner Society is perhaps misnamed. A man named Benjamin Jesty inoculated his sons with cowpox 22 years before Jenner did, the difference being that Jenner published. Perhaps there is a message there for anybody in academics. He wondered what would be done in terms of old vaccines and whether they would be subjected to the GRADE approach when they were re-evaluated. Tetanus toxoid, for example, may not stand the test of the GRADE approach. He also noted that Dr. Schünemann and Dr. Ahmed mentioned cost in passing. Zostavax® has told them that they "may build it, but no one may come if the tickets are too expensive." With that in mind, he wondered what the role of cost should be in recommendations beyond all of the scientific evidence presented by the speakers.

Regarding whether to revisit previous recommendations, Dr. Temte responded that the first task is to use the GRADE approach for new recommendations and for changes in current vaccines and assess the performance. At first this system needs to be piloted. There are certain vaccine issues for which they do not want to conduct the "RCT on parachutes." There has to be a lot of wisdom used in this approach as well.

Dr. Schünemann replied that there are many authorities in the GRADE Working Group, some of whom may be more accomplished than the one authority and in the context of many religions. That is, multidisciplinary approaches may be more appropriate and there may be many authorities "bringing the tablets from the mountains." In terms of the integration of resource used, resource use is a very complicated matter. Examining what guideline developers have done throughout the world in terms of integrating resource use in the development of recommendations, many authorities in this field would acknowledge that there is a lot of room for improvement in terms of how this can actually be done to arrive at recommendations that truly consider resource use. A series of papers will soon be published in which this will be discussed in more detail. It does come down to some degree of modeling the outcomes against the resources that are consumed. There are different ways of doing this, one of which may be to take a very pragmatic approach and do this as a "back of the envelope" approach as is being done for many questions in several large organizations. When there is need for more detailed consideration, then detailed modeling should be done.

While she thought they could have a lot more discussion, and they would not know how perfect this system would be until they began to use it, Dr. Neuzil endorsed moving forward with it. SAGE has used this approach and areas have been identified where the framework is not always perfect. Following a major clinical trial and an effective vaccine, it is very difficult to

conduct placebo-controlled trials of newer, better vaccines and placebo-controlled trials in subpopulations (e.g., HIV, pregnant women, specific age groups). Despite this challenge, she maintained that they should move forward nevertheless.

Ms. Rosenbaum raised an additional contextual issue for discussion, the impact of the Affordable Care Act on ACIP's deliberations. This is not the first time that ACIP has been confronted with this issue. With the 1993 addition of the Vaccines for Children Act, the impact of a recommendation has taken on a much greater meaning than it had previously. There have been observations about the impact of recommendations and its translation into vaccine safety discussions. The impact of a recommendation is the same whether it is for universal use or for selected populations in that insurers will be bound by the recommendation for those populations who are covered under the preventive provisions of health reform. With this in mind, she strongly recommended some rethinking of the terminology being used. For example, terms like "grading the evidence" raises problems. They are classifying certain kinds of evidence. The notion of "high quality" versus "low quality" evidence has the potential for significant ramifications because it leads to the implication that certain strong recommendations are based on low quality evidence though they are not. Certain very strong recommendations are based on certain kinds of evidence because, given the totality of the circumstances, the evidence is appropriate. What has occurred in the world of coverage, which ACIP should be concerned about in the larger context, is that there is a belief that RCT evidence is somehow always superior evidence. The parachute example makes complete hash out of that. Because of the potential to misuse and to draw the wrong conclusions from GRADE, if ACIP is going to adopt a formal approach to the weighing of evidence and the transparency of how evidence is connected to recommendations, they should discuss classes of evidence, which classes of evidence came into play in the weighing of the evidence and why, what classes underlie certain recommendations, and universal uses of vaccine versus selected use and not using the word "optional" because that is not an optional use for coverage at all—it is a selected use. While she did not have any objections to the evidence science presented, as a lawyer, Ms. Rosenbaum pointed out that how one uses the evidence and the larger context in which the evidence is being used has real ramifications. She thought they needed to be cognizant in this era of these ramifications and simply modify GRADE to the extent that they apply the terminology that would get them further in the much more complex discussions they would have to have about what evidence goes into a recommendation.

Dr. Cieslak expressed concern that much of the focus was on the safety and efficacy equations, given that for the most part, that was not what ACIP's deliberations tended to center on. At least for newer vaccines, safety and efficacy have been tested in RCTs and ACIP's discussions focus more on who the risk groups are. The Hepatitis Work Group is trying to better understand exactly what the risk is of Hepatitis B among diabetics in the US. This number is difficult to determine. There are various sorts of data that allude to this, but nothing that addresses this directly. He wondered whether it would be possible for GRADE to assist them in grading the quality of evidence of the issues the ACIP discussions tend to center on, such as the quality of epidemiological studies evaluating risk and what the risk is in different groups or cost-effectiveness studies. For HPV vaccine, he was very concerned about assessing the vaccine for males because there were three studies about cost-effectiveness with fairly different results, and it was not clear which of those was the higher quality study. The Merck study showed the lowest cost per quality adjusted life year (QALY) saved. This was a manufacturer-sponsored study, but perhaps it was the best model. He wondered how GRADE could help them to get at those types of questions, which seem to be the pivotal questions for ACIP's recommendations.

Dr. Temte responded that on first pass, when considering a new recommendation, ACIP has always been asked specifically to make recommendations based on safety and efficacy first. Other considerations follow that. ACIP has never been asked to make a recommendation based solely on the cost of a vaccine. In fact, ACIP should be fairly neutral to that based upon its charge. That being said, as time goes on, there are numerous pieces of additional information that ACIP reviews, digests, and puts thoughtful consideration into in making recommendations. They are not proposing to use the GRADE methodology to address questions such as: What is the burden of illness? What is the potential herd immunity effect? While these issues could be approached by the GRADE methodology, Dr. Temte deferred to Dr. Schünemann about that. The consumers and stakeholders who are applying these recommendations on a daily basis are not typically lawyers, but are clinicians who are increasingly familiar with the GRADE approach. Within his academy, they are used to seeing this all of the time and are comfortable using it. He looks at this on a daily basis, especially with Preventive Services Task Force recommendations. They are not as concerned with the specifics, nor are they necessarily influenced. If there is a strong recommendation, even if it is based on very low quality, he will assess this carefully. For example, given the situation with avian influenza and oseltamivir, most physicians would not care what the evidence base was because they would believe it to be the right thing to do.

Dr. Schünemann agreed that it is important to choose the right terms. For example, there are clear gradients involved with the term “class.” He would always like to sit in first class in an airplane as opposed to second or economy class. He believes the gradations that are associated with the term “class of evidence” are relatively similar to “grades of evidence.” He did not believe this made any difference. He thought there was agreement that there is sometimes higher and sometimes lower confidence in evidence, in particular in terms of estimates of effect. For example, a small RCT with 20 patients offers less confidence than an RCT with 2000 patients and many events. Avoiding an assessment of how much confidence there is in an estimate of effect is potentially problematic. That does not mean that they cannot make strong recommendations. They just need to express that their confidence in a strong recommendation may not be as good as it could be at a given time. Modifications are possible, but that would to some degree defeat the purpose of developing systems that can be used and communicated across various departments and divisions. In regard to assessing cost-effectiveness studies, there are critical appraisal frameworks for such studies. Dr. Schünemann believes that the work that needs to be conducted in order to move to recommendations should be based on the systematic reviews that assess efficacy and should be based on new models. He would not suggest using existing cost-effectiveness studies that will not fit the purpose, models, or questions that the Guideline Panel has developed. A starting point is to describe a body of evidence with all of the outcomes believed to be important, and then to consider what associated resources need to be spent in order to implement a recommendations.

Regarding Dr. Cieslak’s question, Dr. Wharton noted that when the FDA licenses vaccines, they are licensed based on safety and effectiveness. When they come to ACIP, they are licensed products. Although the safety and effectiveness information is very important for ACIP’s deliberations, there are a number of other factors that go into that determination that the agency looks to ACIP for, for example: Is it really a good idea to use this vaccine in a particular way in the US population? Factors that contribute to that have to do with the burden of disease and feasibility to use the product in a proposed way. While safety and efficacy concerns are critical, they are not the only issues that matter. Perhaps by the time it comes to ACIP, there are other important factors that must be considered as recommendations are being made.

Regarding the complexity of the issues, Dr. Judson was reminded of Professor Roy Anderson once quoting a mathematician who said that there was no problem in the world, no matter how complicated and how difficult to understand, which when looked at in the right way could not be made to seem more complicated and more difficult to understand. He thought they must be very careful to define the terms and then use them consistently. Additional schemes or approaches to evaluating evidence would probably not be helpful if they simply divided items up slightly differently. It would be very useful if those who work in the area of evaluating evidence to devise a single approach, the outline for which is generally agreed to be standard. As an example, the D category was added for evidence, which he thought he had seen before. However, from the definition "additional complexity that does not add to clarity or ability to discriminate problems" is not going to be helpful. C really translates into "our confidence is limited." D translates to "our confidence is very little." It would be useful to weed some of this out.

Ms. Ehresmann thought it was obvious that they needed to move in the direction of evidence-based guidelines. She appreciated that they would be utilizing the GRADE approach as a pilot, which would give them the opportunity to determine how it works in the ACIP setting. She agreed with the terminology issues, and pointed out that they were discussing this in a group that is very familiar with the subtleties of evaluating. As they thought about moving to this approach, she stressed the importance of thinking about how this will be translated for the general public. Currently when ACIP makes a recommendation, it sounds very confident. Use of the GRADE approach is likely to be very complicated to translate for the public, and must be placed high on ACIP's priority list in addition to evaluating how well this approach works.

With regard to determining the strength of the recommendations, Dr. Englund expressed concern with the issue of cost. She believes that cost is absolutely important, although it should be termed "resource allocation." Determining the strength of recommendation based on cost / resource allocation is a problem, given that this is really a separate issue. Cost changes over time and depends upon the patient population. It is very important for ACIP to not consider cost as just a bullet point. The HPV Work Group has spent an incredible amount of time assessing cost, cost analyses, cost-effectiveness, and grading cost-effectiveness such that when they are presenting the cost-effectiveness they show much more data than would be potentially allowable on the GRADE schema. She expressed hope that the cost issue could be drawn out and even separated as they make recommendations. She believes that decisions in the upcoming decade are going to be increasingly related to cost-effectiveness.

To Dr. Baker, GRADE is an opportunity for ACIP to join together as they have with their important practitioner groups who actually implement recommendations so that there is a single common system.

Dr. Schünemann said that he could not agree more in regard to two issues, the first of which was that they should speak of "resource use" versus "cost." It is important to tease apart what manpower is required in order to implement a recommendation rather than stating what it costs. This will change over time not only across, but also within jurisdictions. Therefore, it is extremely important to disaggregate resource use and label it explicitly. In fact, the second issue relating to the consideration of resources separately was included on one of his summary slides that stated "if relevant, consider costs." Sometimes, much more effort needs to be spent on evaluating resource use, but resource use will always be important. In a 45-minute presentation, it is extremely complicated to address this. Nevertheless, he thought they were in agreement with these comments and simply need to lay this out more clearly.

Dr. Chilton commented that the change in grade of evidence from high to very low to A to D seemed to obscure the actual meaning of those terms. With that in mind, he wondered whether it was necessary to have a table regarding what A to D mean, since they mean the same thing as high to very low.

Dr. Temte responded that the intent, as with any recommendation, is to include a footnote indicating what those mean. GRADE actually provides a luxury of definitions, not to say that the definitions are imprecise, but for example, the Grade A high level of evidence also coincides with an expression of the confidence in the estimate of effect. That would be a very high confidence if the estimate of effect is correct. They particularly liked the way Dr. Ahmed presented this in one of his slides with very brief statements regarding the meaning of confidence in level of effect. A comment was made regarding the difference in a Grade C and D. He believed that ACP had utilized three levels of evidence to address that, basically combining C and D. He thought that had been done with the tacit approval of GRADE as well. They are used to seeing recommendations using a different system of evidence to some extent from the United States Preventive Services Task Force (USPSTF) which uses the grades A, B, C, D, and I. As clinician, Dr. Temte tends to lump A and B together and C and D together. That is the way it is laid out on the electronic tools that integrate with electronic medical record (EMR) systems. Because physicians are used to seeing this all of the time, they have stopped being concerned about the nuances and are more responsive to what this means in terms of operational activities during their clinical day.

As a clinician, Dr. Baker said that she either hears “recommend” or “don’t recommend.”

Dr. Wharton thought Dr. Reingold’s example about the strength of evidence to support the recommendation for use of HPV vaccine routinely and in a vulnerable subpopulation was particularly interesting. The evidence rating was low. The clinical trials that are available at the time of licensure really dictate what is included in the product labeling. There are many questions that are not answered by those clinical trials. One of the great values of ACIP statements is the helpful guidance this committee has provided to address the questions that the clinical trials did not address (e.g., interchangeability of vaccine products, use of vaccines in populations that may not have been included in the clinical trials, et cetera). While she did not know what the EBRWG’s considerations were pertaining to whether the GRADE criteria would be applied to all ACIP recommendations or simply certain key high level ones, but this is an area where there data are sparse or non-existent at the time recommendations are made sometimes. Yet, ACIP has considered the totality of knowledge about vaccines to make those recommendations even in the absence of explicit evidence. This is an issue that is going to need consideration going forward.

Dr. Temte responded that with the GRADE methodology, one of the first tasks is to decide which questions are critical for decision making, which are less critical, and which are not critical at all. For example, the use of rotavirus in a newborn nursery is based largely on expert opinion. Is this a critical component of making a universal recommendation for the use of rotavirus vaccine? It would be on the list, but it would not rank high. Nevertheless, it can be considered. They must learn to live, as they already do, with the fact that a lot of information is going to be based on very well-informed expert opinion that will generalize from other experiences.

To crystallize her observation further, Dr. Rosenbaum said that her concern focused on the application of a recommendation the first time that ACIP is very transparent and makes a strong recommendation based on low quality evidence. Payers are bound by a recommendation and may potentially protest it. Also of concern is safety. It appeared to her that in this taxonomy, it is totally appropriate to make a strong recommendation based on low quality evidence because there are certain situations in which clear evidence is simply lacking and in which other evidence is being used because the circumstance of the situation allow them to draw major conclusions from low quality evidence. If they opt to utilize the GRADE terminology, she strongly recommended that the adoption of the GRADE system be accompanied by a lengthy and very accessible explanation of what they are doing, why they are doing it, how they do and do not intend this adoption to be used, and with the inclusion of many applications showing that there can be an absolute strong recommendation based on what GRADE classifies as lesser quality evidence. Without that, she was extremely concerned with the consequences for the deliberations.

Dr. Ahmed clarified that the terms used (e.g., high quality, low quality, etc) were discussed within the EBRWG. The group would benefit from input regarding exactly what terms to use. He called upon Dr. Campos-Outcalt to discuss this further.

Dr. Campos-Outcalt replied that some of the concerns were addressed with the EBRWG's recommendation. The work group is saying that they believe ACIP should recommend or not and that the evidence is A, B, C, or D. The terminology being discussed was not suggested by this work group. They did have concerns about making a strong recommendation based on low quality evidence, which is why they recommended terminology that avoids this.

Dr. Rosenbaum pointed out that every time they choose a moniker, they will have to explain what it means because it will take on a concept that needs to be clarified with the public in a way that can be addressed.

With all ACIP vaccine recommendations, Dr. Pickering stressed that CDC has excellent communications staff who can help to translate meaning such that the recommendations can be implemented. Two other major issues to consider are the simplicity of the process and the support needed to implement the GRADE system. He called upon Dr. Reingold to discuss what support he found to be needed and what support he had received to utilize this system.

Dr. Reingold responded that the answer depends upon the vaccine. With a new vaccine like HPV, there are relatively few well-done recent studies. Thus, it is not an enormous lift to apply the GRADE approach. However, applying the approach to all of the studies of pneumococcal polysaccharide vaccine is a major lift. Furthermore, the GRADE approach does not guarantee that the two people using it will reach the same conclusions. In fact, their assessment of those studies was challenged by people who had a very different view of the effectiveness of that vaccine. Use of the GRADE approach requires a fair amount of work and someone competent who has the time to work on it is needed. SAGE suffers from the fact that they basically have only one person who assists all of its subcommittees.

Dr. Jim Turner (ACH) went on the USPSTF website where he found that their grading system differed from what was being proposed. It seemed to him that they were going to create additional confusion by devising another grading system.

Dr. Schünemann replied that there is on-going conversation with the USPSTF. With respect to the organizations that have adopted one of the other systems, GRADE has been adopted by many more groups. The criteria being used for evidence evaluation are extremely similar. In the end it comes down to health research methodology. He thought what had occurred with the revision of the USPSTF system was that there was a lot of common ground. There are perhaps some differences in transparency laying out how to move from research evidence to a recommendation. This will always be a work in progress, given that nobody has an answer currently.

Dr. Poland raised a consideration for the future, born of the observation that the science moves quickly but adaptations of that change tends to move more slowly. That is, this discussion centered on a population-based approach, which for the most part is an appropriate approach. However, while they are doing this, the science is moving to an individualized approach. Thus, the caution for the future regards how to address genotypes that code for non-response to Hepatitis B vaccine or increasingly in the future genotypes that will predict serious adverse events.

Dr. Schünemann agreed that science evolves, as will any grading system over time. It is good to begin with a common approach that can be evaluated on the basis of various examples. In terms of moving to individualized medicine, by considering patient values and preferences explicitly, the system addresses some of these aspects (e.g., genetic predictors). This information will frequently come from contextual evidence, observational study evidence, and it will influence a panel's judgment about how applicable a certain body of research evidence is to a certain condition. This evidence needs to be included in ratings about the directness of the evidence, for example.

Dr. Baker pointed out that this was similar to how they currently must deal with high risk groups in the face of little evidence and known high risk.

Dr. Campos-Outcalt said he thought there was more consistency with the USPSTF framework than it may appear. He sees movement toward consistency in that they no longer have "strongly recommended." They just have one category based on A or B level evidence. They also have an "optional" category which is C. Their D is "recommend against." The category they use that no one else has is "insufficient evidence" to say one way or the other, or category I. Very few other groups are willing to do that. Regardless of what system is adopted, an advantage of adopting a system is to establish some consistency within the ACIP itself. Examining the ACIP recommendations over the years, various terms have been used to mean the same thing. This system was used once before in ACIP in the late 1990s for the pneumococcal recommendation. That statement is very clear, very easy to interpret, and it starkly differs from other recommendations that have been made since. He thought there was a lot of value in stating that a recommendation was being based on C or D level evidence, because if nothing else, it drives research. Of the recommendations published currently, 80% are C and D level evidence. That does not stop people from acting on it, but it does point toward where research is needed and drives the research agenda, which is very valuable.

Dr. Samuel Katz (IDSA) pointed out that one problem practicing physicians implementing recommendations face is erosion of public confidence. Practicing pediatricians spend an inordinate amount of time answering questions from parents who have doubts and concerns about vaccines. While he thought GRADE was a fine system for ACIP, his concern pertained to the transparency with which all of their deliberations are viewed by the public. He assured them that within seconds of making a recommendation on evidence B or C instead of A it would be

quickly picked up by the doubters and the anti-vaccine groups. This will be another way for them to exploit the system to enhance public doubt and lack of confidence in what ACIP recommends. Thus, he thought the GRADE system would have to be very carefully utilized by ACIP and the rationale for recommendations would have to be very carefully explained to the public.

Dr. Alexis Elward (HICPAC) reported that HICPAC adopted a modified GRADE system several years ago and had used it to produce two recent guidelines for the prevention of catheter-associated urinary tract infections and a norovirus prevention guideline, which is in draft. HICPAC has experienced a tremendous improvement in their efficiency, consistency, and transparency. They are often in the situation that ACIP may be with older vaccine studies such that there are no RCTs. There is a lot of variation in study designs, and HICPAC has really needed a systematic methodology for evaluating the strength of the epidemiologic evidence. That said, they do have a number of things that are strongly recommended that are not based on evidence. They may be based on regulatory requirements or standard of care, so HICPAC has made those distinctions in the grading system. Their categories include: strong recommendation based on evidence, strong recommendation based on standard of care, or strong recommendation based on a regulatory requirement.

Dr. Sandra Fryhofer (ACP), a practicing general internist who sees patients in her office every day, expressed her excitement about the move toward evidence-based guidelines, transparency, and consistency. As a practicing doctor, with new vaccines there remain many things that are not explained. In the past, ACIP guidance has gone beyond the label to fill in the blanks for practicing physicians. She expressed her hope that ACIP would continue to provide clinical guidance.

Dr. Plotkin endorsed the recommendation of the EBRWG. He thought the GRADE system incorporated expert opinion and public health need into the recommendation, rather than relying on the so-called quality of epidemiologic evidence. What is missing is the biology, which is a particular criticism of the Cochrane analyses. For example, in terms of HPV and the prevention of cancer, there is abundant evidence that the vaccine prevents infection and there is abundant biologic evidence that HPV incites oncogenic transformation. Therefore, it is hardly a leap of reason to say that HPV vaccine will prevent cancer. The same is true with respect to Hepatitis B and prevention of liver cancer, which was not known or proven at the time the recommendation was made for neonatal and other immunization, but it was known that the vaccine prevented infection. As another example, there were no RCTs showing that the rubella vaccine prevented congenital rubella syndrome, but knowledge that it prevented rubella allowed one to make the inference that it also will prevent CRS. Taking into account the biologic information as well as the epidemiologic studies allows recommendations to be made without using the pejorative terms.

Dr. Zimmerman wondered what thought was given to calculating, in a routine fashion, the number needed to treat, or in this case to vaccinate, on a routine basis.

Dr. Ahmed responded that while he did not state this specifically, this is the proposed format for presenting evidence.

Dr. Baker said she heard fairly good consensus on several important caveats.

Meningcoccal 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 conjugate vaccines that were the focus of discussion during this session were as follows:

- Recommended for adolescents aged 11 through 18 years and others at increased risk for meningococcal disease:
  - → $MenACWY_D$ (Sanofi Pasteru) licensed in January, 2005 for persons 2 through 55 years
  - → $MenACWY_{CRM}$ (Novartis) licensed 2/19/2010 for persons 11 through 55 years

- Infant vaccines in late-stage development
  - → HibMenCY (GSK): 2,4,6 and 12-15 months (BLA Filed)
  - → $MenACWY_{CRM}$: 2,4,6 and 12-15 months
  - → $MenACWY_D$ (Sanofi Pasteur): 9 and 12 months

With the increasing number of conjugated meningococcal vaccines, it is necessary to clearly define the abbreviations for each vaccine. The designated nomenclature for these conjugate vaccines is indicated above.

The Sanofi Pastuer vaccine contains polysaccharides from meningococcal serogroups A,C,W-135, and Y conjugated to a chemically detoxified diphtheria toxoid protein. This vaccine had been referred to as MCV4, but will now be abbreviated as $MenACWY_{D.}$ The Novartis vaccine consists of capsular polysaccharide from serogroups A,C,W-135,and Y conjugated to CRM-197, which is a naturally occurring mutant diphtheria toxin. CRM refers to cross reacting material. This vaccine will be abbreviated $MenACWY_{CRM.}$ Three conjugated meningococcal vaccines are under development for use in infants and young children. The GlaxoSmithKline HibMenCY vaccine includes polysaccharide from *Haemophilus influenzae* type b and polysaccharides from meningococcal serogroups C and Y,respectively, conjugated to tetanus toxoid. This vaccine would be administered as a 3 dose primary series followed by a booster dose. The Novartis vaccine also would be administered as a 3-dose primary series followed by a bosster dose. The SanofiPpasteur vaccine would be administered as a 2-dose series at age 9 and 12 months.

During the meningococcal vaccine session at the February ACIP meeting, a cost-effectiveness analysis of an infant or toddler meningococcal vaccination program in the US was presented. This analysis demonstrated that the cost per quality adjusted life year saved was driven primarily by disease incidence and the cost of the vaccine. Based on characteristics of the currently available vaccines and the historically low levels of meningococcal disease in the US, routine immunization of infants and toddlers was felt to be difficult to justify. Major considerations included the following:

- Serogroup B disease accounts for >65% of disease in children <5 years of age and serogroup B is not in the vaccine.
- The peak of serogroup C and Y disease occurs at 4 to 5 months of age, too early in life to be prevented by doses administered at 2,4, and 6 months of age.
- Serologic protection is unlikely to last until 11 years of age, making booster doses necessary in order to maintain protective immunity until the adolescent dose. However, in February 2008, ACIP recommended against routine vaccination of children 2 through 10 years of age except for children at increased risk of disease.

Thus, a general consensus was reached during the discussion that a recommendation for routine immunization of infants or toddlers with any meningococcal conjugate vaccine is not appropriate at this time.

HibMenCY vaccine was not licensed as of the June 2010 ACIP meeting. This vaccine was discussed during the last ACIP meeting, and the work group continued these discussions during monthly conference calls. Discussion focused upon whether the HibMenCY vaccine might be considered as a *Haemophilus influenzae* type b vaccine. A persisting reservation is the concern that this combination vaccine will be more expensive than a monovalent *Haemophilus influenzae* type b vaccine. Even if the cost of HibMenCY were the same as monovalent *Haemophilus influenzae* type b vaccine, the benefit from the Men C and Y components will be low and of limited duration for the general population based on the issues already stated.

In addition, new safety data have become available with regard to the risk of Guillain-Barre Syndrome (GBS) during the 6 weeks following administration of the Sanofi Pasteur vaccine ($MenACWY_{D)}$. In October 2005, the FDA and CDC issued an alert regarding a possible association between GBS and $MenACWY_D$ based on Vaccine Adverse Event Reporting System (VAERS) reports. There was insufficient evidence to conclude a causal association as the number of cases reported within 6 weeks of vaccine administration was not unusual. However, the clustering within 2 to 5 weeks raised a concern. During the next year, in April and October 2006, updates were published in the *MMWR* as additional cases of GBS were reported to VAERS. Because the risk of meningococcal disease clearly exceeded the risk of GBS, routine vaccination with $MenACWY_D$ for adolescents, college freshman living in dormitories, and others at high risk continued to be recommended during this time. However, as a cautionary note, it was recommended that those with a previous history of GBS not receive and $MenACWY_D$ unless they were at especially high risk of meningococcal disease.

During this session, two presentations were delivered pertaining to the risk of GBS during the 6 weeks following administration of the Sanofi Pasteur vaccine, $MenACWY_{D.}$ Dr. Priscilla Velentgas discussed the results of a multicenter, retrospective cohort study sponsored by

Sanofi Pasteur which estimates the risk of GBS among 11 through 18 year old vaccinees during the 42 day period after receipt of MenACWY$_D$ as well as during other time periods. These risks were compared with the risk among non-vaccinees. Eric Weintraub offered an update on VAERS data and Vaccine Safety Datalink (VSD) data in relation to the risk of GBS following MenACWY$_D$ administration. Currently, there is disparity between the package inserts for the sanofi pasteur and Novartis vaccines in terms of classifying the risk of GBS as a contraindication or as a warning. In addition, the *MMWR* statements presently contain various wording for the risk of GBS following vaccination, including those with a history of GBS. Dr. Amanda Cohn addressed these differences and presented the work group proposal for new wording in regard to the issue of GBS following vaccination with meningococcal conjugate vaccines and the issue regarding whether the wording should be the same for all meningococcal conjugate vaccines, and addressed the proposed a change in the recommendation for use of any conjugated meningococcal vaccine in persons with a history of prior GBS.

When the Sanofi Pasteur meningococcal conjugate vaccine was licensed in January 2005, insufficient data were available to address the question of long-term efficacy. The expectation was for vaccine-induced immunity that would last through the college years. Studies now indicate that antibody levels decline over time and because circulating antibody, not immunologic memory, is most important in protection against meningococcal disease, there is concern about susceptibility among college students.

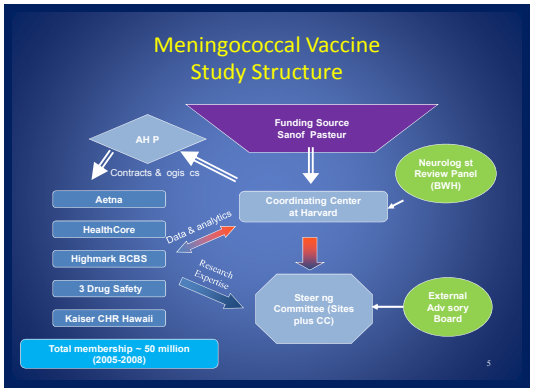
One year ago in June 2009, ACIP voted to recommend a second dose of MenACWYD for persons at increased risk of meningococcal disease because of concern regarding waning immunity. College students whose only risk factor for meningococcal disease was living in on-campus housing were not included in the group for whom a second dose of conjugate vaccine was recommended. Because of this concern for loss of protectiom and return of susceptibility among college students, this topic was discussed by Dr. Cohn who outlined the various options.

Guillain-Barré Syndrome (GBS) After Receipt of Menactra®

Priscilla Velentgas, PhD
Meningococcal Vaccine Study Investigator Group
Department of Population Medicine
Harvard Medical School and Harvard Pilgrim Health Care Institute
Outcome Sciences

Dr. Velentgas reported that the goal of the meningococcal vaccine study was to design and conduct a study with adequate power (e.g., large enough base population) to answer the question of increased risk of GBS following MenACYW$_D$ vaccination. The challenges were that GBS is a rare condition (1/100,000 PY), and prevalence of MenACYW$_D$ vaccination is <10 % overall in the 11 through 18 year old population, and much lower within specific 6-week time window (0.614% estimate). The study required combined efforts of several large health plans (n=10) with active health research divisions. Dr. Velentgas disclosed that funding for this study was provided by Sanofi pPasteur under a contract with the Coordinating Center at Harvard. The contract granted exclusive control over the study protocol and content of study reports and publications to the investigator group. The Data Coordinating Center was located at Harvard. Americas Health Insurance Plans (AHIP) was involved in contracting and logistics for the study. The five research sites included Aetna, HealthCore, Highmark Blue Cross Blue Shield, i3 Drug Safety, and Kaiser Permanente Center for Health Research of Hawaii. All of these sites provided data and analytics for the study, and each of these sites contributed one or more

investigators to be active as part of the study steering committee. This study also had an external advisory board, including a pharmaco epidemiologist from Vanderbilt, a neurologist from Tufts Saint Elizabeth Medical Center, and various others (including Drs. Broder and Iskander from CDC ISO). At Brigham and Women's Hospital, there was a panel of three neurologists who were responsible of adjudication of the GBS cases based on medical record abstractions. The study structure is reflected in the following diagram:



The primary aims of the study were to estimate the risk of GBS among 11 through 18 year old vaccinees during 42 days after MenACYW$_D$ vaccination relative to the risk of GBS among vaccinees at other times and among non-vaccinees, and to estimate attributable risk of GBS following MenACYW$_D$ vaccination. The secondary aims were to identify and describe additional GBS cases among 19 through 21 year olds, and estimate the risk of GBS among 11 through 18 year old vaccinees during the 42 days after administration of other vaccinations (e.g., MPSV4, Tdap, Td, HepB, HPV, tetanus, and influenza). The 19 through 21 year olds were designated as a secondary population because of the concern that the investigators might not be able to identify all vaccination exposures using health plan claims data in this group, given that they represent a largely college age population who may be receiving additional health care at their college health services.

The investigators employed a cohort with nested case-control design. The study population and vaccinations were identified through health plan enrollment data and automated claims data. The primary cohort was comprised of 11 through 18 year olds, and the secondary cohort was comprised of 19 through 21 year olds. A distributed research network approach to data sharing and pooled analysis was utilized. Potential GBS cases were identified through claims data, confirmed through medical chart review, and adjudicated by the team of three neurologists who were blinded to vaccine exposure. A modified Brighton case definition was used [Registered at ClinicalTrials.gov (NCT00575653)].

The case definition that was used for the primary GBS endpoint included three possible categories. A case could meet any one of these categories and be included in the primary endpoint. Most of the cases met at least two of these. The first category was any of the levels 1, 2, or 3 of the Brighton Collaboration GBS case definition, based on draft definition version 17, dated June 22, 2007. The study neurologists developed an additional set of criteria to identify Miller Fisher Syndrome, given that at the time the Brighton Collaboration definition did not include a category for Miller Fisher Syndrome, although this has since been added to the definition. An additional category was included that represented cases for whom a clear

statement regarding a diagnosis of GBS from a neurologist was identified in the medical record in the absence of any contradictory information.
The characteristics of the cohort are shown in the following table:

	No. (%) of Cohort
Total cohort	N=12,589,910
Age at study entry (yrs)	
11-13	4,552,926 (36.2)
14-16	3,007,720 (23.9)
17-18	2,018,042 (16.0)
19-21	3,011,222 (23.9)
Sex	
Male	6,369,250 (50.6)
Female	6,218,810 (49.4)
Length of enrollment (days)	
Mean (SD)	524.4 (415.6)
Range (min,max)	1279 (1, 1280)
Total contributed time (yrs)	18,322,800

With regard to the key results, MenACYW$_D$ vaccination level was 15% overall through May 2008, and nearly 45% among 11 through 13 year olds in 2008. A total of 99 GBS cases were confirmed during the full 18,322,800 person years of observation, translating to an incidence of approximately 5.4/million person years. Over 1.4 million vaccinations were observed. No confirmed cases of GBS occurred within the 6 weeks following the 1.4 million vaccinations. The 95% upper confidence limit for the attributable risk of GBS associated with MenACYW$_D$ was estimated as 1.5 cases per million doses. The investigators concluded that this study provided no evidence of increased risk of GBS associated with MenACYW$_D$. The characteristics of the GBS cases are reflected in the following table:

Cases (N=99)	N(%)
Age at Onset (yrs)	
Mean (SD)	16.7 (2.7)
Median	17
Range (min, max)	10 (11, 21)
Sex	
Male	53 (53.5)
Female	46 (46.5)
Season	
Winter	16 (16.2)
Spring	35 (35.4)
Summer	21 (21.2)
Fall	27 (27.3)
Vaccinations within 42 Days of GBS Onset	
MCV4	0 (0.0)
MPSV4	1 (1.0)
Tdap	0 (0.0)
Tetanus	0 (0.0)
Td	0 (0.0)
Influenza	2 (2.0)
HepB	1 (1.0)
HPV	2 (4.3 - % of females)

With regard to GBS case identification and adjudication, 585 potential GBS cases were identified in claims among 11 through 21 year olds (e.g., identified as having an ICD-9 code for GBS in their medical claims at any time during the study period). Of these, 395 were abstracted and following adjudication included sufficient information to determine case status, 108 of these (~27%) met the primary study endpoint definition, 99 of the 108 cases had onset dates that were confirmed to be during the study period (72 from primary / 27 secondary), and 0 of those following adjudication were found to be exposed to MenACYW$_D$ within the prior 42 days. The investigators commented in the study report that the difference between those identified and those confirmed largely represents rule out diagnoses and in some cases erroneous diagnoses, such as Group B Streptococcus, which were evident following review of the medical record.

In terms of the conclusions, MenACYW$_D$ uptake from initial availability in March 2005 through August 2008 reached as high as 44% among 11 through 13 year olds. This is consistent with ACIP recommendations for vaccination to occur at the 11 through 12 year old well visit. Having identified zero cases of GBS identified within 6 weeks following 1.4 million MenACYW$_D$ vaccinations, an upper bound for the one-sided 95% confidence interval for the rate of GBS in MenACYW$_D$ vaccine-exposed cases using the "Rule of 3" (e.g., 3 cases per 1.4 million vaccines). Using exact binomial confidence intervals yields the same results. Subtracting the expected number of MenACYW$_D$-exposed cases (0.89), which was based on applying the overall confirmed rate of GBS in the rest of the study population to the total person time in the 6 weeks following vaccination, yielded an estimate of the upper bound to the attributable risk of 2.1 cases per 1.4 million vaccines, or about 1.5 cases per million doses.

Regarding the interpretation of the findings and study limitations, there was incomplete retrieval of medical charts for 21% of potential GBS cases, which included 6 cases with MenACYW$_D$ immunization during preceding 42 days. Applying an overall confirmation rate of 27% that was applicable for the rest of the cases, there would be an expectation of having missed 1.6 true cases of GBS with MenACYW$_D$-exposure in the prior 42 days. In comparison, none of the 12 potential GBS cases with MCV4 exposure for whom charts were available were ultimately confirmed following the blinded neurologist adjudication, so there is some suggestion that surveillance bias among MCV4 exposed patients may exist. If the investigators had observed one rather than zero cases of GBS within 42 days of MenACYW$_D$ vaccination, the upper bound on the attributable risk calculated as previously described would be 2.8 excess cases per million doses, with a point estimate of less than one excess case per 10 million doses.

Discussion Points

Dr. Judson inquired as to why the investigators did not conclude that MenACYW$_D$ was associated with a statistically significant lower risk or incidence of GBS. The upper bound was far less than the actual observed non- MenACYW$_D$ recipients.

Dr. Velentgas replied that they did not consider the hypothesis of MenACYW$_D$ being protective with regard to GBS given the overall biologic expectation that immunization exposures could be considered to promote GBS.

Dr. Keitel wondered what the alternative diagnoses were among the cases adjudicated by the neurologists, given that it may be helpful for practitioners to understand potential other diagnoses. Dr. Velentgas responded that Dr. Amato and rest of the team felt that there were a

number of similar syndromes which were evaluated for possible GBS by the treating neurologist, but these ultimately did not meet the criteria for GBS. These included a range of other neuropathies and conditions which ultimately were found not to have a neurological basis.

Dr. Cieslak asked whether vaccine efficacy was assessed.

Dr. Velentgas indicated that the investigators did not compute vaccine efficacy.

Menactra® and GBS: Summary of VAERS & VSD Rapid Cycle Analysis Data

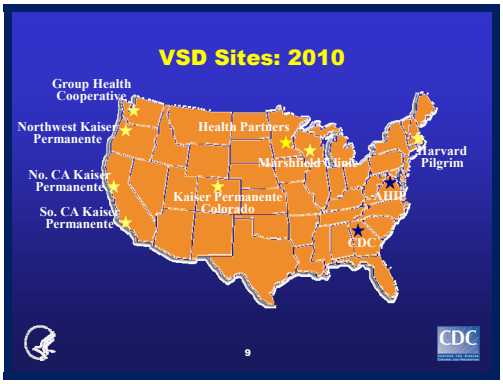
Eric Weintraub, MPH
Immunization Safety Office
Centers for Disease Control and Prevention

Mr. Weintraub presented an update on Menactra® and GBS based on examination of VAERS and VSD Rapid Cycle Analysis (RCA) data. He apologized for using the term Menactra® in the presentation, but he did not want to confuse people with the acronyms.

Within 6 weeks of receiving Menactra®, VAERS confirmed reports of GBS to date included 42 confirmed reports for ages 11 through 19, of which 8 were ages 11 through 14 and 34 were ages 15 through 19 (which is one of the areas that was cause for the level of concern and the additional meningococcal vaccine study and the additional follow-up of the RCA VSD study). Of these, 17 were Brighton Level 1; 22 were Brighton Level 2; and 3 were Brighton Level 3. One of the MenACYW$_D$ / GBS reports had GBS twice before this incident and both diagnoses occurred after receiving a tetanus-containing vaccine. According to sanofi pasteur, the total number of Menactra® doses distributed from 2005-2009 was 25,049,486.

Temporal clustering has been consistent since early in this investigation (2005-2006). The onset interval of the 42 cases was between days 2 and 37. The mean was about 16.7 days. When a temporal scan statistic is done, there is a significant cluster in days 10 through 15 (p=.002). This finding, along with the slight elevation potentially in the disproportionate number of cases in the 15 to 19 year olds, was why the meningococcal study was done and why there has been continual follow-up in the VSD and continued RCA.

The VSD was established in 1990. It is a collaborative project among CDC and 8 managed care organizations (MCOs) shown in the following map:



The VSD allows for planned immunization safety studies as well as timely investigations arising from hypotheses from medical literature and pre-licensure; reports to VAERS; and changes in immunization schedules or the introduction of new vaccines. It is important to highlight that the

VSD now conducts what is termed RCA. The VSD population collects medical care and vaccination data on more than 9.2 million members annually (3% of the US population). As of December 31, 2008 2,239,219 children under 18 years of age were enrolled (3.0% of the US population) and 7,235,448 adults ≥18 years of age are enrolled (3.2% of the US population). The average yearly birth cohort is ~ 95,000.

In terms of RCA, for each vaccine, specific outcomes to monitor are selected. Each week, the number of outcomes in vaccinated persons are evaluated and compared to the expected number of outcomes based on a comparison group. This is hypothesis testing, not data mining. To simplify this, maximized sequential probability ratio testing (maxSPRT) is utilized.

The VSD has conducted RCA for Menactra®. The VSD lead site is Harvard Pilgrim Health Care, and Tracy Lieu is the principal investigator of the study. Investigators have been continuous monitoring predefined outcomes (e.g., GBS, Bell's Palsy, thrombocytopenia, seizures) since 2005 for 11 through 19 year olds. Since mid-2008, the only outcome that has been continually monitored is GBS because of power and continual concern. The case definition for GBS for signal detection included the ICD-9 Code 357.0; the exposure window of interest was days 1 through 42; and the diagnosis of GBS could occur from any location (e.g., hospitalization, outpatient visit, or emergency room visit). The incident definition for the automated codes was a first event within 42 days, which allowed for the opportunity to collect a few more cases. Diagnoses were confirmed with chart review.

One of the difficulties with a vaccine such as this is that it is very cyclical in its uptake. For example, every August there is a peak in uptake, which was an original concern from one of the VAERS findings in 2005-2006. As the ACIP recommendations slightly changed in 2006-2007, there was a shift to giving vaccine more in the older age group. The predominance of the doses in VSD currently are given to the younger age groups (11 through 14 year olds).

About 889,684 doses administered at 8 sites in the VSD (538,596 in 11-14 year olds; 351,088 in 15-19 year olds. The number of GBS cases observed in the automated data was 5, and 4 of the 5 had simultaneous vaccinations. After chart review, there were no true cases of new onset; 2 had a pre-existing GBS diagnosis; 1 had a related diagnosis, not GBS (e.g., chronic inflammatory demyelinating polyneuropathy: CIDP); 1 had "rule out GBS" and a different subsequent diagnosis (numbness and tingling in lower extremities, muscle strain, was also reported to VAERS); and 1 had onset of symptoms on day 0, which was not within the formal risk window. A handful of CIDPs occur following all other vaccinations that have caused some confusion when evaluating GBS.

In summary, VSD has observed 0 cases following 889,684 doses. The current plan is to stop monitoring routinely for GBS following Menactra®. However, surveillance may continue depending upon the statistical approach when monitoring the new meningococcal $MenACYW_{CRM}$ (Menveo) depending upon the uptake within the VSD sites. The RCA protocol for $MenACYW_{CRM}$(Menveo) is currently being developed, and GBS will be included.

The true strength may be in combining the two very large post-licensure studies (the Meningococcal Vaccine Study and the VSD RCA Study). The best ascertained background rate of GBS in this age group is from the Meningococcal Vaccine Study with 99 GBS cases confirmed during 18,322,800 person years (5.4/million person years). Combining the two studies, there are over 2.3 million Menactra® vaccinations. Within 6 weeks (e.g., days 1-42) following vaccination, 0 confirmed cases of GBS occurred. Using exact statistics, the upper 95% confidence limit for the attributable risk of GBS associated with $MenACYW_D$ is estimated as 1 case per million doses. The two studies provide no evidence of an increased risk of GBS associated with $MenACYW_D$.

Meningococcal Conjugate Vaccines and Guillain-Barré Syndrome

Amanda Cohn, MD
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Dr. Cohn reviewed the Meningococcal Work Group's interpretation of the data just presented pertaining to GBS. GBS is an autoimmune acute inflammatory demyelinating polyneuropathy, which causes progressive symmetric weakness in the arms and legs. The incidence is approximately 1/100,000 and is even lower in children and adolescents. Therefore, the prevalence of adolescents with a history of GBS will be extremely low. There are case reports of post-vaccination GBS, but there is no estimate of incidence. Cases of GBS were detected after administration of Menactra® through VAERS reports in 2005-2006. These reports, as Mr. Weintraub described, were clustered with onset dates approximately 2 weeks after vaccination. One case had a prior history of two episodes of GBS post-vaccination. There were no fatalities, and most patients fully recovered. At the time, analyses of VAERS data using background GBS rates suggested a small increased risk in excess of 1-2 cases per million Menactra® vaccinations.

In response to these initial VAERS reports, a contraindication for persons with a previous history of GBS for $MenACWY_D$ was added to the FDA package insert for Menactra®. ACIP added precautionary language for persons with a history of GBS. A risk-benefit decision analysis was initiated and the Harvard-Pilgrim Study was initiated. The decision analysis was presented at ACIP and strongly favored vaccination. 2397 QALYs were saved by vaccination compared to 5 QALYs lost by excess GBS cases. The risk for meningococcal disease lasted for several years, while the risk for GBS pose-vaccination was time-limited to six weeks. Long-term sequelae and deaths were more common with meningococcal disease. Sensitivity analyses did not change the conclusions of this risk-benefit analysis, even at an excess risk of 10 cases of GBS / million doses of Menactra® vaccine [Cho et al. Vaccine, 2010: 817-822]. Data from the VSD and Harvard Pilgrim Studies were both large undertakings, as a large population source was needed to detect a small risk. Combined, over 2 million doses of meningococcal conjugate vaccine were given, and there were zero associated GBS cases. Of note, these studies examine the risk in the general population and not in persons with a history of GBS.

The work group has been contemplating how these new data should inform the issue of the precaution for persons with a history of GBS. The current ACIP language reads, "Persons with a history of GBS might be at increased risk for post vaccination GBS; therefore, a history of GBS is a relative contraindication to receiving MCV4" [CDC MMWR, August 2007]. The Menactra® FDA package insert states, "Known history of Guillain-Barré syndrome is a contraindication to vaccine administration." The warning section of the FDA package insert for $MenACYW_{CRM}$, Menveo®, indicates that, "Data are not available to evaluate the potential risk of GBS following administration of MENVEO."

The work group agreed that no risk for GBS after vaccination with $MenACWY_D$ was detected in two large studies, and extrapolated these data to conclude that persons with a history of GBS are not at higher risk than they are after any other vaccine. Persons with a history of GBS are at a higher risk for another episode of GBS than the general population. There was consensus that these data are sufficient to support policy change. The work group discussed that language around the risk for GBS should be general for both licensed vaccines.

In the revised meningococcal vaccine ACIP statement, these new data on risk of GBS will be added. Proposed draft language pertaining to data interpretation would be included the background section to read:

- No risk for GBS after vaccination with $MenACWY_D$ was detected in two large studies. There were no cases of GBS in pre-licensure clinical trials of $MenACWY_{CRM}$.

- There is no data on the risk in persons with a history of GBS. The likelihood of coincidentally experiencing GBS after $MenACWY_D$ is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. [Influenza ACIP statement, 2009].

For the recommendation itself, including the precautions section, the work group has discussed three options:

1. Remove precaution for all persons with a history of GBS
2. Maintain precaution only for persons with a history of post-vaccination GBS
3. Make no changes to current language: "Persons with a history of GBS might be at increased risk for post-vaccination GBS; therefore, a history of GBS is a relative contraindication to receiving $MenACWY_D$ or $MenACYW_{CRM}$ vaccines."

Among the work group members there was support for Options 1 or 2. Most of the work group members supported Option 1 because this precaution was added based on an estimate of risk that the current data do not substantiate. Language should be similar for other vaccines with no associated risk of GBS. There was some support of Option 2, given that persons with a history of post-vaccination GBS may be at risk for another episode after any vaccine. Regardless of preference, there was strong support for ACIP to address the issue of post-vaccination GBS in the context of general vaccine safety rather than specifically for meningococcal vaccine. That is, work group members are not against Option 2, but many feel that this statement does not belong specifically in the meningococcal conjugate vaccine recommendations. There was strong consensus against Option 3.

In terms of language for the precaution regarding persons with a history of GBS, the work group requested that the full ACIP consider the following options:

- "There is no evidence that persons with a history of GBS are at increased risk for GBS after vaccination with meningococcal conjugate vaccines."
- "A history of GBS with onset within 6 weeks after vaccination is a precaution for MenACWY vaccines."
- Make no changes to the current language: "Persons with a history of GBS might be at increased risk for postvaccination GBS; therefore, a history of GBS is a relative contraindication to receiving $MenACWY_D$."

Discussion Points

Dr. Baker congratulated the work group and investigators for a yeoman's job of addressing a very concerning safety issue that arose shortly after the recommendation for this vaccine.

Given the lack of association observed in the two large studies, Dr. Sawyer wondered how else the clustering seen in VAERS dada might be interpreted (e.g., reporting bias, some other potential explanation).

Dr. Cohn responded that it was thought to be due to reporting bias in that more cases were reported during that time period.

Regarding the two cases with pre-existing GBS diagnoses, Dr. Temte wondered whether they were seeing cases of another report from a case that started right before.

Mr. Weintraub replied that he was pretty sure this was a follow-up visit for a prior diagnosis rather than a recurrence of GBS. He did not believe they were cases with a history of GBS. He thought it was a prior diagnosis closer to the time of vaccination.

Dr. Temte reported that he had seen two cases of CIDP, both of which were associated with vaccines. This really jumps to the forefront for him because when it first appears, it looks just like GBS. It is only after appropriate treatment and recurrence that the diagnosis is known to be CIDP. He was curious about why this was pulled out separately.

Mr. Weintraub responded that this was because of the chronic nature of CIDP, and because it was not believed that it was anything related to prior vaccinations. That was just the ultimate diagnoses. It has come up in another study the VSD is conducting in which a lot of CIPDs occurred and there was confusion with regard to how to treat CIDPs in relationship to the GBS cases.

Dr. Iskander pointed out that an estimated attributable risk of 1 to 2 per million is essentially accepted as a matter of policy for seasonal influenza vaccine. That is accompanied by a precaution for persons with prior GBS. Certainly, they are dealing with a younger population with meningococcal vaccine that is expected to have a lower baseline incidence. Contraindications and precautions are typically at the level of the individual patient. In speaking with clinical colleagues who are neurological specialists in GBS regarding whether there should be precaution or whether in some cases there might be benefits to vaccinate those populations, this can be a tricky clinical question.

Mr. Weintraub indicated that the temporal scan statistic has been difficult to interpret because it has been consistent since early on. It is important to highlight that when clustering or aberration is observed in VAERS, the next step would be to conduct large epidemiological studies, which is what was done in this case.

Dr. Wharton's recollection of the original VAERS data was that the increase in risk, if there was any, appeared to be in the older adolescents (15 to 19 year olds). Given that there was a broad age range examined in these two large studies, and understanding that there were no cases observed in the 15 to 19 year olds, she wondered what the upper limit of the 95% confidence interval was for that population group.

Dr. Velentgas did not calculate this.

Mr. Weintraub also did not calculate this. He reminded everyone that Dr. Sawyer had suggested previously that calculations be done for the 18 to 19 year olds. Also interesting about the five automated VSD cases was that only one was in the older age group.

Dr. Marcy noted that 40% of the doses were in 15 to 19 years, but 80% of the cases were 15 to 19 year olds. He wondered what the explanation was for this.

Mr. Weintraub replied that this was in VSD and that it is difficult to interpret what happened in VAERS in the rest of the country in terms of where the doses are actually going. He could only attest to what they observed in VSD. What they witnessed in the Menactra® vaccine study was that no cases were observed. One of the issues is that this is an extremely rare outcome. To find very small risks, they would need to assess an even larger population than they had (2.3 million doses). The amount of doses would probably have to be doubled in order to find minimal risks.

Dr. Baker noted that this showed the importance of a chart review versus just using ICD-9 codes in a rare disease that can be confused with other neurologic complications. Dr. Ben Allis was on the committee when this safety signal was first observed. Even though there were three cohorts (11 to 12 year olds, 15 year olds, and 18 year olds), the greatest uptake with the first season of the recommendations coincided with

Campylobacter season and was in the older adolescents (e.g., those going to college). There is now a much different distribution of how vaccines are being given.

While she recognized that the package insert was not within ACIP's purview, Dr. Keitel pointed out that whatever decision ACIP made would have to be reconciled by practitioners with the package insert.

Dr. Cohn replied that the work group discussed this issue. Their perception was that it is unlikely that the package insert from the FDA can be changed. The problem was that she was not sure that no risk could be proven. The work group was comfortable with the discrepancy in the package insert. In fact, the discrepancy existed already as there is not a contraindication in ACIP's current language.

Dr. Baker added that practitioners have already been coping with this for three years. The information that ACIP had early on about the benefit from immunization versus the risk of GBS has been helpful in guiding practitioners. She wondered what "relative contraindication" meant and whether it was the same as a precaution. If it was a precaution, then she thought they should say "precaution." A contraindication is consistent with the package insert.

Dr. Cohn responded that this occurred just as she began working on this work group. She did not put the rest of the language in this statement, but there is an additional sentence that describes this somewhat better that addresses providers evaluating the benefits and risks of vaccination prior to making a decision. She agreed that "relative contraindication" was not that clear.

To Dr. Baker, "weighing benefits and risks" suggests a precaution not a "relative contraindication." Relative to what?

Dr. Judson strongly agreed that the term "relative contraindication" would not be helpful to clinicians.

Dr. Sumaya reported that the General Recommendations Work Group had a similar issue in that they had language for a "true contraindication" and grappled with how that differed from a "contraindication."

Dr. Messonnier indicated that the Meningococcal Work Group felt strongly that the language in Option 3 should be struck since it was not helpful, but he had not heard much discussion yet about Option 1 versus 2.

Dr. Sawyer requested that Dr. Sumaya or others from the General Recommendations Work Group remind them what was included in the general recommendations about GBS.

Dr. Cohn responded that there was currently no language about this issue in the General Recommendations.

Dr. Pickering added that the general recommendations will follow what ACIP stated for the recommendation for that vaccine. They will not develop a new recommendation. The wording should be similar.

Dr. Neuzil said that she favored Option 1, given that she had not yet seen any evidence that supported Option 2.

Dr. Cieslak expressed confusion by what seemed to be a slight difference between Dr. Cohn's slide 11 that read, "Option 2: Persons with a history of post-vaccination GBS may be at risk for another episode after any vaccine" and slide 12 that read, "a history of GBS with onset within 6 weeks after vaccination."

Dr. Cohn clarified that slide 11 was not the option. It simply explained the reason why the work group members considered that option. Slide 10 is actually the option.

Dr. Cieslak wondered what was the intent. Was it that people with any history of GBS are likely to react to vaccines in the future, or that people who have reacted with GBS within 6 weeks following a vaccination?

Dr. Cohn clarified that it was within 6 weeks after a vaccination.

Dr. Englund supported Option 1, given that the goal of ACIP is to make evidence-based recommendations. Option 1 is evidence-based and Option 2 is not.

Ms. Ehresmann supported Option 1 as well. In terms of Option 2, if they really believed that there was an issue with regard to a history of post-vaccination GBS from any vaccine, this should be discussed and included in the general recommendations and not added to each vaccine recommendation.

Dr. Judson noted that on the larger study, all of the other vaccines were tracked as well. He wondered whether the results relative to other vaccines were sufficiently powered. That is, aside from GBS after the 1976 swine flu vaccine, was there any conclusive evidence that GBS was more likely to occur after any other vaccine?

Dr. Velentgas responded that they did not make the same calculations regarding upper limits of attributable risk for the other vaccines. To answer this question comprehensively, she would need to bring in the denominators of the number of vaccines observed for each of the other vaccine types assessed. This varied depending upon the vaccine. Nevertheless, the study is capable of further assessing this.

Dr. Sumaya was unclear and unsettled about Option 1 (slide 12) because it began with "there is no evidence." He wondered whether that was saying the same thing as "after sufficient study, there is no evidence." His concern regarded whether this had been sufficiently studied.

Dr. Cohn replied that the work group members felt that this issue had been sufficiently studied, and they did discuss what constituted "sufficiently studied."

Dr. Offit, a work group member, pointed out that the thinking of the work group was that if any of the terms "contraindication" "relative contraindication" or "precaution" were used, people would be less likely to administer the vaccine than for a child who had a previous history of GBS. As always it is a matter of weighing relative risks. The question is: What is the risk of getting GBS following meningococcal conjugate vaccine in a child who has had GBS? This is arguably theoretical and, as far as is known, is higher than the risk of getting meningococcal disease, which is a real risk. The work group did not want to elevate a theoretical, non-existent risk over a real risk and, therefore, did not want to use the term "precaution" because they thought it would limit use. In terms of how many studies are enough, this has been studied enough for the work group to be very comfortable that the risk of GBS following meningococcal conjugate vaccine in a child who has had GBS is less than the risk of getting meningococcal disease. Thus, the majority felt comfortable with Option 1.

In the spirit of transparency, Ms. Rosenbaum wondered whether they had to say that this is not a situation in which an RCT could be conducted of people with this condition who were and were not given the vaccine, and that given the evidence made available, there was no evidence of increased risk.

Dr. Temte responded that the context for the evidence-based approach to vaccine recommendations was aimed primarily at the major recommendations (e.g., universally recommend or not). All of these small nuances do not go into a generalized recommendation for a vaccine. It will be nearly impossible to find evidence for the small things. If a study showed no effect, they could say that there was ample evidence, but they could not say that if they had nothing. Rather than cluttering all of the recommendations and statements with expert opinion, they are choosing not to do so and are leaving the evidence-based systems for the large recommendations that have effects on large populations.

Ms. Rosenbaum stressed that they must be very clear about how they are using the discussion from earlier in the morning. They must be very clear with the public about when ACIP will not be using the GRADE system. As a layperson, she felt confused about this.

Dr. Baker reminded everyone that once the FDA licenses a vaccine, ACIP is on the readiness path to make a recommendation or not to make a recommendation. That is the charge of the ACIP. When ACIP made the recommendation for the first licensed meningococcal conjugate vaccine, there was a safety signal and it was taken seriously. There was nuanced evidence for a very small number of people, and it did not sound to her as though the GRADE process was meant to be applied to such nuances.

Dr. Temte replied that it could become overly-complicated if a clinician received 20 different instructions for any vaccine. He agreed that ACIP must be very clear about when GRADE would be applied. The approach is not to hobble ACIP or clinicians with too much information. With any recommendations ACIP makes, they can assess the nuances, and if they wish to address a sub-categorization of patients, they can. For example, dealing with genomics issues could become an impossible task.

Dr. Marcy thought they were forgetting that people who get GBS may be different and that there are data to substantiate this. There are reports of people who have gotten GBS following tetanus vaccine who were given the vaccine two more times. Each time these individuals got GBS. "Unable to evaluate the risk in persons with a previous history of GBS" is not the same as "there is no evidence." That is an important difference. The total number of people who get GBS within 6 weeks of vaccination in the entire country is probably a few 100 people. However, they should at least err on the side of conservatism for those few people in the entire country who had a prior reaction with vaccination. Dr. Marcy supported Option 2.

Dr. Cieslak noted that while the statement in Option 1 that there is no evidence is a true statement, it is misleading in that it suggests that this has been assessed. However, they had no power to examine the specific issue of people who have had an episode of GBS previously. Therefore, his preference was either to say nothing about the issue or to say that the data are insufficient to comment on this.

Dr. Messonnier referred everyone to the proposed background language that goes with this entire section, which reads, "No risk for GBS after vaccination with MenACWY$_D$ was detected in two large studies. There were no cases of GBS in pre-licensure clinical trials of MenACWY$_{CRM}$. There is no data on the risk in persons with a history of GBS. The likelihood of coincidentally experiencing GBS after MenACWY is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome."

Dr. Keitel inquired as to whether this should be included in every individual vaccine recommendation.

Dr. Baker stressed that the GBS and Menactra® issue arose because of an early signal after licensure. In fact, the FDA almost pulled Menactra®'s license based on minimal information and a small cluster of GBS cases in a short period of time. RCTs are not likely to be conducted given the risks-benefits, nor is it probable that there will be motivation to conduct more very expensive studies in light of the ones that have already been conducted.

Dr. Schuchat pointed out that it was worth remembering that there was a signal detected at the beginning of use. At pre-licensure, there would not have been sufficient use to detect the kind of low rate that the signal implied. The original question upon which the two large studies focused related to the risk in the general population. The

signal was detected and the issue was that some interim approach was needed that focused on the group considered to be at possible higher risk (e.g., those with previous GBS). Language was crafted (that people now do not like) but which was a compromise to alert clinicians that they should be cautious with those who experienced previous GBS following vaccine while other studies were being conducted on the general population. Regarding the question pertaining to whether this was needed in every statement, she thought that when there was a signal, it was important to say something about it because they are not erasing history. Three *MMWR*s address this issue. In terms of the question regarding what is known about those with previous GBS, vaccine trials are never going to be conducted in such people, so this is beyond the policy.

If ACIP voted for Option 2, Dr. Keitel pointed out that they would then be hypothesizing biological plausibility that there is a subset of individuals who may be susceptible to developing GBS after any vaccine. Hence, if ACIP voted for Option 2, they would have to grapple with the issue about all other vaccines.

Dr. Schuchat noted that the risk of GBS has been associated with preceding infections. Particularly in the influenza literature, there is an issue of whether a vaccine is going to increase or decrease the risk of antigen-related GBS. Anyone with preceding GBS still might be better off with prevention of a common infection that is potentially a risk. It is difficult to generalize from one vaccine to another in all people with GBS.

Pertaining to Dr. Cieslak's comments, Dr. Iskander pointed out that there is a well-documented positive re-challenge with this vaccine. While he did not "have a dog in the fight" between Options 1 and 2, the wording as it stood was not in the spirit of the evidence discussion held earlier in the morning. While there is no controlled evidence, they do have a re-challenge that was part of the initial signal. Again, it may be suggested as evidence that supports a subset with increased risk, but if ACIP was going to consider Option 1, he thought they needed to tackle the precision of the wording because he did not think it was factually accurate as stated.

Given that evidence was supposed to be important to them, Dr. Baker thought that ACIP was reassured by the data that in the general population, this vaccine is not associated with onset of GBS within a biologically plausible period of time. The rarity of immunizing people who have prior GBS with this vaccine will never allow ACIP to state that there is no risk, increased risk, or so forth.

It was not clear to Dr. Campos-Outcalt in Option 2 whether the second line pertained to GBS following meningococcal vaccine or following any vaccine. He thought this needed to be clarified and noted that there is an incidence of 1 / 100,000 for GBS over a 10-year period may be 1 / 10,000; the risk of getting meningococcal dusease is 1 / 100,000; and there is a 1 per billion chance of not vaccinating someone and them getting meningococcal disease.

Ms. Ehresmann commented that the proposed background language was pretty explicit in terms of the issues, and they were debating two additional statements for a vote. She wondered whether it would be sufficient to include the proposed background language and then not use the stronger language. That seemed clearer and might capture the issues people were raising.

Having heard the discussion and some discontent with the specific language in Options 1 and 2, Dr. Baker proposed that the work group revise the wording during the lunch break and present it upon reconvening.

Meningococcal Conjugate Vaccines and GBS Revised Language for Vote

Amanda Cohn, MD
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Dr. Cohn summarized the working group's perspective on this issue. There were VAERS reports of GBS following receipt of Menactra®. Two large epidemiologic studies were conducted, and in the meantime a precaution was included in the meningococcal statement for persons with a prior history of GBS. Now that the two epidemiological studies have basically disproven that there was any evidence of increased risk after receipt of Menactra®, the work group essentially believed this vaccine to be the same as any other vaccine that has no association with GBS. The language of the ACIP recommendation was not revised. Instead, the actions were revised. Thus, the work group proposed the following:

- Remove any language with precautions about persons with a history of GBS from the meningococcal statement

- Include an extensive background section, including the draft language presented earlier. The background would discuss the history of the VAERS reports and the data from the subsequent studies showing no risk of GBS after MenACYW$_D$ in the general population.

- The General Recommendations Work Group should address the issue of post-vaccination GBS, and consider language to provide guidance for persons with a history of post-vaccination GBS. The meningococcal work group felt that this risk-benefit would differ for each vaccine, but the general recommendations could address the issue for all vaccines together, even though the actual risks and benefits would have to be weighed for each individual vaccine.

Discussion Points

Dr. Judson thought that in general, they should avoid providing information that neither ACIP nor the readers of the recommendations could understand or interpret. Since there is no quantitative objective risk-benefit data for people receiving any vaccine with a history of post-vaccine GBS, a statement that risk-benefit will be different for each vaccine is not useful.

Dr. Cohn clarified that the difference was that the risk for disease would be different for each person. Persons with a history of post-vaccination GBS are a different group of individuals and they very well may be at risk for another episode of post-vaccination GBS. Then consideration

must be given to which vaccine is being given and the risk for that particular disease. For example, a microbiologist working with *Neisseria meningitidis* in the laboratory might still be given meningococcal conjugate vaccine; whereas, a healthy adolescent may not be given the vaccine.

Ms. Ehresmann liked the compromise language, and thought it was very appropriate to address vaccination in persons with a history of post-vaccination GBS in the general recommendations as opposed to including individual statements. She wondered whether a vote was necessary.

Dr. Messonnier replied that the work group felt that ACIP should vote on the removal of the precaution from the meningococcal section. The second component outlining what will be included in the background and the suggestion of the actual recommendations for the General Recommendations work group, and if there are changes in the General Recommendations, those would be presented to ACIP for a vote.

Dr. Baker inquired as to whether there would be a *Notice to Readers* changing the relative contraindication.

Dr. Messonnier replied that they would be happy to hear input on this. Dr. Cohn is in the midst of preparing a revision of the statement since it has been 5 years since the last statement. Given that there have been so many *Notices to Readers* in the interim, they would not suggest highlighting this specifically in a *Notice to Readers*. Instead, they would suggest incorporating it into the revised statement.

Dr. Marcy thought that because most practitioners do not read the general recommendations, every vaccine statement presented should include the following language, “The recommendation regarding persons who have previously had GBS are applicable to this vaccine as they are to all other vaccines.” Otherwise it would be missed.

Ms. Rosenbaum expressed concern about changing anything in a published statement without an explanation of why it was changed.

Dr. Baker clarified that there would be an explanation.

Dr. Messonnier stressed that the background section would include the complete story of how this occurred and why.

Dr. Meissner inquired as to when the next edition of the general recommendations would be published.

Dr. Pickering responded that the General Recommendations were making their way through clearance, so if they wanted to include the statement in this edition, they would probably need a motion to refer it to the General Recommendations Work Group.

Dr. Messonnier indicated that CDC would update the Vaccine Information Sheet (VIS) quickly.

Dr. Chilton pointed out that the background statement as written was incorrect. It was not that there was “no risk after MenACYW^{D},” it was that there was “no risk of GBS due to” because there is a risk of GBS in the period after immunization.

Dr. Cohn responded that “there is no increased risk,” which she would clarify.

Motion: Meningococcal Recommendation

Ms. Ehresmann made a motion to remove the precaution from the meningococcal statement, and to submit this to the General Recommendations Work Group. Dr. Sawyer seconded the motion. The motion carried with 13 affirmative votes, 2 abstentions, and 0 negative votes.

Update on the Adolescent Meningococcal Vaccination Program

Amanda Cohn, MD
LCDR, US Public Health Service
Advisory Committee on Immunization Practices

Dr. Cohn presented an update on the adolescent meningococcal vaccination program, and brought to the ACIP's attention the question regarding whether the current recommendations for adolescents meets prevention goals. In August 2007 after initial issues with vaccine supply were resolved, ACIP expanded the meningococcal recommendation to all adolescents, but secifically, the vaccine was preferred at the 11 to 12 year-old visit as part of the adolescent vaccination platform. Vaccination was also recommended for adolescents 13 to 18 years of age who were not previously vaccinated. There are currently two licensed conjugate vaccines for meningococcal disease, $MenACWY_D$ and $MenACWY_{CRM.}$

The work group has continuously revisited the issue of adolescent vaccination to ensure that the program will prevent the majority of serogroup C and Y cases among adolescents. Five years after the initial recommendation, children vaccinated at 11 to 12 year olds are entering the period of increased risk at 16 to 18 years of age. Children initially vaccinated at 13 to 14 year olds are now entering or are in college. Increasing evidence of waning immunity has led the work group to be concerned that vaccinating 11 to 12 year olds may not protect a child through college.

In terms of whether the current program meets prevention goals, these goals were to protect during the peak in risk during late adolescence and to protect college students, especially college freshmen living in dormitories who have been shown previously to be at increased risk. The strategy is to vaccinate prior to the period of increased risk to ensure high coverage and potentially induce some herd immunity during the period of risk.

Dr. Cohn reported on coverage with $MenACYW_D$ among 13 to 17 year olds determined by the National Immunization Survey for Teens 2006-2008. In all age groups, steady increases have been observed each year in coverage. In 2009, overall coverage was approximately 40%, but coverage ranged by state from less than 20% to greater than 60%. The 1994 cohort was the first cohort eligible who turned 11 after the 2005 $MenACYW_D$ recommendations. In the 1994 and 1995 cohort, most children who have been vaccinated received the vaccine at ages 11 to 12. The National College Health Assessment assesses undergraduate vaccination coverage among participating colleges. Data from the 2009 survey show that although no colleges had greater than 90% coverage, a majority of colleges had coverage between 60% to 89% and very few had less than 30% coverage.

In summary, meningococcal vaccination coverage is increasing. While coverage varies by state, this increasing trend is expected to continue. There is also a trend toward the 2007 recommendations in that more adolescents are being vaccinating at 11 to 12 years of age, which has implications for the discussion regarding duration of protection. The majority of surveyed colleges have achieved high coverage.

Regarding the current epidemiology of meningococcal disease in adolescents, rates of disease among 11 to 14 year olds are similar to the rest of the population. Rates begin to increase around age 15 and remain higher until age 21 to 22 [Active Bacterial Core surveillance (ABCs); Rates of Meningococcal Disease (A/C/Y/W-135) by Age, United States, 1999-2008]. The meningococcal recommendations are focused on decreasing this period of increased risk.

In terms of rates of serogroup C,Y,W-135 meningococcal disease among adolescents compared to younger and older age groups, rates of disease were cut in half in the two year intervals from 2006 and 2007, to 2008 and 2009. This is the first evidence of vaccine impact on rates of disease among adolescents. However, these same decreases were not observed in infants less than one year of age or adults. The same decreases were also not observed for serogroup B disease in adolescents.

With respect to meningococcal conjugate vaccine effectiveness, last June a simulation model was presented to ACIP that modeled breakthrough disease to give a vaccine effectiveness for meningococcal conjugate vaccine. These data suggest the vaccine effectiveness of $MenACWY_D$ to be 75% to 85%. CDC is conducting a case-control study evaluation of vaccine effectiveness, for which preliminary data will be available in October. Results are likely to be similar to modeling estimates. These estimates are lower than the estimates from the MenC vaccination program in the UK, which was 93% to 96% effective in adolescents. However, some of this effectiveness in the UK may have been indirect due to herd immunity.

Regarding the epidemiology of meningococcal disease among older adolescents ages 18 to 23, in 1998 and 1999, while college freshman living in dorms had a much greater attack rate than all 18 to 23 year olds, they comprised only 10% of the total disease. Therefore, a focus on vaccinating only college freshman living in dorms would not necessarily prevent the additional 90% of cases in this age group. More recent data (2006-2010) show a similar picture for cases of C and Y meningococcal disease among older adolescents. Among 34 cases of C and Y meningococcal disease in 18 to 22 year olds, only 5 (71%) were college freshman living in dorms and 11 were not in school at all [Preliminary data, Meningococcal Vaccine Effectiveness Case-Control Study].

Data from a multivariate analysis of cases and controls enrolled in a high school risk factor study show that even among high school students, there are behavioral risk factors for meningococcal disease such as marijuana use or attendance at a club or disco. These adolescents at increased risk may also be more difficult to reach for vaccination, highlighting the importance of vaccination prior to the onset of some of these behavioral risks [Harrison et al. PIDJ, 2008. 49 case-patients and 185 controls]. Disease continues to peak in late adolescence, but some impact of $MenACWY_D$ vaccination is being observed on disease rates. College freshmen living in dorms are at high risk for disease, but there is a high burden of disease in this entire age group.

The work group also considered duration of protection, with the assumption that a person needs an adequate level of circulating serum bactericidal antibody (SBA) to prevent invasive disease. Dr. Cohn pointed out that SBA was measured with different assays in each of the studies she was presenting, so the data were not comparable across studies. While the number tested in each study was low, the data are consistent.

The adolescent recommendations were initially made with the assumption vaccine would protect for ≥10 years. It was initially presumed that conjugate properties in the vaccine would initiate a memory response that would be protective. Recent data suggest that memory alone is not sufficient to protect against meningococcal disease and protective levels of circulating antibodies are needed.

In a study comparing MenACWY$_D$ and MPSV4 antibody persistence three years after vaccination in 11 to 19 year olds, using a cutoff of ≥ 1:4 human SBA, only 35% of persons vaccinated at 11 to 18 years old had protective antibody levels three years after vaccination with either vaccine [Vu, D et al. JID 2006:193, 821-828; Granoff, D et al. PIDJ 2005:24, 132-136].

Another study measured the percent of subjects with titers ≥ 1:128 (baby rabbit SBA) at 1 month, 3 years, and 5 years post-vaccination. The 3-year subjects were initially vaccinated at 11 to 18 years of age and the 5-year subjects at 2 to 10 years of age. Three years after vaccination, the subjects vaccinated with Menactra® had higher titers than those vaccinated with polysaccharide (MPSV4) vaccine and controls. However, at 5 years, only 54% of those vaccinated with Menactra® had titers at or above 1:128, which is only 12% higher than the proportion of the vaccine-naïve population who had naturally occurring protective antibody [data courtesy of Sanofi Pasteur, 3 year follow-up of MTA02 (11-18 year-olds), 5 year follow-up of 603-02 (2-10 year-olds)].

In terms of the geometric mean titers (GMT) of the SBA for these same data, there is better persistence of SBAs in subjects vaccinated with Menactra® compared to polysaccharide (MPSV4) vaccine, but the absolute values of these titers are low. In a smaller study of 11 to 18 year olds, the GMTs at 5 years in subjects vaccinated with Menactra® were lower than the subjects vaccinated with polysaccharide (MPSV4) vaccine [data courtesy of Sanofi Pasteur, 3 year follow-up of MTA02 (11-18 year-olds), 5 year follow-up of 603-02 (2-10 year-olds), 5 year follow-up to MTA02 (11-18 year-olds).

The concern for antibody persistence is a concern for other meningococcal conjugate vaccines as well. Based on recent data from the UK on persistence of antibody levels 6 to 7 years after vaccination with MenC vaccine, only 48% of children vaccinated at age 5 to 6 years were adequately protected 6 to 7 years later with an SBA titer of ≥1:8, and only 38% had an SBA titer of ≥ 1:128.

In summary, limited data do not support that the majority of children vaccinated at age 11-12 years will maintain protective antibody levels through college. Some additional data will be available on antibody persistence in the next year; however, these data are not anticipated to change the picture. There are also no data regarding whether herd immunity has been achieved in this age group which would provide some indirect protection. The sense of the work group is that with dropping circulating antibody levels, herd immunity cannot be relied upon with the current program. There is consensus among ACIP members that the current strategy (e.g., vaccination preferred at age 11-12 years) is not optimal for achieving program objectives.

Additionally, the decision-making is time-sensitive as state mandates are being implemented and colleges need time to incorporate any policy changes. There have also been educational campaigns focused on targeting vaccination at 11 to 12 years of age.

The work group has discussed the follow two options for ACIP consideration:

1. Booster dose at age 17 years
   - → For those going to college / living in dorms
   - → All adolescents

2. Moving the first dose closer to period of risk
   - → Expanding preferred age of vaccination
   - → Shifting from 11-12 years to 14-15 years

A major issue with adding a booster dose at age 17 years is that these vaccines are only licensed as a single dose. This recommendation would be off-label, but limited data show the booster dose to be safe and immunogenic. This strategy would have a high cost per QALY saved, and the cost of the program would essentially be doubled. Vaccines for Children (VFC) program covers children through age 18 years, so this program could be implemented through VFC. The work group proposed two options for the booster dose:

Option 1: 17 Year-Old Booster

- ❑ Only college freshmen living in dorms
  - → Limits off-label use
  - → Limits additional program cost
  - → Is an easier group to capture for vaccination
  - → Would prevent a low proportion of disease in age group; there would be continued disease in adolescents outside this age group if the vaccine is truly not protective

- ❑ All 17 year-olds
  - → Would prevent more disease
  - → Would align better with the original program goals of protecting adolescents through the increased period of risk
  - → Challenging group to reach with vaccine

Option 2: Moving the First Dose Closer to Period of Risk

- ❑ Optimize protection with fewer total doses given

- ❑ May not attain high coverage prior to the increase in risk
  - → No current vaccination visit later in adolescence

- ❑ Impact on the adolescent platform

- ❑ Expand age group recommended (vaccinate between age 11-15 years)
  - → Flexible but also confusing for providers and programs to implement
  - → Children vaccinated at 11-12 years may still need a booster

- Change recommended age group (vaccinate at age 14-15 years)
  - → Leaves 11-13 year-olds unprotected
  - → May not achieve high coverage prior to increase in risk

In conclusion, there has been early success of the adolescent program, including increasing coverage and impact on rates of disease in adolescents. However, the work group feels compelled to address the concern for waning immunity. The risk-benefits and programmatic implications of options are quite challenging. Prior to moving forward, the work group requested feedback from the full ACIP regarding the following questions:

- Should current recommendations be modified to address waning immunity?

- Does ACIP have a preference for either option?
  - → Booster dose at age 17 years
  - → Moving 11-12 year-old vaccination to later in adolescence

Discussion Points

Dr. Chilton wondered whether, among the 304 cases of meningococcal disease in 18 to 23 year olds, it was known what proportion were immunized at age 11 or after.

Dr. Cohn replied that the data on the 304 cases was from 1998 to 1999, which was prior to vaccination. The number of cases among adolescents is substantially lower at present and probably ranges around 100.

Dr. Chilton inquired as to whether there was any evidence of vaccine effectiveness other than serologic protection.

Dr. Cohn responded that a year ago they presented data on breakthrough meningococcal disease in persons who had been previously vaccinated, and they are continuing to collect data on cases vaccinated. There certainly are cases vaccinated who develop disease. Part of the problem is that coverage was still low five years ago, so they do not have a sense of whether these are children who did not respond to vaccine initially or if it is due to waning immunity. It will probably be another year before this can be assessed.

Dr. Sawyer did not like the option of expanding the range of first vaccination from 11 to 15, given that he could not imagine the language needed to make that clear to providers and it will be extremely difficult to implement. It is also challenging to raise the age and capture older populations.

Dr. Meissner agreed based on the rising incidence of disease, which really does not begin until 15 years of age. While this would be missing 13 and 14 year olds, this is well before the peak.

Dr. Cohn noted that it would be leaving the group of children who are currently protected unprotected in the future.

Dr. Baker agreed that a great increase occurs at 15, but it begins to rise at 13 to 14. From the parents' and providers' perspective, moving upward would cause difficulties based on the information available.

Dr. Temte inquired as to how much of the secondary peak at ages 17 to 18 was due to college freshman living in dorms. He also wondered whether they knew what the population of freshman per year living in a dorm is.

Dr. Cohn replied that college freshmen living in dorms are ages 18 to 19. The data collection forms for surveillance do not specifically ask grade level in the school. Among the cases of meningococcal disease enrolled in the Vaccine Effectiveness Study, only about 10% of persons in this age group are college freshman living in dorms.

Dr. Turner (ACHA) added that ACHA does have information on the number of freshmen living in dorms, though he did not readily have the information available (later someone called out 600,000). While they were discussing recommending a booster at 17 years, he thought they needed to think in terms of a booster after having received the conjugate 4 to 5 years before because some 17 year olds may have received the vaccine when they were 14. This should be clarified.

Dr. Meissner pointed out that if they were to add a booster dose only for college students that would address only 10% of the burden of disease in that age group. This would not address 90% of the burden disease,which is problematic.

Dr. Cohn clarified that in the data from the MCVE study, it could be that there is higher vaccination coverage among college freshmen living in dorms, which could be why the number is so low. The data from the 1998 to 1999 study prior to vaccination was also 10%, but it was 10% among adolescents ages 18 to 23 years. Among just college freshmen, it was about 70% among those living in dorms.

Dr. Cieslak noted that the disease rates are currently very low at .27 / 100,000. This is an expensive vaccine. He would have difficulty supporting basically a doubling the recommendation without good evidence about decreasing effectiveness of the vaccine over time.

Dr. Lett expressed concern about the change in the abbreviation for meningococcal conjugate vaccine to the long abbreviation and a subscript to be the one in general use. She wondered whether the work group considered other abbreviations such as MCV2 to make it more like HPV and rotavirus.

Dr. Cohn responded that the rationale for not using MCV4 versus MCV2 or 3 is that in the future there may be vaccines that cover 3 different serogroups. This could become very complicated. It is important to ensure that serogroup A is in the vaccine, for example, if it is being administered for a traveling vaccine. This was also to be more consistent with the way meningococcal conjugate vaccines are named in other countries.

To speak to this minor issue, Dr. Baker said she thought pediatricians were pretty familiar with this. They are talking about the same four antigens. This is unlike HPV that has a 2-antigen versus a 4-antigen preparation. She agreed that it needed to have the four common antigens, but D is a common conjugate that is known to pediatricians as is CRM. Whether the 197 is needed is debatable. She suggested that the manufacturers could weigh in as well.

Dr. Pickering said that in the recommendations used by ACIP and in the Red Book, only CRM would be used. In the scientific literature, the number 197 is included.

Dr. Meissner pointed out that college students are in a high risk category, but they were excluded from the recommendation a year ago to give a second dose of meningococcal vaccine. Thus, they may be excluding college students from optimal protection.

Dr. Baker reminded everyone that the excellent data pertaining to college students living in dorms are not current data. With teen smoking down, some behaviors and risks may have changed. They have been waiting for more data, and Dr. Cohn rightly stated that there are unlikely to be more data by the time of the October ACIP meeting.

Dr. Englund thought that the ACIP needed to think about the impact of whatever changes they make on the adolescent vaccine platform in the context of the practitioners. This vaccine is just now becoming accepted into the pediatric population. Making a change will not merely impact the meningococcal vaccine, but also has the potential to impact other vaccines such as Tdap, adolescent pertussis, and HPV.

Dr. Baker added that state mandates vary. For example, Texas has a mandate for middle schoolers who are certainly not 15 years of age.

Dr. Schuchat pointed out that much of the discussion was focused on the waning of bactericidal antibody. ACIP is supposed to consider many issues, including programmatic feasibility. She thought what they were talking about was a partially implemented recommendation with about 40% coverage. Practitioners and state programs have been through a whipsaw of recommendations, as well as a shortage in the midst of all of that. She thought it would be beneficial to consider what contribution a second dose might have, and what the potential additive benefits would be to the adolescent platform. They must realize that 60% of the people in the entire age group were not receiving any vaccine. Of course, they would need to update the cost-effectiveness of the final options being considered.

Phil Hosbach (Sanofi Pasteur) thought it was good to see that there had been some impact, especially given that at the last ACIP meeting, no impact was acknowledged. Regarding the adolescent platform and opportunities to immunize, children above the age of 12 years are increasingly difficult to get. There are a couple of opportunities to do so. Around ages 10 to 12, at the middle school entrance age, school requirements and physical exams represent a major opportunity. The next major opportunity after that is either high school graduation or entry into college. In between, this group is very hard to reach. Sanofi Pasteur has distributed more than 30 million doses of the vaccine in the US to date, and their estimate is that about 60% of population has been immunized at this time. While it is good to see an impact, they should keep in mind the platforms where these adolescents are most likely to be reached.

Amy Middleman (SAM) noted that SAM had changed its name to the Society for Adolescent Health and Medicine (SAHM). She thought it would be helpful to increase the input from Immunization Services in some of the work groups. A decision would be helpful for this particular vaccine fairly soon, and she agreed that this could potentially impact other vaccines. SAHM and always advocated for more than one platform during adolescents, one of which is at the entry point for high school at ages 14 to 15. They must also ensure that the impact for other vaccines is not harmed. For example, having a 15 year old platform may make it tempting for people to delay other needed vaccines such as HPV to the 15 year old group. VFC utilization

should be assessed for the 15 year old age group and as children age out at ages 17 to 18. Consideration should also be given to new vaccines coming down the pike, and what makes sense epidemiologically for those vaccines as well in order to build a platform. It is also important to assess other vaccines that are already recommended, where the implementation may be shifted by virtue of new work. Overall, SAHM supports the introduction of additional platforms to fully protect this age group.

Dr. Katz (IDSA) remembered that much of the initial impetus for meningococcal vaccine came from the Armed Forces experience. He was interested in hearing from their colleagues at the DoD regarding who in the Military currently receives meningococcal vaccine.

COL Cieslak (DoD) indicated that this is a very important vaccine for the Military. Every recruit receives this vaccine in basic training. An officer entering through some other route may "slip through the cracks," but the vast majority of troops receive this vaccine. They have not yet had to address to any great degree the question of a booster dose because it has not been given to 11 to 12 year olds long enough for that to be a factor for very many recruits. However, it soon will be. He and the DoD are very interested in following this story. DoD always follows ACIP recommendations. He expressed concern with this vaccine because it already is one of the more expensive vaccines. The last data he recalled was well in excess of $30 million per death prevented. They could easily be talking about doubling that cost by adding the booster dose. Obviously, this would be a major cost to the taxpayer if they had to foot the bill for the entire DoD.

Dr. Baker inquired as to whether DoD had any plans to test serology in those who were vaccinated 5 years ago.

COL Cieslak (DoD) responded that he was virtually certain that serology studies were being done, but he did not know the specific data.

Dr. Cohn added that CDC is collaborating with the DoD in San Diego on this project to evaluate those who received Menactra® and polysaccharide vaccine. Every six months they have a group of persons whose serum they have been able to obtain from the serum repository. The problem is that the DoD did not implement this until about 2006 to 2007, so there really are not any 5 year data yet. They will have data on 3 years probably by Spring 2011.

Reflecting on Dr. Cieslak's comment about the rates of disease being low, Dr. Turner (ACHA) thought one of the reasons was because tremendous uptake had been achieved among high risk individuals. He hated to see them wait for breakthrough cases as a result of waning immunity to prove that the booster is needed. Meningococcal disease has always been rare on college campuses, but has become even rarer in the last 5 to 6 years. Based on a 60% uptake among college students, they estimate that between 2005 and 2008, 300 cases and 35 deaths have been prevented. That represents a lot of young people and families who have been spared a dreadful disease. Programmatically, from a college health standpoint, it would be much easier for a booster to be given at college entry for those who received their vaccine more than 5 years prior to that. The vaccine was licensed in January 2005 and a recommendation was made in June 2005, so the first cohort of vaccine recipients will likely begin college in the Fall of or 2011. That is why it is important to make a decision about a booster soon.

Dr. Fryhofer (ACP) indicated that she is also a member of the American Medical Association (AMA) Council on Science and Public Health (CSAPH), and stated that she was speaking for

both organizations and on behalf of Dr. Tan to urge ACIP to consider the infrastructure for adolescent vaccines when choosing an option.

Regarding the mention that 5 years might be an optimal time between immunizations, Rick Dosky (AHIP) pointed out that at age18, several options for insurance change and there is a scatter of coverage after age 18 years of age. A relatively substantial change in policy would be required among several self-insured employers nationwide. In addition, under age 18, there is almost universal acceptance across the board of almost every recommendation made by ACIP.

Katie Brewer (ANA) mentioned in a forward thinking way that hopefully in the reformed health care system there would be pilot projects around school-based health centers, which may also factor into the decision regarding whether to expand the age recommendation for vaccination. There may be a better chance of capturing youth in that age range if there is a more comprehensive school health program. She wondered whether there would be changes when health plans were required to cover children to the age of 26.

Rick Dosky (AHIP) replied that the final rules had not been published, so this remained unknown.

Regarding coverage, Ms. Rosenbaum thought that in addition to age, as grandfather plans expired, there would be a bringing up of immunization coverage up through adulthood. Thus, the problem of children versus of adults, which is a rather arbitrary issue anyway, would begin to fall away and would be a great boon to how they think about immunizations.

Dr. Decker (Sanofi Pasteur) expressed concern with several issues regarding the proposal to increase the age for initial meningococcal vaccination. In addition to having a tendency to harm to adolescent platform, diffusing the recommendation may actually decrease the proportion of adolescents who are vaccinated. Moreover, this does nothing to address the issue that brought this in front of ACIP, which was the question regarding whether the millions of children who are already vaccinated need a booster before entering college. Selecting the option to increase the age for initial immunization will not address the problem initially brought before the committee. He thought maintaining the current recommendation for initial vaccine at ages 11 to 12 and adding a booster pre-college, if believed to be needed, would directly address the issue that was presented to ACIP without risking harm to the adolescent vaccination platform.

Human Papillomavirus (HPV) Vaccine

Lauri Markowitz, MD
NCHHSTP
Centers for Disease Control and Prevention

Dr. Markowitz indicated that the primary purpose of the HPV presentation during this meeting was to remind and update the ACIP members about current issues regarding HPV vaccine and HPV Vaccine Work Group plans.

Regarding the current ACIP recommendations for HPV vaccine in the US, the quadrivalent vaccine was licensed in June 2006 and was recommended for routine immunization of females

11 to 12 years of age and catch-up for ages 13 through 26 years. In October 2009, the bivalent vaccine was licensed for use in females, and ACIP revised the recommendation to state the either the quadrivalent or bivalent vaccine could be used for routine vaccination in females 11 to 12 years of age and for catch-up in females ages 13 through 26 years. The quadrivalent vaccine was also licensed for use in males in October 2009. ACIP stated that the vaccine may be given to males 9 through 26 years of age, but it was not included in the routine vaccination schedule.

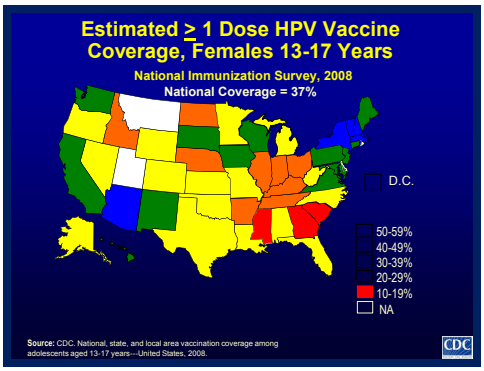
In terms of additional information related to quadrivalent HPV vaccine for males, as just noted, FDA licensed this vaccine for males 9 through 26 years of age with an indication for prevention of HPV 6/11-related genital warts in males [http://www.fda.gov/BiologicsBloodVaccines/Vaccines/Approved Products/ucm094042.htm]. ACIP stated that HPV vaccine may be given to males 9 through 26 yrs [MMWR 2010; 59: 630]. ACIP also voted to include HPV vaccine for males in the VFC program, and the manufacturer included HPV vaccine for eligible males ≥19 years in their patient assistance program. Private insurance coverage for the vaccine for males appears high. At the work group's request, AHIP was asked to query a group of their health insurance plans. Based on the large plans queried, (although this may not represent all of the plans AHIP represents), AHIP estimated that approximately 90% of male beneficiaries 9 through 26 years of age are covered for HPV vaccine, although the criteria and language of coverage may vary in the different plans. The HPV work group hopes to have more information on insurance coverage as well as data from a national survey of provider practices for presentation during the next ACIP meeting in October 2010.

Data on prevention of anal intraepithelial neoplasia grade 2/3 in males became available following the October 2009 ACIP meeting. These data showing efficacy of about 75% (95% CI = 9,95) in men who have sex with men (MSM) were presented to ACIP in February 2010. A supplemental BLA (sBLA) has been submitted to the FDA. The FDA review is expected to be complete after the October 2010 ACIP meeting. The work group is continuing to discuss and consider issues regarding quadrivalent HPV vaccine for males. The group plans to review the clinical trial data, cost-effectiveness with different coverage assumptions, epidemiology and cost-effectiveness in MSM, and the feasibility of reaching MSM when they would benefit most from vaccination. As has been presented previously to ACIP, adding males to a female only vaccination program does not appear to be cost-effective if there is high vaccine coverage in females, but at lower coverage in females the program may be cost-effective. There will be further consideration and discussion of these issues during the October 2010 ACIP meeting.

With respect to HPV vaccines for females, as mentioned, ACIP revised the recommendations in October 2009 to state that either the quadrivalent or bivalent vaccine could be used for routine and catch-up vaccination of females. The CDC contract for bivalent HPV vaccine was established in April 2010. The VFC pediatric contract price for the bivalent vaccine is $96.08 and for the quadrivalent vaccine is $108.72 [http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm#pediatric]. Both manufacturers have patient assistance programs for eligible females older than the VFC age.

Data on coverage were presented to ACIP previously, but Dr. Markowitz presented them again due to the importance of coverage in models for male vaccination cost effectiveness. The estimated overall coverage with ≥ 1 dose of vaccine in females ages 13 through 17 was 25% in 2007 and increased to 37% in 2008 [National Immunization Survey. MMWR 2008;57]. There remains wide variation in vaccine initiation across the country, with initiation being less than 20% in some states shown in red and as high as the mid 50% range in the states shown in blue,

which is reflected in the following map:



National and state-specific data from 2009 will be available later in the summer of 2010 and will be presented to ACIP during the October 2010 meeting.

While there are no data from the NIS beyond 2008, there are data from immunization registries for more recent years showing that coverage has continued to increase. For example, the Citywide Immunization Registry in New York City includes data on coverage among females ages 13 through 17 years of age for 1, 2, and 3 doses from 2008-2010. Coverage increased during these years, such that by the first quarter of 2010, coverage with at least 1 dose was over 50% and coverage with all three doses was 25% [Citywide Immunization Registry, Bureau of Immunization, NYC Department of Health and Mental Hygiene].

Another issue that the work group is addressing is HPV vaccine for women over age 26 years. ACIP first considered this issue in 2008 when interim data from a trial in women 24 to 45 years of age was submitted to the FDA. Further data were requested from this trial, and Merck submitted a sBLA to the FDA in November 2009 with end-of-study data from that trial in women 24 through 45 years of age. The work group had been preparing for a vote, and had an extensive session during the last ACIP meeting about this issue. Most work group members support no catch-up recommendation beyond age 26 years. The FDA has not completed review of the sBLA. This issue will be revisited in the future.

The proposed agenda for the October 2010 ACIP meeting will be full. Plans are to discuss further data and considerations for quadrivalent HPV vaccine for males and quadrivalent HPV vaccine for women over 26 years; present a vaccine safety update; have a presentation from the Health Resources and Services Administration (HRSA) on the Vaccine Injury Compensation Program; and discuss any additional issues that arise prior to the next meeting.

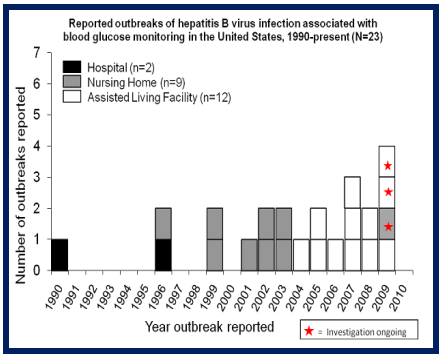
Hepatitis Vaccines

Introduction

Mark Sawyer, MD, Chairman
ACIP Hepatitis Work Group

Dr. Sawyer reported that the Hepatitis Work Group has been in deliberations since February 2009 on its second term of reference, “To review data from recent hepatitis outbreaks among

diabetics in institutional care to determine whether vaccination is appropriate." Considerable progress has been made on this topic. This term of reference originated because of an increasing number of reports of hepatitis B outbreaks among adults with diabetes, as depicted in the following diagram:



As of June 2010, 24 outbreaks had been reported since 1990, some involving more than one facility. Outbreaks were initially in hospitals and nursing homes. More recently, an increasing number have been reported in assisted living facilities. A recurring theme found in the outbreak investigations is failure of infection control practice, and misuse of devices to monitor blood glucose or to administer insulin to adults with diabetes.

Infection control guidelines for preventing transmission of bloodborne pathogens among adults with diabetes, and in long-term care, date to the 1980s and before. To highlight a few, in 1988, the American Association of Diabetic Educators issued a position statement on preventing transmission of bloodborne infections and avoiding injuries from sharps. In 2005, CDC made specific recommendations for glucose monitoring practices in long-term care facilities. In 2009, the FDA issued a health alert after learning that more than 2000 people were exposed in two hospitals that used the cartridge component of insulin pens intended for single patients, to administer insulin to multiple patients. Despite guidelines for infection control practice addressing the specific issues found in these outbreaks, outbreaks continue to be reported.

There are biological reasons for the ease with which hepatitis B infection is transmitted when lapses in infection control practice occur. A feature of hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV is that all three viruses cause acute and chronic infection, and a large proportion of the infections are asymptomatic. The estimated reservoir of chronic HBV infection is more than 1.25 million people. Although not as large as the reservoir of HCV, the reservoir of chronic HBV, provides ample opportunity for exposure to HBV in the setting where even minor breeches in infection control practice occur. Moreover, the titer of HBV in infection is considerably higher (10^{8-9}) than the titer of HCV (10^{6}) or HIV (10^{3-6}) and HBV is stable in the environment for more than a week, and remains infectious in dried blood in amounts too small to be visible. In contrast, HCV and HIV are found in lower titer, and are less environmentally stable. The characteristics of HBV translate into high infectivity as demonstrated after a needle stick. The infectivity of HBV is 10-fold higher than HCV and ~100-fold higher than HIV. Given the high stability and infectivity of HBV, it is not surprising that transmission might take place in settings with poor infection control practice [Beltrami et al, Clin Microbio Reviews, 2000. MMWR 2001;50(No. RR-11). Bond et al. Lancet 1981; 8219:550-1. Shikata et al.. J Infect Dis 1977;136:571–76].

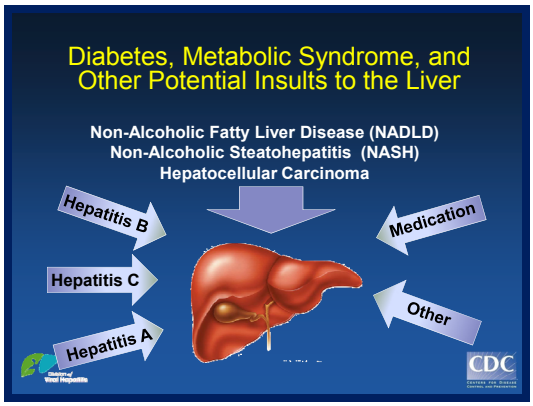
This is compounded by the fact that licensing, regulation, and inspection in long-term care facilities are highly variable, especially for assisted living facilities, which generally follow more of a "social" rather than healthcare model. Infection control practices or polices are lacking in a substantial proportion of these facilities, and adherence with good infection control practice is often suboptimal, even when polices are in place. Accumulating evidence suggests that outbreaks in long-term care are recognized primarily because of the clustering of cases and poor infection control practice is much more widespread, disproportionately affecting adults with diabetes [Thompson N et al. JAGS 2010; Patel AS et al. ICHE 2009; Richards CL, Jr. JAMDA 2007;8:S18-S25].

Almost half of all adults with diabetes will eventually become long-term care residents. Progression of diabetes disease and its complications, along with aging, lead to a requirement for assistance in the activities of daily living, including monitoring blood glucose. Adults with diabetes make up a substantial proportion of residents in long-term care. The proportion of current long-term care residents who have diabetes has been estimated at 20% - 26% in nursing home, and 15% -26% in assisted living facilities, and these adults are already vulnerable to insults to the liver from all causes [Resnick HE et al. Diabetes Care 2008;Hendrick S et al. Gerontologist 2007; Travis SS et al. JAMDA 2004; Narayan KM et al. Diabetes Care 2006; US Dept of HHS Assistant Secretary for Planning and Evaluation Office of Disability, Aging and Long-Term Care Policy. November 2002].

As reported during the February 2010 ACIP meeting, adults with diabetes are at increased risk of chronic liver disease and hepatocellular carcinoma. In a retrospective study of medical records from Veterans Administration (VA) hospitals, all patients (n=173,643) with a discharge diagnosis of diabetes were examined from 1985-1990. Each patient with diabetes was matched to 3 patients without concomitant liver disease (n= 650,620) identified any time since 1980 and the outcomes analyzed through 2000, excluding first year of follow-up. Using a Cox proportional hazard model, the incidence of chronic liver disease was higher among patients with diabetes than patients without diabetes at 18.3 versus 9.5 per 10,000 patient years, an incidence rate ratio of 1.9 for patients with diabetes. The incidence of hepatocellular carcinoma was also higher among patients with diabetes than among patients without diabetes at 2.4 versus 0.9 per 10,000 patient years, an incidence rate ratio of 2.75 for patients with diabetes [El-Serag HB Gastroenterology 2004;126:460-468]

Also reported during the February 2010 ACIP meeting were the results of a retrospective study suggesting that among adults with chronic hepatitis B infection, those with diabetes had accelerated progression to cirrhosis. In this study of 500 adults aged 42 ± 15 years with chronic hepatitis B attending a "liver clinic," 71 patients with chronic hepatitis B and cirrhosis were compared with 102 control subjects with chronic hepatitis B without cirrhosis, matched by sex and age. Patients with other risk for liver disease were excluded. The most important factor associated with developing cirrhosis was the added presence of diabetes, with an odds ratio 4.3 (1.5-12.1) [Huo T-L. J Clin Gastroenterol 2000].

This cartoon summarizes some of the potential insults to the liver among adults with diabetes:



Diabetes is associated with non-alcoholic fatty liver (metabolic syndrome), development of non-alcoholic steatohepatitis, and increased risk for cirrhosis and hepatocellular carcinoma (as we have seen). Persons with diabetes are at risk for added liver injury from medications, risk behaviors such as alcohol abuse, hepatitis A, and bloodborne infections including hepatitis B and C. They may be disproportionately at risk because of regular exposure to blood during glucose monitoring and diabetic care. Thus, prevention of further liver injury by preventing transmission of bloodborne pathogens should be a priority.

To raise awareness of the problem of healthcare related transmission of bloodborne infections and to find solutions, the CDC Foundation in collaboration with CDCs Divisions of Healthcare Quality Promotion, Viral Hepatitis, and Diabetes Translation organized two recent meetings, the final reports from which will be available soon and will be part of the considerations of the work group in terms of other strategies that might affect this situation:

- *Sticking with Safety: Eliminating Bloodborne Pathogen Risks during Blood Glucose Monitoring:* This meeting, convened on May 3, 2010 brought together representatives from CMS, industry, FDA, diabetes educators, state health departments, the VA, academia, infection control, and clinical practice. The purpose of the meeting was to raise awareness of the infectious disease risks related to blood glucose monitoring and to discuss voluntary strategies and opportunities for prevention in this area, including product innovation and improved education and marketing.

- *Safety by Design: Innovative Approaches for Safe Injection:* This meeting, convened on May 24, 2010 assembled representatives from additional organizations with a goal to promote safe use and innovation in product development to eliminate transmission of bloodborne pathogens and other infections associated with the intravenous delivery of parenteral medications.

With respect to the work group deliberations to date, the work group has had many discussions covering a wide range of topics including infection control and LTC, diabetes, glucose monitoring, risk of hepatitis B infection among adults with diabetes, vaccine coverage, and vaccine seroprotection. After these discussions, the majority opinion of the ACIP Hepatitis Working Group favored hepatitis B vaccination for adults with diabetes as an important part of a solution for preventing hepatitis B infections, an approach similar to the one used to prevent hepatitis B infections among health care personnel. This approach was characterized by hepatitis B vaccination for adults with diabetes; improving implementation of infection control practices, especially for assisted blood glucose monitoring; and encouraging innovation in

labeling, cleaning, and design of blood glucose monitoring devices to prevent transmission of all bloodborne pathogens.

On June 18, 2010, the Division of Viral Hepatitis (DVH) presented an update on the activities and deliberations of the ACIP Hepatitis Working Group, to the Healthcare Infection Control Practices Advisory Committee (HICPAC). HICPAC members acknowledged the increasing evidence of widespread breeches in infection control practice and the urgent importance of finding solutions. The discussion reflected support for hepatitis B vaccination of adults with diabetes as an appropriate part of a solution for preventing bloodborne infections, including hepatitis B virus infection.

Given the majority opinion in support of vaccinating adults with diabetes and the agreement of HICPAC, the work group faced significant challenges in defining policy options for hepatitis B vaccination among adults with diabetes. The number of adults with a diagnosis of diabetes has increased exponentially in the US during the last several decades. In 2006, the National Diabetes Surveillance System reported that 17.7 million adults had diagnosed diabetes [CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/ diabetes/statistics from NHIS]. The life-time risk of diabetes is now greater than 30%, and by 2020, it is expected that 28.5 million adults will have a diagnosis of diabetes [Narayan KM. Diabetes Care 2006].

The prevalence of diagnosed diabetes in the US adult population, as determined in the 2005-2006 National Health and Nutrition Examination Survey (NHANES), was 7.7% of the US adult population 20 years and older. However, the prevalence of diabetes was considerably higher among adults greater than 60 years than among younger adults (e.g., 17.5% of adults 60-74 years and 14.8% of adults 75 years and older). Adults over the age of 50 or 60 years might be expected to show a less robust response to hepatitis B vaccine than younger adults, based on experience with other vaccines. The working group examined the possible advantages of vaccination soon after diagnosis of diabetes, or at as young an age as possible, to maximize seroprotection [Cowie et al., Diabetes Care 2009;32:287-94].

Data pertaining to the incidence of diabetes diagnosis by age group in 2008 data show that 2/3 of adults who will ever have the diagnosis of diabetes will have the diagnosis by age 60 years. The proportion of new diagnoses decreases in older age groups, especially after age 65 and older [Adapted from: CDC. Diabetes Data and Trends. Available at: http://www.cdc.gov/ diabetes/statistics/age/fig1.htm; Source: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Health Interview Statistics, data from the National Health Interview Survey].

Data from the National Nursing Home Survey (NNHS) from 2004 show that the age distribution of nursing home residents by diabetes status is somewhat older overall than the age distribution of persons with a new diagnosis of diabetes. The age distribution of adults with diabetes in nursing homes peaks at 80-84 years, slightly younger than the peak age for adults without diabetes (85-89 years). It is important to observe that few nursing home residents are younger than age 65. Therefore, if hepatitis B vaccination is administered soon after diagnosis, these data suggest that over time, the majority of adults with new diagnosis of diabetes could be vaccinated before an age when they require long term care services, optimizing opportunities for a good response to hepatitis B vaccination. These data were taken into consideration by the work group during their deliberations on possible policy options [Zhang X et al. JAGS 2010;58:724, CDC unpublished analysis].

During this session of the June 2010 ACIP meeting, presentations included an update on national surveillance in the US for acute hepatitis B infections; information about the risk of hepatitis B virus infection among adults with and without diabetes; data on hepatitis B vaccine seroprotection and safety among older adults; and the policy options proposed by the work group.

During the October 2010 ACIP meeting, the work group plans to present a cost-effectiveness analysis covering the proposed policy options and considerations for implementation. Following review and discussion during that meeting, the work group plans to call for a vote.

Epidemiology of Acute Hepatitis B

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Division of Viral Hepatitis
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Dr. Jiles described the incidence, trends, and associated outcomes / complications of acute hepatitis B disease among adults ≥ 50 years of age. For these analyses, data were utilized from three sources.

The first source was the National Notifiable Diseases Surveillance System (NNDSS). Acute hepatitis B is a legally mandated reportable condition in all states. Clinical laboratories and healthcare providers send reports of acute hepatitis B to local or state health departments. These reports have been submitted to CDC voluntarily using the electronic infrastructure of the NNDSS since 1990. The case reports include basic demographic data, but often do not include information about risk behaviors or exposures. States may collect information about risk behaviors or exposures; however, these data are not always sent to CDC. For this presentation, NNDSS data were used from 1980 through 2007 to describe trends. All other analyses used 2007 data, which is the most recently published data.

The second data source for these analyses was the Sentinel Counties Study of Acute Viral Hepatitis, which was a special study for hepatitis that was conducted from 1981 through 2006 to supplement data from the passive NNDSS. This study included 6 counties with populations of approximately 4.5 million. A rigorous protocol was used to identify and characterize cases of acute viral hepatitis using both clinical and laboratory criteria. Follow-up interviews were conducted to ascertain risk behaviors and exposures, and sera were collected for serologic characterization. For these analyses, sentinel county data were used from 2002 through 2005.

A demonstration project of enhanced hepatitis surveillance served as the third source of data. This project was initiated in 2004 and was funded through the Emerging Infections Program (EIP). The goal of the EIP project is to develop best practices for improving case ascertainment, application of case definitions, data quality and completeness of reports, reporting of risk factors, and serologic characterization. For these analyses, data were used from 2005 through 2007, which covered a population of approximately 36 million.

NNDSS data from 1980 through 2007 show that incidence of acute hepatitis B in the US peaked in the mid-1980s and declined over time. The most rapid decline occurred between 1989 and 1992. This decline coincided with the stepwise implementation of the national vaccination strategy to eliminate hepatitis B viral transmission. Further examination of these data show that the decline varied by age. From 1998 through 2007, the decline was 92% among children and young adults less than 20 years of age and 59% among adults 20 to 49 years of age. The

smallest decline, 46%, was observed among adults ≥ 50 years of age. To describe the burden of disease by age group, the proportion of cases that were ≥ 50 years of age was determined. Because of the small number of cases in the < 20 age group, they were combined with the 20 to 49 age group. In 1998, 16% (n=10,108) of all acute hepatitis B viral cases reported through NNDSS were ≥ 50 years of age. In 2007, 24% (n=4,499) of all cases were ≥ 50 years of age. These data indicate that as the disease decreased among the younger vaccinated group, the burden of disease shifted to the older age group [Source: National Notifiable Diseases Surveillance System (NNDSS)].

The following table reflects acute HBV disease per 100,000 population by age group and source of surveillance data, and for each source, the number of cases reported during the period presented are also noted:

Age group (years)	NNDSS 2007		Sentinel Counties 2002-2005		EIP 2005-2007	
	n	rate	n	rate	n	Rate
< 20	83	0.1	8	NC	16	NC
20-49	3,319	2.6	543	6.9	814	2.1
≥ 50	1,097	1.2	102	1.9	242	0.9

NC = rates for cells with <20 cases on average were not calculated

There were very few cases in the group < 20 from each of the three sources. All sources indicate that rates were highest for the 20 to 49 age group, intermediate for those ≥ 50 years of age, and lowest for the age group < 20 years. These data show that the older age group does experience acute hepatitis B disease.

Hospitalization and deaths were used as outcome indicators of severity of disease. With regard to the frequency of reported hospitalization due to acute hepatitis B by age group and source of data, from 2007 NNDSS data, a similar proportion of hospitalizations were reported for cases in the two age groups. In the < 50 age group, there were 817 / 2008 (41%) hospitalizations and in the ≥ 50 group there were 258 / 655 (39%) hospitalizations. Sentinel Counties data from 2002-2005 showed 150 / 534 (28%) hospitalizations in the < 50 age group and 32 / 101 (32%) ≥ 50 group. EIP from 2005-2007 reported 234 / 661 (35%) hospitalizations in the < 50 age group and 85 / 198 (43%) in the ≥ 50 group. Reported deaths among acute HBV cases by age group in the three data sources were consistent. Compared to the < 50 age group, the proportion of deaths among cases ≥ 50 years were higher at 3% versus 1% in the NNDSS data, 2% versus 1% in Sentinel Counties, and 4% versus < 1% in the EIP sites.

Vital statistics data were used to determine the number of deaths attributable to acute hepatitis B viral infections, which showed that more deaths were reported among the older age groups as anticipated. The trends in these data also mirror that of the 20 to 49 year old group, which suggests at least consistency in reported hepatitis B as a cause of death [National Center for Health Statistics Mortality Files].

These surveillance data have several limitations. First, more than half of all cases of hepatitis B infections in adults may be asymptomatic. As a result, a large proportion of persons with incident infection will not be diagnosed or reported with this condition. A significant amount of under-diagnosis and / or under-reporting of acute hepatitis B is also likely if physicians who

diagnose cases or laboratories performing diagnostic testing do not report these findings to state and local health departments, or if states do not report these cases to CDC. These data reflect cases of acute disease, not high risk groups such as diabetics and residents of long-term care facilities. Unfortunately, diabetes status and residential information are not routinely collected in these surveillance systems.

In summary, these data indicate that acute HBV infection occurs among adults ≥ 50 years of age and older. The smallest decline in incidence was observed in this age group compared to the younger age group. As a result, the proportion of cases ages 50 and older has increased over time. Cases ages 50 and older are only slightly more likely to be hospitalized due to acute hepatitis B virus, but are two to four times more likely to die from hepatitis B disease. Currently, efforts are underway to collect information on residents in long-term care facilities, diabetes status, and possibly other relevant co-morbidities in the EIP demonstration sites. These data will be used to provide answers to relevant questions about relationships between vaccination status, diabetes, and hepatitis B viral infection.

Hepatitis B Risk among Adults With and Without Diabetes

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Division of Viral Hepatitis
NCHHSTP / NCIRD / CDC

Dr. Hu described the risk of hepatitis B among adults with and without diabetes from a variety of sources, and presented an overview of HBV prevalence and estimates of HBV incidence among adults with and without diabetes. He offered a brief update on the outbreaks of hepatitis B among persons with diabetes and their related morbidity; provided data showing the broader problem of hepatitis B transmission associated with glucose monitoring; and discussed the seroprevalence and estimated incidence of hepatitis B among adults with diabetes compared to adults without diabetes.

Although the risk of hepatitis B has been most dramatically highlighted from reported outbreaks, as Dr. Sawyer illustrated earlier, these are most likely the “tip of an iceberg” of unknown size [Thompson, Perz. JDST, 2009; and unpublished data].. Recently, another outbreak investigation was initiated by CDC in Texas among persons with diabetes, which as of mid-June has yielded at least 14 patients with acute hepatitis B infection and 3 deaths. At this point, the outbreak has extended to at least 8 assisted living facilities

With regard to the morbidity associated with such outbreaks, data from 21 outbreaks show that 90% of persons with acute hepatitis B (e.g., persons positive for anti-HBc and anti-HBc IgM) were persons with diabetes monitoring blood glucose. However, 10% were other contacts who did not have diabetes (e.g., roommates, family members, staff at long-term care facilities). The morbidity from acute hepatitis B can be substantial as illustrated in additional data from 21 outbreaks where 38% of 151 persons with acute hepatitis B were hospitalized and 18% died from acute hepatitis in this predominantly elderly population. Data from 13 outbreak investigations with complete ascertainment of hepatitis B infection and diabetes status show again that the percentage of adults with diabetes having acute infection is much higher (30.5%) than the percentage of adults without diabetes (1%). Similarly, the prevalence of chronic infection among adults with diabetes classified by serology at the time of the investigation was also higher at 6.3% versus 0.4% among adults without diabetes [CDC. Unpublished Data 2009].

Although the proportion of persons developing chronic infections tends to decrease with age, the risk of chronic infection among older adults is higher. Among healthy adults, approximately 5% to 10% develop chronic HBV infection. Among older adults, especially adults with co-morbidities, the risk of chronic infection is much higher at 45% to 59% [Shepard CW ,Epidemiol Rev 2006; Polish LB. N Engl J Med 1992; Kondo K . Hepatology 1993].

Data from the Behavioral Risk Factor Surveillance System (BRFSS) shows that a high proportion of adults with diabetes have regular exposure to blood through glucose monitoring. In the 2006 survey, adults using insulin had the highest rates of daily glucose monitoring (84% using insulin and oral medication and 91% using insulin only). One-third of adults taking no medication monitored blood glucose daily. Overall, almost 2/3 (65%) of adults with diabetes monitored blood glucose at least once a day. Short-term assisted glucose monitoring is likely to be common during hospitalization, outpatient surgery, and in community clinics and screenings, even if not monitored on a daily basis. Most adults with diabetes will eventually monitor blood glucose [Adults 18+ yrs. Behavioral Risk Factor Surveillance System MMWR 2007;56 (43):1133-1137].

In a recent study by Walter Hellinger, which was presented at the Society for Healthcare Epidemiology of America (SHEA) meeting in March 2010, Hellinger described an innovative approach for assessing the use of computerized glucose meters in a Florida hospital. The glucose meters recorded the time of use with different patients. The data were analyzed for one month in October 2008. In this facility, 38 glucose meters performed 11,665 tests on 803 patients. Almost 80% were sequential tests on different patients. Of these, almost all were done within 24 hours. More than 60% were sequential tests on different patients that were done within one hour. In this particular facility, there were strict efforts to clean glucose meters between users. The study illustrates the potential for transmission of bloodborne pathogens if proper cleaning is not performed between patients (e.g., during periods of peak demand for completing testing on multiple patients) [Hellinger et al. Presented at SHEA, March 2010 (abstract # 199)].

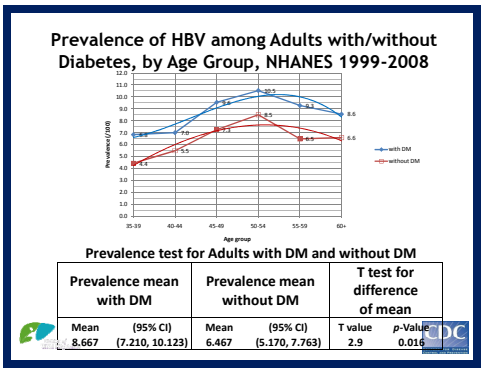
Blood contamination of glucose monitors is frequent as shown in a study by Louie and co-workers of glucose meters used in 12 hospitals represented by academic, community, urban, and rural settings. In this study, there was wide variation by hospital on the policy for cleaning the meters. Only 1 hospital policy recommended cleaning after each patient, 4 of the hospitals recommended cleaning the meters daily, 1 hospital recommended weekly cleaning, and 6 of the hospitals did not have a policy. The 608 glucose meters were examined for visible blood and then tested with phenolphathalein for evidence of hemoglobin. Almost a third (30%) of the glucose meters tested positive for blood. The presence of blood increased with the number of people operating the glucose meter, but interestingly was not related to the academic affiliation, hospital size, or the cleaning schedule. The data in this study suggest that there is a lack of appreciation of the significance in transmission of bloodborne pathogens for blood contamination of glucose meters, and suggests there might be barriers to rapid effective cleaning of the meters [Louie RF et al. Point of Care 2005;4:158].

In a study published in the Journal of the American Medical Association (JAMA) in June 2010, Melissa Schaefer in the Division of Healthcare Quality Promotion (DHQP) collaborated with the Centers for Medicare and Medicaid Services (CMS) in an assessment of the infection control practices at 68 ambulatory surgical centers in three states. More than 2/3 of the facilities had at least one lapse in infection control, 21% of facilities used single-use lancing penlets on multiple patients, and 32% failed to clean and disinfect glucose meters after use [Schaefer MK et al. JAMA 2010;303:2273].

Data presented by Nicola Thompson to the Council of State and Territorial Epidemiologists (CSTE) earlier in June 2010 summarized some recent patient notifications after misuse of diabetes equipment (e.g., the use of equipment designed for individual use on multiple patients). Misuse took place in both hospitals and community settings. The problems continued for 6 months or more in 3 of 4 of the notifications, and the misused equipment affected large numbers of adults with diabetes [Thompson ND. CSTE June 2010 Portland, OR]. This information, coupled with the data presented by Hellinger about frequent sequential use of glucose meters and Louie about blood contamination of glucose meters, and the finding of common infection control lapses in ambulatory surgical centers, highlight a significant potential risk of bloodborne pathogen transmission for adults with diabetes in a variety of settings that are not limited to long-term care.

Given these examples of poor infection control practice, the seroprevalence of hepatitis B infection on a national basis among adults with diabetes compared to adults without diabetes using NHANES data were assessed. 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. Survey results were used from 1999 through 2008 to examine the seroprevalence of hepatitis B infection among adults with and without diabetes. Diabetes status was determined by asking respondents if they had ever been told by a doctor that they had diabetes, excluding diabetes during pregnancy. Hepatitis B infections were determined by positive serology for hepatitis B core antibody indicating past or present hepatitis B infection. A major limitation of this survey for determining the seroprevalence of older adults is that it excluded persons in institutional setting. Therefore, NHANES data do not have information for persons in long-term care facilities. The findings for overall seroprevalence of hepatitis B infection among non-institutionalized adults > 18 years with and without diabetes showed that 8.3% of adults with diabetes had evidence of past hepatitis B infection, and that 5.2% of adults without diabetes had evidence of past hepatitis B infection. The odds ratio and prevalence ratios were both elevated, suggesting that adults with diabetes had a 60% higher prevalence of hepatitis B infection than adults without diabetes [CDC. Unpublished data].

The following graphic shows the prevalence of hepatitis B infection with and without diabetes by age group during the same period:



The point estimates of seroprevalence for each age group and the prevalence means for adults with and without diabetes are not statistically different, in part because the sample sizes are small. However, the test of the mean shows a significant difference overall, suggesting that the increase in hepatitis B infection is likely to be higher among adults with diabetes extending across ages group, even without data from the older adult age groups represented in the hepatitis B outbreaks in long-term care facilities.

Turning to estimates of the incidence of hepatitis B infection, Dr. Hu reported that catalytic modeling using a method previously reported by Patrick Coleman in 1998 was used. Age-specific seroprevalence of diabetes was calculated from NHANES data for 2007 and 2008, and age-specific antibody to hepatitis B core antigen was calculated from NHANES 1999-2009. National surveillance reports of acute hepatitis B, adjusted for under-reporting, were used to estimate the force of hepatitis B infection (lambda) per 100,000 susceptible persons. A susceptible person was defined by having no serological markers of hepatitis B infection or vaccination on testing in NHANES. There were several important considerations. The Coleman model assumed a constant force of infection for age groups younger than 40 years [Coleman P. J Infect Dis 1998]. This assumption may not be accurate for older adults, who are the focus of this analysis. The data sources had limited numbers, even in NHANES, and did not allow for estimates in subgroups. In addition, the incidence was estimated of hepatitis B infection among adults with diabetes identified in NHANES because data were lacking for adults with diabetes in long-term care facilities who were not surveyed in NHANES.

The following table shows the methodology used to arrive at the number of adults with diabetes:

Step 1 & 2. Estimate Prevalence of Diagnosed Diabetes, by Age Group – United States, 2007- 2008

Age group	A1 Prevalence of diabetes (/100)	A2 US population	Diabetes population N_D = Prev x US Census
25-59	6.19	138,109,000	8,548,947
60-69	17.02	24,901,000	4,238,150
>=70	19.93	26,463,000	5,274,076
Overall		189,473,000	**18,061,173**

A1 NHANES 2007-2008.
A2 – US population in 2007, www.census.gov/prod/1/pop/p25-1130/p251130a.pdf, reported by U.S. Bureau of Census.

For 3 age groups (25-59, 60-69, and ≥70 years) the prevalence of diabetes was determined from NHANES. The total number of adults with diabetes was then estimated by multiplying the by the US Census populations in these age groups. The total number of adults with diabetes in 2007 and 2008 was estimated at ~18 million. Given that NHANES does not include institutionalized adults (e.g., long-term care facilities), the prevalence of adults with diabetes in older adult age groups is believed to be conservative.

The following table illustrates how the total number of hepatitis B infections among adults with diabetes was estimated:

Step 3 & 4. Estimate of Total Number of Acute Hepatitis B (HBV) Infections among Adults with Diabetes, by Age Group - United States, 2007-2008

Age group	A3 Incidence of acute HBV (/100,000) I_T	Ratio of prevalence of acute HBV with vs without diabetes $k=I_D/I_{ND}$	Incidence acute HBV without diabetes (/100,000) I_{ND} [a]	A4 Incidence acute HBV with diabetes (/100,000) $I_D=k*I_{ND}$	A5 Number acute HBV infection with diabetes $HB_D=I_D*N_D$	A6 Under-reporting multi-plier	A7 Adjusted for under-reporting (A5xA6)	A8 Proba-bility of jandice (Pj)	A9 Final multi-plier (A6/A8)	Total number of HBV infections (A5xA9)
25-59	2.51	1.60	2.42	**3.87**	331	2.79	924	0.30	9.3	3,079
60-69	0.80	1.60	0.73	**1.16**	49	2.79	137	0.30	9.3	458
>=70	0.80	1.60	0.71	**1.14**	60	2.79	168	0.30	9.3	561
Overall					**441**		**1,229**			**4,097**

A3 – MMWR, May 22, 2009 / Vol. 58/ No. SS-3, page 24, report by CDC ,Division of Viral Hepatitis.

$I_T = (k*I_{ND}*N_D + I_{ND}*N_{ND}) / (N_D+N_{ND})$

k: k=1.6 is based on the ratio of seroprevalence of HBV with vs. without diabetes finding from NHANES 1999-2008, manuscript in preparation

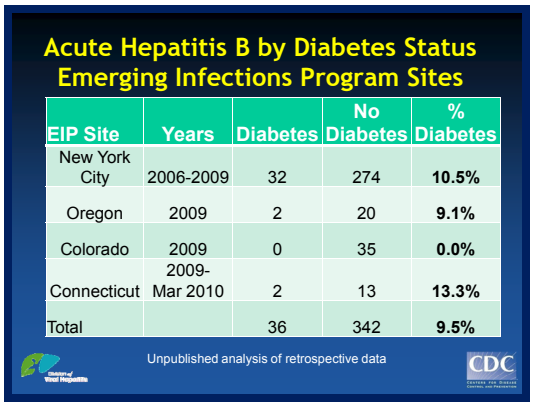
[a] - $I_{ND} = I_T*(N_D+N_{ND}) / (k*N_D+N_{ND})$

A6 - CDC unpublished used for annual surveillance summaries

The incidence of reported acute hepatitis B cases was taken from national surveillance data (column A-3), which ranges from 1-4 per 100,000 population. Using approximate prevalence ratio of 1.6 of HBV among persons with and without diabetes from NHANES (column 3), calculated in column A4 is the incidence of acute hepatitis B among adults with diabetes that would be reported to the surveillance system. The number of adults with diabetes calculated in the previous table is multiplied to obtain the number of acute HBV infections among adults with diabetes (n=441; column A-5).

By adjusting for under-reporting (2.79; column A-6) and the probability of symptomatic versus asymptomatic infection by age group (0.30; column A-8) using the same factors employed for national surveillance estimates, the total annual number of HBV infections among adults with diabetes can be estimated to be approximately 4097. Overall, it can be summarized that the estimated incidence of acute hepatitis B infections among adults with diabetes that are likely to be reported is 1-4 / 100,000, and the total incidence of acute hepatitis B infections among adults with diabetes is ~22.7 / 100,000. In the model, it is estimated the annual number of hepatitis B infections is more than 4000 per year among adults with diabetes, or about 10% of the estimated 40,000 total cases of hepatitis b infection among adults > 25 years of age in the US.

The following table shows a retrospective analysis of data from 4 sites of the Emerging Infections Program:



Each of these sites had some form of data identifying the diabetes status of persons reported with acute hepatitis B infection. Although an age breakout and denominator data were not available, these data suggested again that acute hepatitis B cases among persons with diabetes constitute approximately 10% of all reported acute cases.

In conclusion, outbreaks of hepatitis B virus infection and related morbidity and mortality continue to occur among adults with diabetes related to poor infection control. The increased risk of HBV is not limited to residents of long-term care, as shown in recent data. Prevalence and incidence of HBV infection is higher among adults with diabetes than among adults without diabetes. The increased prevalence of HBV infection among adults with diabetes (8.3%) is comparable to the historical prevalence of HBV among certain groups of healthcare personnel (9% - 28%). Hepatitis B vaccine has been effective in reducing the prevalence and incidence among health care personnel and has potential to do the same among adults with diabetes.

Hepatitis B Vaccine for Adults with Diabetes: Seroprotection and Safety

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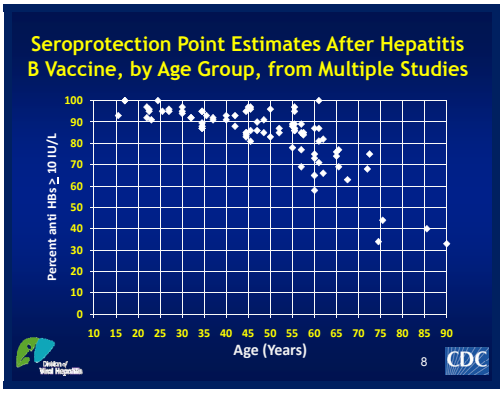
Dr. Spradling pointed out that many studies have documented a high proportion of seroprotection among children and young adults, with and without diabetes, who receive a standard series of hepatitis B vaccine. A special challenge for the work group was to determine the best way to achieve seroprotection among older adults with diabetes. Experience with other vaccines suggests that fewer older adults might achieve seroprotection after a standard series of hepatitis B vaccine, and that the proportion achieving seroprotection among older adults with diabetes might be even lower. In addition, although years of worldwide experience with millions of doses hepatitis B vaccine have established that hepatitis B vaccine is one of the safest vaccines, the work group wanted to be sure that no unique adverse events were associated with hepatitis B vaccine administered to older adults with diabetes. During this presentation, Dr. Spradling shared background information to help interpret the data; presented data from clinical trials on seroprotection after a primary series of hepatitis B vaccination and after revaccination among adults without and with diabetes; and summarized data on the safety of hepatitis B vaccine, including adverse reactions reported to VAERS for adults older than 40 years of age. Protection against hepatitis B virus infection is indicated by the presence of antibody to hepatitis B surface antigen or anti-HBs. A level $\geq$ 10 international units per liter (IU/L) after vaccination generally is accepted as the level that predicts protection. Published data from the US and Asia demonstrate that a response to vaccination of at least 10 IU/L predicts at least 22 years of

protection from symptomatic illness and chronic infection among health adults [McMahon et al. J Infect Dis 2009].

Other historical data have shown that seroprotection among persons less than 40 years is greater than 90% after a standard series of hepatitis B vaccination. This includes younger adults and children with diabetes. With aging, however, the proportion of adults who are seroprotected declines. Similarly, the GMTs are substantially lower among older adults, especially adults with co-morbidities. The significance of lower titers is unknown as long as the seroprotected titer of 10 anti-HBs is achieved. For that reason, in this presentation, Dr. Spradling showed seroprotection proportionsrather than GMTs. Among healthy younger adults who do not respond to the primary series of hepatitis B vaccine, seroprotection improves after additional doses of hepatitis B vaccine. A small proportion of adults do not achieve a seroprotective titer regardless of the number of primary and revaccination doses. From experience with younger recipients, it is known that additional doses of hepatitis B vaccine after the primary series do not increase adverse reactions [Data summarized in MMWR 2006; 55 (RR-16)].

The work group reviewed the literature for hepatitis B vaccination among adults. The populations studied in most hepatitis B vaccine trials in adults were healthcare workers, HIV infected adults, and adults with end stage renal disease. A large number of clinical trials of healthcare workers included hepatitis B vaccination of adults 60 years and older, and a few trials focused exclusively on persons with diabetes. However, the number and depth of these data were not optimal, particularly for revaccination studies. These trials, the trials among adults with diabetes, and sub-analyses of published and unpublished trials conducted by the manufacturers contributed to the data shown during this session. No data were found on the duration of vaccine protection among older vaccine recipients for adults with or without diabetes. These are areas that would benefit from additional research.

The following graph depicts seroprotection point estimates (y-axis) after hepatitis B vaccine by age group (x-axis) from multiple studies in total depicts the effect of increasing age on seroprotection after vaccination:



Each white point on the graph represents the midpoint age of the various age groups included in each of the studies. Each point is neither a single patient nor pooled data from a single study, but rather a midpoint for an age range for seroprotection in a given study. Each study has several points, determined by the number of age groups included. Combined in single graph, it is easy to see the effect of advancing age on seroprotection. Based on data from these studies,

seroprotection is found to be high among younger adults (> 90%) and remains relatively high until the age of approximately 55 to 60, after which it decreases quite noticeably to the 10th decade of life, where seroprotection is the lowest.

Some of the data in the previous graph are from a study which was conducted in a long-term care facility in France that was published in 1984. Residents up the age of 96 were vaccinated with 5µg IM of plasma-derived hepatitis B vaccine, the first generation hepatitis B vaccine that is no longer available. A dose was given every month for 3 months and an anti-HBs level was drawn at 4 months, 1 month after the 3rd dose. Although the outcome of this study was seroconversion (any measurable anti-HBs) rather than seroprotection, it demonstrates decreasing response with increasing age. It also shows that even adults in their 90s may respond to vaccine. Overall, the response among those over age 60 was 46%, keeping in mind that most subjects vaccinated were in their 80s [Denis et al. J Infect Dis 1984].

Data from a study published in 1998 that compared seroprotection after administration of two FDA-approved vaccines, Engerix-B and Recombivax HB, show seroprotection in a large number of adults. With both formulations, seroprotection was lower among adults age 40 to 65 years compared with those younger than 40 [Averhoff F et al. Am J Prev Med 1998].

In a study comparing seroprotection after GSK's Twinrix (combined formulation hepatitis A/hepatitis B vaccine) with Engerix-B (single antigen hepatitis B formulation simultaneously administered at a separate site with hepatitis A vaccine, Havrix) vaccine was given at 0, 1, and 6 months and antiHBs levels were obtained at month 7. Seroprotection after each vaccine formulation was compared for adults 41 to 60 years and adults 61 to 81 years. These data, from an unpublished sub-analysis that is a post-hoc exploratory analysis that included small numbers of subjects provided by GSK, show roughly that overall response among adults 41 to 60 years was on the order of 85-90% and among those 61 to 81 was about 65-70% [Van der Wielen M et al. Unpublished subanalysis provided by GSK. In a similar type of comparison of results by age in a trial conducted in the 1990s to determine the response to Merck's Recombivax HB hepatitis B vaccine among older adults (with vaccine was administered at 0, 1, and 6 months) a decrease was shown in seroprotection from 84% among adults 50-64 years to 75% among adults 65-80 years of age [Unpublished subanalysis by age of unpublished data on file; Provided by Merck, Data on File, Protocol 048 Used with Permission].

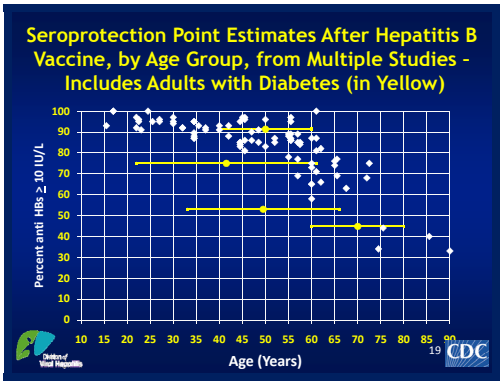
More recent data were presented at IDSA in 2009 pertaining to seroprotection for Merck Recombivax HB and a modified process vaccine available only in Europe. Both vaccines were administered on a 0, 1, 6 schedule. Again, there was a substantial decrease in seroprotection from adults 50-64 years of age to 65-89 years of age [Gilbert et al. IDSA 2009 Abstract # 1171. Merck- Unpublished sub-analysis, Protocol – 059; Used with Permission]. Each of these studies indicates an effect of age and lower seroprotection.

Regarding the effect of diabetes and older age on seroprotection, in an analysis of seroprotection among adults with and without diabetes by type of vaccine (Twinrix hepatitis A/B vaccine and Engerix-B) simultaneously administered at a separate site with hepatitis A vaccine in the 2 groups (at 0, 1, and 6 months), the response among persons without diabetes was roughly 85% and among persons with diabetes was about 68%. There were no pooled data from each group to provide an overall comparison. The mean age for adults with no diabetes was younger than for adults with diabetes, and these data were not adjusted for age. From the same unpublished sub-analysis provided by GSK, seroprotection was compared by age 41 to 60 years and 61 to 80 years among subjects with diabetes. Although the number of subjects available for comparison became quite small (on the order of 5 to 10 subjects per group) and the confidence intervals became quite wide, there appears to be a sizable reduction in seroprotection for adults with diabetes over age 60 [Van der Wielen M et al. Unpublished subanalysis provided by GSK, and is the result of a post-hoc, exploratory analysis including small numbers of subjects].

Additional data are available for adults with diabetes. A study by Douvin et al shows seroprotection of 53% after 3 doses of hepatitis B (Engerix-B) given at 0, 1, and 2 months. Seroprotection was measured at month 3. The age range was somewhat younger in this study [Douvin et al. Diabetes Care 1997].

Better seroprotection of 75% was achieved among 32 subjects with diabetes vaccinated at 0, 1, and 6 months in a study conducted by Wismans et al. The age range of participants in this study was broad, with some subjects as young 22 years of age. Seroprotection among these adults with diabetes, albeit relatively higher, was significantly lower than among controls in the same study without diabetes, which was 97% [Wismans et al. J Med Virol 1991].

The following graph summarizes the results of studies that report separate results for adults with diabetes shown in yellow on the background of the studies of adult seroprotection graph shown earlier:



Again, the points represent the mid-range age among age groups from multiple studies. The horizontal bars in yellow show the midpoint and age range of adults with diabetes. It can be observed in this graph that for a particular age or age group, seroprotection is generally lower among persons with diabetes than among persons without diabetes.

In summary, published studies and unpublished data demonstrate that approximately 2 of 3 adults over age 60, and a smaller proportion of persons with diabetes on the order of 55%, will achieve seroprotection after a primary series. ACIP currently recommends post-vaccination testing for seroprotection after a hepatitis B vaccine series in groups with low seroprotection rates (e.g., persons with HIV infection) and / or groups who have increased risk of exposure (e.g., healthcare personnel). Additional doses in the primary series may improve seroprotective rates. With that in mind, it is important to consider the response to revaccination among non-responding older adults. Possible revaccination options for hepatitis B vaccine non-responders include the following:

- Revaccinate (1 - 3 doses) with the same vaccine in standard dosage used in the primary series
- Revaccinate (1 - 3 doses) with a higher dosage (e.g., dialysis dose 40µg) versus standard dosage used in the primary series
- Revaccinate with a different vaccine formulation

Dr. Spradling then shared data pertaining to seroprotection as a result of administering additional doses of hepatitis B vaccine to persons with and without diabetes who did not responded to the primary series with ≥10 IU/L anti-HBs (termed "non-responders"). He noted that non-responders were defined as having an anti-HBs level less than 2 IU/L. This is important because this likely includes the few adults who will not respond to vaccine regardless of the number of doses—sometimes referred to as "complete non-responders."

In terms of the results of studies that assessed the response to one additional dose of hepatitis B vaccine strictly among non-responders to the primary series, overall the proportion of non-responders who achieved seroprotection after a single dose was approximately 55%. However, the mean age of participants was low, although the studies included a number of adults over age 60. None of these studies included adults with diabetes [Goldwater et al.; Struve et al.; Wolters et al].

In studies of the response of non-responders to an 2 to 3 additional doses of hepatitis B vaccine, the responses ranged from 60% to 100% after three doses. The 5 adult non-responders with diabetes had an 80% response. Of interest, the overall response was ~88% among the 32 adults with diabetes in this study combining primary and revaccination [Bertino et al. (Excluded hypo-responders [2-9.9 mIU/ml]); Averhoff et al.; Clemens et al.; and Wismans et al).

In a study of seroprotection after additional doses of hepatitis B vaccine among non-responders with diabetes, non-responders at month 3 received a 4th dose at month 4, resulting in 88% seroprotection. All subjects received a dose at 12 months, with overall seroprotection of 94%. Seroprotection was 77% among adults ages 60-66 years [Douvin et al. Diabetes Care 1997].

In four studies of seroprotection after high dosage hepatitis B vaccine among non-responders, none of which broke out results for subjects with diabetes, the study pertaining to response to a single high dose of Engerix (44% response) included only complete non-responders [Goldwater et al (only antiHBs negative)]. In the other three studies, 3 doses of high dosage vaccine were used. Seroprotection for the 3-dose studies ranged from 55% to 95% [Kim et al; Bertino et al (excluded hypo-responders [2-9.9 mIU/ml]); and Cardell et al]. The best results were with high dosage vaccine, but overall seroprotection overlapped those in studies of standard dosages.

In summary, older adults have an increase in seroprotection with each additional revaccination dose 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. Available data do not confirm a clear advantage to higher dosage (40ug) or by type of vaccine.

In terms of the safety of hepatitis B vaccine in older adults with and without diabetes, although multiple studies have examined seroprotection among older adults with and without diabetes, few report any adverse events. Product safety information from vaccine manufacturers [Package inserts Engerix-B®, Twinrix®, Recombivax HB®] indicate that local adverse events including soreness are reported in up to 22%, and swelling or redness at the injection site is reported in 1%-10% of doses. Systemic events include fatigue (14% of doses) and fever, headache, dizziness, nausea (1% to 10% of doses). During clinical trials and post-licensure surveillance, no deaths were attributed to hepatitis B vaccine. Anaphylaxis is rare and occurred in only ~ 1 per 1.1 million doses. Although reported clinical and surveillance data are limited in studies of older adults, none suggests a difference in overall safety compared with younger adults.

The data for adverse all events reports to VAERS for hepatitis B vaccine among adults with diabetes for the age groups 40-59 years and 60 years and older span more than 10 years from January 2000 through May 2010. Although this information cannot be put into perspective without denominator data, the number of reports over this period was small in both age groups, and no deaths were reported.

Non-fatal serious adverse event reports to VAERS after Hepatitis B vaccine among Adults with diabetes, age ≥ 40 Years included the following:

57 M Pancreatitis
55 M Respiratory Infection, Injection site reaction, "CHF related to vaccine“
69 F Elevated liver function test results
56 F Right upper extremity swelling, decrease ROM, paresthesia
48 M Chest Pain, Back pain
63 M Increase in diffuse body pains, septicemia, acute respiratory distress
55 M Arthralgias, joint stiffness
70 F GBS-Miller Fisher Variant
51 M Allergic reaction
50 F Epistaxis

Of these reports, 6 of 10 had available medical records for review. From the available records, it was not apparent that any of the events was related to hepatitis B vaccine.

In conclusion, hepatitis B vaccination of older adults with and without diabetes is safe. The proportion of adults seroprotected by a primary series of hepatitis B vaccine varies with age and co-morbidity. Approximately 90% or more are young adults, about 2/3 (67%) are healthy older adults, and about 50% are adults with diabetes. Revaccination of non-responding older adults improves seroprotection. Although data are lacking on long-term immunity among persons vaccinated at older ages or with diabetes, published data suggest achieving anti-HBs $\geq$ 10 IU/L in healthy adults protects against symptomatic acute hepatitis B and chronic infection for 22 years or more.

Discussion Points

Dr. Chilton noted that New Mexico has a "Done by One" campaign. This is an 11-year old immunization platform. Perhaps a 61-year old platform is needed as well. He wondered whether immunization against hepatitis B would be covered under Medicare Part B or D, which plagues practitioners with respect to zoster vaccine.

Dr. Baker said she did not believe Medicare covered this.

Ms. Rosenbaum indicated that, unless someone had Medicare because of a disability, Medicare would not begin until age 65. Therefore, there are two issues. First, there is the B / D question in terms of the limitations on hepatitis vaccine and then age. In the future, some of the age issues may begin to fall away.

Dr. Linda Murphy (CMS) said that she was from Medicaid not Medicare, but suggested emailing the question to her so that she could direct it to the right contact person.

Dr. Schuchat added that Medicare Part B covers influenza, pneumococcal, and hepatitis B vaccine for high risk individuals only for anyone who is Medicare Part B-eligible. All other vaccines are covered under Medicare Part D, if anywhere.

Ms. Rosenbaum said this raised the question regarding whether this would be a high risk group.

Dr. Keitel noted that they seemed to be making a move toward stating that diabetes is a high risk group.

Dr. Judson indicated that he had been working on hepatitis vaccines and epidemiology for most of his career. With that in mind, he suggested that the first priority on the list should be to ensure that nursing homes and long-term care facilities follow accepted infection control procedures. He did not believe they should be discussing vaccine if the lack of such practices continued. The first issue to be dealt with is proper use of blood glucose monitoring devices and injection materials. Once that is dealt with, the explanation for hepatitis B being more common in diabetics than non-diabetics must be broken down epidemiologically into whether there are covariates that lead to higher rates of exposure. One of those would certainly be risk. Then they must deal with whether, once someone is exposed as a diabetic, they are more likely to become infected and if infected they are more likely to become chronically infected. There is some evidence that individuals with obesity and metabolic syndrome are less likely to clear and handle a number of infections. The rate of seroconversion in diabetics can also be a function of the length of the needle used in diabetics, given that most of them are obese. All of this must be sorted out.

Dr. Baker noted that Dr. Middleman had conducted a needle length study in adolescents. She wondered whether there were studies about needle length in Type 2 diabetic adults.

Dr. Spradling responded that he was not aware of any.

Dr. Neuzil pointed out that since there were a number of adjuvanted hepatitis B vaccines in various stages of development, it would be beneficial to hear a review of those and know whether any were close to licensure.

Ms. Rosenbaum inquired as to whether there was any information about those under age 65 regarding the heightened risk by income. One of the major issues that will remain even after health reform is the state of immunization policy coverage under Medicaid for the poorest adults.

Dr. Hu replied that with the NHANES data, subgroup analysis is very difficult. People often think of NHANES as very large, but when broken down into smaller groups, subgroup analyses are generally not recommended for cells of less than 30. Especially when assessing persons with diabetes, that small group becomes even smaller. Regarding a comment made earlier, it is true that a number of population groups who are at risk for diabetes are also at risk for hepatitis B infection (e.g., American Indians, Asians, Hispanics). Thus, a lot of this is difficult to tease out.

Dr. Stephen Foster (APhA) agreed with Dr. Judson. The Needlestick Safety and Prevention Act stated that multiple use lancets could not be used in nursing home settings. Thus, multiple use of a single use devise is breaking the law. This must be resolved, especially since this pertains to about 150 versus 18 million people for whom a recommendation is being made for vaccines. One of the conclusions that states that "compared to the historical prevalence of hepatitis B among certain groups of healthcare personnel" the term "certain groups" is confusing. According to CDC statistics in 2001, fewer than 400 healthcare workers actually acquired hepatitis and it was not specified whether this was due to needle sticks. He agreed that before ACIP made a recommendation for expenditures for 18 million people, they should find out what other potential high risk behaviors may be.

Dr. Temte wondered what specifically the risk factor was and whether there was any estimate of incidence for diabetics in long-term care versus diabetics alone. It seemed to him that at least the entry was all in terms of long-term care facilities. There is a major and growing population moving into assisted living. What is not clear whether a diabetic living in the community on their own with their own supplies is a risk factor, or the risk arises when entering a long-term care facility.

Dr. Hu responded that despite a number of recommendations that have been in place for close to 20 years, there continue to be breeches of infection control. ACIP's argument could go both ways. They could argue that before vaccination is recommended, the problem of breeches should be solved. They could also argue the importance of vaccination due to the very fact that these breeches continue to occur. CDC has had a number of consultations with several other federal agencies to assess how to approach the problem of healthcare transmission in three ways. The first is to strengthen existing recommendations and improve oversight. The second would be to improve technology and labeling of devices (e.g., glucose meters, medication vials, et cetera) to stress that these are for single use only. The third would be the use of hepatitis B vaccine. Regarding how to determine the risk for diabetes within various age groups, just as for the general population, this list can come from a variety of risks (e.g., MSM, IDU, et cetera). It is very difficult to determine whether high risk is due to the increased blood exposure that diabetics encounter. Unfortunately, so far there are no data on the incidence in long-term care facilities. However, from very small studies (some from outbreak studies and some from general long-term care studies) the prevalence of HBV appears to be much more elevated than the general prevalence. This suggests that there may be a much higher incidence in these facilities. Regarding healthcare workers, there were a variety of healthcare settings. He assessed vaccination data. There was a very nice set of studies, one of which was conducted by CDC's former director, Dr. Julie Gerberding. A survey was conducted of different classes of healthcare workers in the UCSF system, and enrolled healthcare workers who were

seronegative for HBV and followed them over time. By doing so, they were able to measure the incidence. The success of not only hepatitis B vaccine, but also universal precautions in improving infection control, have dramatically reduces the incidence and prevalence of HBV among healthcare workers.

To illustrate the discussion around improving infection control, Dr. Sawyer pointed out that everyone must keep in mind that the level of training of people working in these facilities, particularly assisted living facilities, is much lower than in a typical healthcare setting in which they are used to trying to improve infection control. There is also a great deal of turnover of those staff, so this requires continuous retraining. Thus, he thought they needed to be careful in assuming that they could achieve the same level of success in implementing infection control policies in long-term and assisted living settings that they do in more organized healthcare settings.

Dr. Baker added that skilled nursing facilities all have rules, laws, inspections, et cetera. They may lose their certification. Assisted living is increasingly becoming populated by people who need skilled nursing who are at greater risk, yet there is no regulation at most of these facilities.

Robert Malone (Independent consultant for a variety of vaccine developers and supporting companies) said he was struck by the analogy in transition in the understanding of influenza vaccine effectiveness in the elderly. Reasoning by analogy suggests that one co-morbidity on which they may wish to have data would be the incidence of chronic cytomegalovirus infection in these populations because of the hypotheses for why a decreased effectiveness of influenza vaccines is observed in elderly populations.

Focusing on her experience in a State of Maine public health agency, Kathleen Gensheimer (Sanofi Pasteur) said she was clearly delighted to see the emphasis placed on enhanced patient safety. Regarding the residential care population over the age of 50, she followed a cluster of men over the age of 50 for a few years many of whom were obese, had diabetes, and were at home doing their own glucose monitoring. After a lot of careful questioning, it turned out that they were closeted MSMs who were going to a truck stop in central Maine. She wondered whether they were missing what could still be an unrecognized factor for transmission of hepatitis B, whether healthcare providers were still thinking about targeting that cohort that really needs vaccine, and whether there was any information on men over the age of 50 with other potential risk factors on a national level.

Dr. Hu said he thought one piece of data that supported that there may be under-recognized MSM. If the reporting of hepatitis B cases by age group are divided by sex, the rates for men, even in the older age groups, are higher.

Regarding Dr. Neuzil's earlier question, Dr. Plotkin reported that there was an adjuvanted hepatitis B vaccine currently in Phase 3. The defect may be exacerbated in diabetes, but as Dr. Spradling emphasized, this is a defect that is inherent to immunosenescence and involves at least antigen processing and lack of naïve lymphocytes. Thus, it has to be remedied. Repeat dosing is not really a practical answer. If a recommendation is made, he would wager than more than one company would manufacture adjuvanted hepatitis B vaccines not only for diabetes, but also for hemodialysis patients, others who do not respond as well, and all people over a certain age.

Georges Peter (Warren Alpert Medical School, Brown University) agreed with Dr. Judson's very important comment about obesity. Obesity is a risk factor for diabetes and there is an epidemic of obesity. He wondered to what extent body mass had been taken into account in the studies of adults over the age of 40 in terms of seroresponse to vaccination.

Dr. Spradling responded that ironically, the data from the GSK sub-analysis of the 41 to 81 age groups, which broke the data down even further into diabetes and no diabetes, suggested that patients with lower body mass had a poorer seroprotective response to vaccine than those with a higher body mass. However, there is plenty of evidence to suggest the contrary. In terms of the analyses CDC / NCHSTP dealt with, they focused purely on diabetes and tried to stay away from additional factors such as body mass. Assuming that these populations who have Type 2 diabetes are an older age group, a certain proportion of them by nature are going have high body masses.

Dr. Deborah Wexler (Immunization Action Coalition) resonated with Dr. Hu's comment about the "tip of the iceberg" in that these cases are being identified because diabetics get so many finger sticks. However, every day in every medical practice in the country, glucose meters are being used. They are being used on pregnant women in their one-hour glucose challenge test in every pregnancy. She wondered whether any cases had been seen in practice setting, because she thought that the same problems being observed in assisted living settings were also occurring in primary care settings.

Dr. Hu replied that this pointed out that even though the focus is on persons with diabetes, once someone becomes infected, they can transmit as a source patient to other susceptible people. There is frequent glucose meter use in hospitals. In speaking with nurses and doctors, he often inquires as to why they use a glucose meter to determine blood glucose if they are obtaining daily blood chemistries. One response he has heard is that nurses like to use glucose meters because they are able to get blood data right away instead of going to a lab or accessing it from a computer.

Dr. Catherine Counard (Public Health Physician from Northern Illinois and the NACCHO liaison to the ACIP Hepatitis Vaccine Work Group) thanked ACIP for taking on this very concerning issue. She investigated two of the hepatitis B outbreaks in assisted living facilities that were presented, both of which were caused by nurses transmitting infection from resident to resident as they performed finger stick blood glucose monitoring. The published retrospective cohort study revealed a relative risk of 28.5 associated with finger stick blood glucose testing. Nursing staff at both of these facilities were not aware, despite multiple trainings, that they could transmit infection from person to person. From being in the halls during an outbreak, she could attest to the fact that the toll at the two facilities of infected individuals was substantial. There were 14 ill, 6 who required hospitalization, and at least 3 have not cleared their infection and have chronic disease as a result. Additionally, the outbreaks required significant resources from the health department and the medical community to determine the scope and cause of the outbreaks. She drew blood on 109 residents at this facility because they were unsure of the cause of the outbreak initially. She was there at 6 am, she processed the specimens, and she drove them to the state laboratory so they could be sent to CDC for further analysis. Although it is known that the outbreaks could have been prevented by adhering to standard infection prevention measures, the lack of appropriate training and oversight for personnel and rapid turnover of staff in these facilities provide formidable barriers. In response to the first case at one of the facilities investigated, an on-site investigation was done, all of the staff was interviewed, and training and

guidance were provided for nursing staff. When the second case surfaced 15 months later, they revisited this site and were amazed to find out that every nurse had turned over, including the director of nursing. There was no institutional memory that there had been a case at this facility, nor did anyone remember any of the training that was delivered previously. Thus, she regretted to report that hepatitis B transmission continued to occur in this facility. When they returned for the second case, they found 7 other cases. Unfortunately, she did not believe this was unusual. She has visited many of these sorts of institutions for various outbreaks. These are not rogue facilities. On the surface, they look like a nice place for someone to be. With all of this in mind, she encouraged ACIP to give serious consideration to broadening vaccination to protecting diabetics. She also extended her gratitude to CDC staff who have been very supportive of her in these outbreak situations.

Dr. Leonard Friedland (GSK) indicated that in the subanalysis of the data Dr. Spradling presented, indeed, individuals with large body mass did not have a decline in response. It is important to note that these were very small numbers of subjects, and the majority of the subjects in the trials were obese. Regarding adjuvanted vaccines, GSK has a licensed adjuvanted vaccine licensed in the European Union for people above the age of 15 that is indicated for renal insufficiency.

Policy Considerations: Hepatitis B Vaccination for Adults with Diabetes

Dr. Trudy Murphy
CDC / NCHHSTP

Dr. Murphy reviewed the policy options considered by the Hepatitis Work Group for hepatitis B vaccination of adults with diabetes. Some of the options included vaccinating all previously unvaccinated adults with diabetes, *or* vaccinating a subgroup of adults with diabetes, for example only residents of long-term care with diabetes, *or* only adults with diabetes who monitor blood glucose, *or* only adults with a new diagnosis of diabetes. The work group considered hepatitis B vaccine-induced seroprotection by age, type of vaccine, and dosage. They considered pre-vaccination screening for susceptibility and issues related to revaccination such as post-vaccination testing, and they considered whether to give a booster dose to previously vaccinated adults with diabetes. The work group also considered hepatitis B vaccination for a variety of contacts of adults with diabetes in long-term care facilities (e.g., roommates, family contacts, and even vaccinating all residents in these facilities).

The guiding principle in these discussions was that any proposal should be consistent with current recommendations for hepatitis B vaccination. The priority was to maximize seroprotection in all age groups by vaccinating adults with diabetes as soon as feasible after diagnosis and by post-vaccination testing and revaccination, if necessary, for older adults with diabetes who are most likely to be non-responders to the primary series. The work group did not favor booster dosing for previously vaccinated adults with diabetes, consistent with current recommendations, and did not feel that vaccinating contacts of adults with diabetes in long-term care facilities was practical, unless the contact met criteria for vaccination already specified by ACIP (for example, the sexual partner of an adult with diabetes known to have chronic hepatitis B infection). The wording proposed by the work group was as follows:

- Hepatitis B vaccination is recommended for (*all)* unvaccinated adults with diabetes. The vaccination series should be completed as soon as feasible after diagnosis.
- Available data do not confirm an advantage to any specific hepatitis B vaccine or dosage for adults with diabetes.

- For adults with diabetes ≥ 60 years, post-vaccination serology for antibody to hepatitis B surface antigen (anti-HBs) is recommended 1–2 months after completion of the hepatitis B vaccination series.
- Adults with diabetes who do not achieve a seroprotective level of ≥10 mIU/mL anti-HBs should be revaccinated with 3 additional doses of hepatitis B vaccine and post-vaccination serology should be repeated.
- Additional guidance on revaccination can be found in Appendix A of the recommendations (MMWR 2006;55 [RR-16]).
- No additional hepatitis B vaccination is recommended for adults with diabetes who received a complete series of hepatitis B vaccine at any time in the past.

The Working Group proposed repeating the wording in current recommendations as a reminder for hepatitis B vaccination of employees in long-term care facilities:

Reminder for Healthcare Workers

- Hepatitis B vaccination is recommended for healthcare workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids. (MMWR 2006; 55 [RR-16])
- Facilities should provide a full hepatitis B vaccination series to all previously unvaccinated staff members with exposure to blood or body fluids. (MMWR 2005; 54:220-223)

Reminder for Medical Management, Training, and Oversight

- Guidelines for preventing patient-to-patient transmission of hepatitis viruses from diabetes-care procedures in long-term care settings are available (MMWR 2005; 54:220-223)

Discussion Points

Dr. Pickering noted that several of the slides Dr. Murphy shared showed an improved seroresponse utilizing the combined hepatitis A / B vaccine. As a follow-up to what Dr. Neuzil alluded to, he wondered whether it was potentially an option to utilize the combined vaccine rather than single antigen, knowing that even though diabetes is not on the high risk group for hepatitis A, people with chronic liver disease are. Perhaps a more thorough review could be presented during the October 2010 ACIP meeting of the responses of people with the combined A / B vaccine.

Dr. Murphy said this could be provided and she could offer a preview as they had tried to do this to some extent. In younger age groups, there does appear to be a slight increase in seroprotection with the combined vaccine (ages 50 to 60 years and younger). It is a marginal difference. In the older age groups, the data that are available are limited and there does not appear to be any advantage.

Regarding the infection control issues, Dr. Elward (HICPAC) reported that historically they had had a lot of success with infection prevention when addressed at multiple levels (e.g., regulatory oversight, reimbursement, educating the public, industry / technology, et cetera). CDC has done an excellent job of bringing this problem to light, measuring the problem, and beginning the process of communicating this information with CSTE, HICPAC, industry partners, stakeholders, et cetera and publishing information quickly (including in the popular press).

Thus, there is a lot of good foundation for a lot of these deeper, more complex fixes to be implemented. Vaccination could certainly be done with relatively ease and more quickly than some of the big infrastructure fixes that are starting to be addressed.

Dr. Gall (ACOG) pointed out that with the addition of diabetes as a risk group who would bring the number of risk groups for hepatitis B to 27. One of the risk groups to be included is if a patient is screened for a sexually transmitted disease (STD). For obstetricians, every patient is screened for 5 STDs and for gynecologists, 1 to 3 STDs are screened at every visit. The recommendation is universal to age 19, and now there are 27 risk groups. He wondered what percent of the general population is covered to universal to 19 and 27 risk groups, and whether it was time to say that this vaccine should be universal. Or were they going to do the same thing that was done with influenza and chisel at it before eventually reaching the universal stage?

Dr. Judson agreed. He also thought that with hepatitis being universal with youth through high school they would get to a universal recommendation before too long anyway. He also pointed out that it had not been conclusively shown that diabetics, because they are diabetics, are at greater risk of being exposed to and infected with hepatitis B. As everyone knows who works in that area, there are many potential methodological problems. Their higher risk is probably due to something other than the diabetes. One issue could be the misidentification of acute infection and other problems (e.g., obesity, metabolic syndrome, steatohepatitis, elevated enzymes).

In the interest of transparency, Dr. Schaffner (NFID) disclosed that he was much more interested in promoting more widespread use of hepatitis B vaccine in adult populations. If they were not ready for a universal recommendation, he would take any additional “bit of the apple” he could. He encouraged ACIP to recommend immunization of all diabetics. However, he stressed that recommendations do not implement themselves. On the basis of local experience with the diabetic community and influenza and pneumococcal vaccine, long recommended for that community, neither of those vaccines have been on the quality assurance list for appropriate diabetes care for such patients. Therefore, if a recommendation is made, he expressed hope that the hepatitis folks would reach out to the diabetes community to get these vaccines introduced into the quality assurance activities. He also emphasized that recommendations are cheap, but the implementation comes with a cost. When last this committee considered hepatitis B vaccine in adults, they chose to stick with high risk groups. However, they were told then that efforts were made and resources would be found to be directed toward enhanced immunization of at least some people in some high risk groups (e.g., those being evaluated for STDs, prisoners, MSM); however, he did not believe ACIP had ever been given a report about whether this occurred. If they were going to recommend that adults in the US with diabetes be immunized, he expressed his hope that this came with good will and determination and resources to effect that good result.

Dr. Baker emphasized that ACIP’s job as a committee is recommendations. While they should be aware of implementation issues as they make recommendations, there is a next step of action beyond ACIP.

Dr. Schuchat reported that over the last several years, substantial resources from the Section 317 vaccine purchase funds have been directed to hepatitis B vaccine for adults. The state health departments have been able to work in collaboration with STD, correctional facility, and HIV programs to try to promote greater uptake. Evaluation of this is in the early stages, and a recent *MMWR* summarized some of this work.

Dr. Judson requested a report on the cost-effectiveness data in view of the declining trend of hepatitis B, with incidence down 85% to 90% and still dropping. Cost-effectiveness must look forward, and with those trends, the estimates will become increasingly less favorable.

Dr. Baker agreed that ACIP needed to hear cost-effectiveness data in light of current epidemiology.

Dr. Plotkin thought that the recommendation that people who have been previously vaccinated do not need to be revaccinated was reasonable at present, but there are some data suggesting that the anamnestic response to vaccines does not last forever. It begins to diminish. He thought this recommendation should be revisited after more data have accumulated showing that adults who were vaccinated when they were younger actually still have immune memory.

Dr. Murphy responded that this is the next term of reference for the Hepatitis Vaccine Work Group.

Dr. Whitley-Williams (NMA) proposed that there be improved surveillance for hepatitis B. This certainly is under-reported and, in fact, cases do not come to light until they become symptomatic. There are segments of the population, particularly Asian Pacific Islanders, who come to the US as adults and either know they have hepatitis and do not seek care until they are symptomatic, or do not even realize that they are infected having grown up in an HBV-endemic country. She also echoed support for universal immunization, given that there are many risk factors. Surveillance does not always capture ethnicity, country of origin, how long someone has been in the US, et cetera. Regarding Dr. Plotkin's suggestion, the DoD has a wonderful database that would permit assessment of youth who have been immunized to examine their duration of immunogenicity.

Pertussis

Introduction

Mark Sawyer, MD
University of California – San Diego
Chair, ACIP, Pertussis Vaccines Working Group

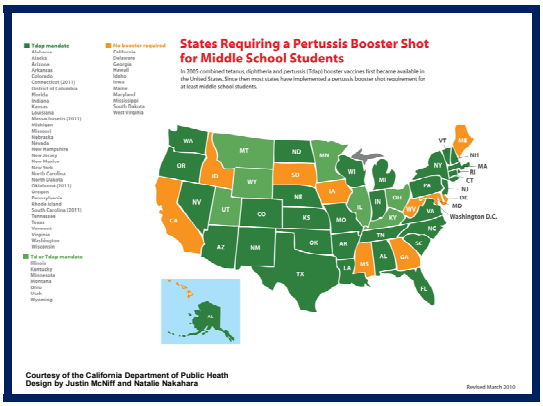
Dr. Sawyer indicated that the terms of reference for the Pertussis Working Group, and its primary charge, was to review existing statements on infants and young children (1997), adolescence (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate those into a single statement. In the process of doing so, the group plans to review new data that may speak to the effectiveness of the current Tdap (Tetanus, Diphtheria, Pertussis) program including uptake of current recommendations and barriers to uptake; the interval between Td booster and Tdap with respect to safety and reactogenicity; use of Tdap in those ≥65 years of age and pregnant and breastfeeding women, use of Tdap; cocooning strategies, Tdap in healthcare workers and the need for post-exposure prophylaxis. The updated epidemiology of tetanus and diphtheria are also being reviewed.

To date, the activities of the Pertussis Working Group have included the following:

- April 2009
  - → Introduction and overview of pertussis epidemiology in the United States
  - → Explored the potential early impact of Tdap vaccination
- May 2009
  - → Review current ACIP Tdap recommendations
- June 2009
  - → Safety and reactogenicity of Tdap
  - → Interval between Td and Tdap
  - → Pertussis diagnostics
- July 2009
  - → Impact of pertussis vaccination of health-care personnel on post-exposure prophylaxis
- August 2009-February 2010 (hiatus)
- March 2010 (reconvene)
  - → Review/update Terms of Reference
  - → Reassess where WG is regarding topics and data
- April 2010
  - → Use of Tdap in persons ≥65 years of age
- May 2010
  - → Epidemiology of diphtheria and tetanus
- June 2010
  - → Improving Tdap coverage

The work group has carefully examined available data pertaining to the interval between Td and Tdap, and is anxiously awaiting data from on-going studies regarding the use of Tdap during pregnancy. As soon as that information is available and the working group has an opportunity to complete its review, an update will be presented to the full ACIP.

The presentations during this session focused on an overview of pertussis epidemiology in the US, an evaluation of the current pertussis vaccine program, and a review of the current ACIP recommendations for use of DTaP and Tdap in the US. Those recommendations, at least with regard to adolescents, still have not been fully implemented. Recent coverage rates estimate Tdapuptake of approximately 40% in adolescents. Middle school entry requirements have been implemented for Tdap booster administration, which are hoped to increase coverage rates. The following map reflects the states for which mandatory booster requirements are in place:



Dr. Sawyer requested that everyone consider the following questions as they listened to the presentation:

- ❑ Are we using our vaccines as well as possible?
  - → Coverage
- ❑ Are there barriers to vaccination that can be removed?
- ❑ What else can we do to optimize each of these components of the program?
  - → Infant/Children
  - → Adolescent
  - → Adult

Program Update on Pertussis Vaccine

Jennifer L. Liang
Meningitis and Vaccine Preventable Diseases Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention (CDC)

Dr. Liang presented a program update on pertussis-containing vaccines since the 2005 recommendations. She explained that pertussis (e.g., whooping cough) is a highly contagious respiratory disease caused by the gram negative bacillus, *Bordetella pertussis*. Clinically recognized to cause severe debilitating cough illness, the highest morbidity and mortality occurs among infants. Pertussis is the most poorly controlled bacterial disease despite high childhood vaccine coverage. The first US pertussis vaccine for adolescents and adults, Tdap, was licensed in 2005. Among the other reportable vaccine preventable diseases, pertussis is still the least well-controlled.

Regarding the impact of pertussis from 1922 through 2009, 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. Between 1990 and 2009, more than 190,000 pertussis cases were reported to CDC. Over time, cases less than 1 year of age and cases 1 through 6 years of age contributed less to the overall burden of disease, while

cases in adolescents and adults contributed to an increasing proportion of cases. Around 2007, there appears to have been a shift in the distribution, with an increasing contribution from 7 to 10 year olds. By 2009, this age group accounted over 23% of cases [2009 Data are provisional Source: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service].

In terms of the reported pertussis incidence by age group from 1990 to 2009, infants have substantially higher rates of disease compared to other age groups. The use of polymerase chain reaction (PCR) has become more common since PCR was approved in 1997 by the Council of State and Territorial Epidemiologists (CSTE) for use in confirming pertussis cases. Laboratories have increasingly used PCR instead of culture and there are fewer culture-confirmed cases. Changes in laboratory diagnostics remain a concern and do impact interpretation of surveillance data. In general, it is believed that culture, PCR, and serology should be used in a complementary way to diagnose pertussis. CDC and its partners have multiple activities aimed at optimizing use of these tests [2009 data are provisional; source: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System; data collection for PCR and epi-link began in 1995].

During this presentation, ACIP members were asked to reflect on vaccine coverage among infants, children, adolescents and adults; Tdap vaccine effectiveness and duration of protection; and the feasibility and effectiveness of cocooning.

Young infants have the highest rates of disease and pertussis-related complications. From 2000 to 2009, among infants aged less than 1 year (n=25,179), reported complications included apnea (n=10127; 58.0%), pneumonia (n=1875; 19.2%), seizures (n=202; 1.2%), and death (n=182; 1.1%). More than half (n=11571; 66.3%) of these reported cases required hospitalization [Source: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis; Surveillance System, 2000-2009; 2009 data are provisional; percentages are based on total number with information; for 19% of infant cases, no information was available on hospitalization or apnea; for 21% no information was available on seizure; and for 34%, no information was available on pneumonia; pneumonia was radiographically confirmed].

The following table shows a breakdown in age groups of reported pertussis-related deaths over the past 30 years. The majority of deaths occurred in infants 0 to 1 month of age, before they were eligible to receive the first dose of DTaP:

Reported pertussis-related deaths by age-groups, U.S., 1980-2009*

Age-Group	1980 1989[1]	1990-1999[1]	2000-2009[2]
0-1 month	38	68	119
2-3 month	11	16	56
4-5 month	5	5	6
6-11 month	7	4	1
1-4 years	13	2	2
5-10 years	1	6	2
11-18 years	0	0	2
>18 years	1	2	6
Total	77†	103	195*

*2009 Data are provisiona
[1] V tek CR e a Pedia r n ect Dis J 2003; 22(7):628-34.
[2] Na ona No able D seases Surveillance Sys em CDC, 2009*
† Inc udes one case w th unknown age

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Infant vaccine coverage for DTaP remains high. Current coverage for children 19 to 35 months of age who have received 4 or more doses of DTaP/DTP/DT is 85% [CDC. National Immunization Survey. Q3/2008-Q2/2009]. Among children entering kindergarten for the 2008-2009 school year, DTaP coverage was 93% [CDC. National Immunization Program. School and Childcare Vaccination Surveys & Reports]. Estimates of DTaP efficacy vary by study, but based on vaccine trial studies, efficacy ranges from 85.2% to 88.7% [* Gustafsson LH et al. A controlled trial of a two-component acellular, a five component acellular and a whole-cell pertussis vaccine. NEJM 1996;334:349-355; and Schmitt HJ et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure JAMA 1996;275:37-41, respectively].

For adolescents and adults with pertussis, there is a wide spectrum of clinical presentation which can range from being quite severe with classic presentation of pertussis to being asymptomatic. However, disease is often milder in adolescents and adults. Pertussis is clinically difficult to distinguish from other causes of cough illness, and persons with mild disease can transmit infection. Several studies have provided evidence that household members were primarily responsible for transmission of pertussis to infants (75%–83%). More specifically, parents and siblings were the most commonly identified source of pertussis: parents (55%), siblings (16%-20%), aunts / uncles (10%), friends / cousins / others (10%-24%), grandparents (6%), and caretakers (2%) [Wendelboe AM., et al. Transmission of *Bordetella pertussis* to Young Infants. Pediatr Infect Dis J 2007;26: 293–299; and Bisgard KM, Pascual FB, Ehresmann KR, Miller CA, Cianfrini C, Jennings CE et al. Infant pertussis: who was the source? Pediatr Infect Dis J 2004; 23(11):985-989].

Coverage for Tdap among adolescents aged 13-17 years was 10.8% in 2006, 20.4% in 2007, and over 40% in 2008. Obtaining 40% coverage 5 years after a new program might be judged as a success, but it falls short of the goals. 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 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].

Although adolescents should be receiving Tdap not Td, in 2008 10% of adolescents who were vaccinated received Td [Vaccine type by year of first tetanus booster among vaccinated adolescents aged 13-17 years*, NIS-Teen 2008; slide courtesy of Shannon Stokley, CDC].

At the time of licensure, 85% to 89% of Tdap efficacy was based on bridging studies from infant vaccine efficacy studies (ADACEL and BOOSTRIX)[1]; APERT study[2] (1997) VE = 92% (95%CI: 32.0-92.0); Australia[3] (2005) VE = 78.0% (95%CI: 60.7-87.6); and St. Croix outbreak[4] (2007) VE = 65.6% (95%CI: -35.8-91.3). Immune response to Tdap was non-inferior to the immune response of infants receiving DTaP. From the adult pertussis trial, overall vaccine efficacy of an acellular pertussis vaccine was 92%. Recent post-licensure studies of Tdap show vaccine effectiveness at 78% and 66%. Although not statistically significant due to limited sample size, the effectiveness from the St. Croix outbreak is comparable to the Australian study [[[1] Schmitt HJ et al. JAMA 1996;275:37-41; Gustafsson LH et al. NEJM 1996;334:349-355; [2] Ward JI et al. Efficacy of an acellular pertussis vaccine among adolescents and adults. N Engl J Med. 2005 Oct 13;353(15):1555-63; [3] Rank C, et al. Pertussis vaccine effectiveness after mass immunization of high school students in Australia. Pediatr Infect Dis J. 2009 Feb;28(2):152-3; [4] Wei SC, et al. Effectiveness of adolescent and adult tetanus, reduced diphtheria, and acellular pertussis vaccine (Tdap) against pertussis. Manuscript accepted to Clin Infect Dis].

Before reporting on the potential impact of Tdap, Dr. Liang reminded everyone that the rates of pertussis increased gradually in the US between 1990 and 2003, before reaching a peak of 8.8 cases per 100,000 population in 2004. The introduction of Tdap in 2005 occurred at the height of this peak when rates of disease in the US were significantly elevated. Since 2005, there has been almost a 50% decline in incidence. By 2008, rates of disease were 4.3 per 100,000.

To determine the impact of Tdap in adolescents, the rate ratios were calculated by dividing the incidence of pertussis among adolescents, by the incidence of disease in all other age groups combined. The rate ratios were used because this allowed evaluation of how trends changed in one age group (adolescents) relative to all other ages. A significant, steady increase was observed in rate ratios prior to Tdap, followed by a reversal in the direction of the slope to a significant decrease post-Tdap. This suggests that the rate of disease among 11-18 year olds in the pre-Tdap period was increasing at a faster rate than disease in all other ages combined. In the post-Tdap period, rates of disease among adolescents declined at a faster rate than other age groups. It is believed that this reversal in the direction of the slope is being driven, at least in part, by the introduction of Tdap.

Another program component is the cocoon strategy. The concept of vaccinating close contacts of newborns to interrupt transmission of disease to the infant has been termed “cocooning.” New mothers who have not previously received Tdap should receive a dose during the immediate postpartum period. New fathers and other close contacts should ideally receive Tdap at least 2 weeks before close contact with the infant. There are known to be a number of uptake challenges to implementation of postpartum immunization. Cocooning is a new immunization platform with little infrastructure to ensure effective implementation, pertussis awareness varies, two populations require vaccination (postpartum women and their families), vaccine history is difficult to determine (date of last Td booster), new immunization providers (postpartum vaccine is not typically administered in these settings), and reimbursement issues [Healy CM, Rench MA, Castagnini LA, Baker CJ. Pertussis immunization in a high-risk postpartum population. Vaccine. 2009 Sep 18;27(41):5599-602].

Several small demonstration projects designed to overcome barriers have been successful in vaccinating mothers, but no other family members received Tdap. However, these have not gone beyond small projects or demonstrated sustainability. In addition, the impact of this strategy is not well-assessed. There are on-going efforts to measure the effectiveness of the cocoon strategy. There are no studies of impact on infant disease.

Many of the challenges regarding control and prevention of pertussis are highlighted in an on-going outbreak in California. From January 1, 2010 to June 15, 2010, California has observed a 4-fold increase in pertussis cases compared to the same period in 2009 (219 cases in 2009 and 910 cases in 2010). Five deaths, all in infants less than 3 months of age, have been reported. From January to May 2010, two counties in California (Fresno and Madera) reported 99 pertussis case patients. The highest number of cases was in 11 to 17 year olds, all of whom received the full primary series. However, only 25% of these received a booster vaccine. There has also been a troubling increase among 7 to 10 year olds who are too young to receive Tdap based upon the current recommendations. There were 12 cases in infants less than 2 months of age whose only protection is from cocooning [courtesy of Michael L. Jackson, CDC].

ACIP Pertussis Working Group aligns with WHO / SAGE Pertussis Working Group efforts to update their global pertussis vaccine recommendations. The WHO / SAGE Pertussis Working Group’s terms of reference are to review the impact of current pertussis vaccination strategy and surveillance efforts in support of current control efforts; propose necessary adjustments of

current control goals and surveillance strategies and efforts; and provide updated recommendations on vaccine use with a view to update the 2005 vaccine position paper on pertussis and identify important information gaps [courtesy of Stacey Martin, CDC].

Based on discussions with the ACIP Pertussis Working Group, the draft pertussis vaccine program evaluation of the overall US pertussis vaccination program suggests that vaccine coverage for infants and children is good, adolescent vaccine coverage is on track and is improving, and coverage for adults is suboptimal. Short-term vaccine effectiveness for Tdap is okay, but the duration of protection is not yet known. The feasibility of cocooning has been shown to be challenging, and the impact and effectiveness of this strategy needs evaluation.

In closing, Dr. Liang reminded everyone of the questions that needed to be considered: Are we using our vaccines as well as possible? Are there barriers to vaccination that can be removed? What else can we do to optimize each of these components of the program?

Discussion Points

Dr. Keitel inquired as to whether Dr. Liang could give them any indication of the ethnicity / race distribution of cases in the California outbreak, and whether she could elaborate on what was known about adult coverage.

Dr. Liang responded that she thought the majority of reported cases in the California outbreak were in Hispanics. Based on several NIS surveys, adult coverage is thought to be less than 6%.

Dr. Neuzil stressed that pregnant women are among those who should be considered as the group contemplates optimizing coverage and reconsidering the recommendation. Persons 65 years of age and older were also absent from the previous recommendations, and should be considered as well.

Ms. Rosenbaum pointed out that coverage for adult vaccines should be addressed. In terms of vaccines for children, an on-going issue is and will continue to be the lag time in the addition of coverage recommendations. For example, insurers desire to have sufficient notice that a recommendation is going to change because it affects their contracts and coverage terms. There is already a precedent for immunizations as part of a maternity package, so perhaps this can be leveraged to help speed changes in coverage.

Dr. Baker noted that post-partum immunization is the recommended strategy for pregnant women. This is not part of the maternity package, which is one of the major barriers to implementation.

Dr. Lett reported that a nurse in her program recently examined post-partum vaccination as part of her doctoral thesis, and found that Tdap and other vaccines are not part of the maternity package. The challenge in terms of health care reform is that there is no insurance coverage for vaccinating the father or any other family members visiting the hospital. Hospitals that overcame the barrier of having standing orders for vaccine faced major reimbursement problems for the mother and other family members.

Dr. Stephan Foster (APhA) noted that information had not been presented lately regarding revaccination with Tdap and immunity waning after 10 years. Given it was approaching the 10-year time period, it would be beneficial to hear input about this issue.

Dr. Messonnier responded that two major points of concern regard whether a single dose in adolescents will protect them through adulthood and how long a single dose will protect an adult. CDC and manufacturers are interested in pursuing this issue. The increase in reported cases among 7 through 10 year olds raises the issue of duration of protection, so CDC is trying to determine how to use the surveillance data and imperfect correlates of protection to asses this immunologically.

Dr. Baker requested input regarding the number of real cases versus the number of reported cases.

Dr. Messonnier responded that they are convinced that the number of real cases is dramatically higher than the number of reported cases for multiple reasons. For instance, people with mild cough illness do not typically seek medical care. If they do seek medical care, adult or pediatric physicians do not necessarily think of pertussis. If they do think of pertussis, they have to know which test to order when, and they have know whether the laboratory performing the testing is actually doing it right. While it is known that these are major barriers and that there is likely to be significant underreporting, how much is unknown.

Dr. Stinchfield wondered about vaccine hesitancy and the role it may be playing, especially in the two California counties.

Dr. Messonnier replied that this is believed to be an issue in some California counties. However, this does not seem to be the primary driving force in the Central Valley.

Dr. Sawyer added that with regard to the San Diego experience, the majority of cases had received the recommended immunizations. Some of them were adolescents who were fully immunized as infants and who either had or had not yet received Tdap. He did not believe that the predominance of the cases was related to under vaccination.

With respect to the question of boosting, Dr. Decker (Sanofi Pasteur) pointed out that the two manufacturers did not expect that no booster would be required. This is a regulatory issue in that FDA is not going to license a booster dose until they determine what occurs when a booster has been administered. A booster cannot be administered until they wait enough time to determine whether a booster is actually needed. Antibody kinetic studies suggest that the 10-year re-dosing interval would be appropriate with respect to the pertussis components as well as the T and D components. In addition, from a programmatic point of view, since the country or FDA are unlikely to prefer Td to be given every 5 or 7 or 8.3 years, it is likely that booster doses of Adacel® or Boostrix® would be administered on a 10-year cycle. The general population will not reach 10 years from their initial vaccinations until about 2015; however, the study populations have reached the 10-year mark. Thus, both companies are conducting studies in their original study populations of re-boosting, and both companies likely hope a booster dose, if needed, will be licensed before 2015. Regarding pregnancy, Dr. Decker reminded everyone that the question of whether intra-pregnancy administration of Tdap has any effect of the immune response of the newborn thereafter remains an unsettled question. Three studies are underway to address this, one of which is sponsored by NIH; one of which is in Canada with Scott Halpern's group, and a natural experiment of a major pertussis outbreak in a large healthcare institution that prompted wide use of Tdap in healthcare workers. A number of pregnant women were vaccinated during that outbreak, so follow-up data on their offspring will be available in a few months, which will be provided to the working group. The NIH and Canadian studies are moving very slowly because it is incredibly difficult to convince a pregnant

woman to enroll in a study that will involve many visits, extra blood draws, and extra diagnostic tests. Until there are additional data, he thought they would have to adhere to the current recommendation to vaccinate before pregnancy or post-partum, but not during pregnancy.

Dr. Plotkin recommended following the international experience on the cocooning strategy, which is accumulating. Costa Rica and countries in Europe are using that strategy. One study showed that Tdap within a month or two after Td did not increase the reaction rate.

Regarding barriers to vaccinating adolescents, Sandra Fryhofer (ACP) indicated that she was often involved in the handoff from the pediatrician to the internist, and sees a number of adolescents for a check-up prior to them entering college. The parents typically have a state form that list immunizations. The form says “last Td or Tdap” but does not specify which one. Thus, her office has to contact the pediatrician’s office to find out which one they actually received. Pediatricians are busy, so it is difficult to get an answer sometimes. If they do not receive an answer, a vaccination opportunity is missed. She wondered whether there were any data to address this issue, particularly with respect to interval.

Dr. Messonnier responded that this is a point of reference the Pertussis Working Group is currently assessing.

Dr. Baker commented that the interval stated in the document for post-partum immunization basically indicates approximately 2 years, although some people prefer 5 years. Often, adults have no clue what immunizations they have received. There is a routine post-partum program in one of the Houston hospitals. The women in this program are largely Hispanic, medically underserved, and under-insured. These women usually have no idea whether or when they have received a tetanus-containing vaccine. If they received an immunization intramuscularly in the arm during the fall and winter, it was probably influenza vaccine. The physicians leading the program decided not to consider the interval because of the high risk of pertussis to the young infant; they have not observed any safety issuesThe to date. This program basically considers the risk / benefit. For the post-partum woman, the risk to the baby is substantial, so Tdap is given. The requirement for a specific interval is a major barrier so many hospitals and / or their attorneys are not comfortable following a no interval protocol.

Dr. Brewer (ANA) stressed that this is a major problem “on the ground” because it is extremely difficult to interpret what that recommendation really means, especially in local health departments where nurses run immunization clinics and may not be confident in making such decisions without advice. If extremely high risk was being observed in infants, perhaps it is time to do away with the interval.

Dr. Baker noted that the working group is considering this possibility.

Dr. Friedland (GSK) reported that in addition to assessing boosting, GSK is examining antibody persistence at certain intervals following vaccination. They have been reporting these data to the working group and will continue to do so. In addition, GSK has been studying the acellular pertussis vaccine (Pa) components of the vaccine in newborns. These data have been reported in the scientific literature and they will be happy to discuss them with the working group.

Dr. Pickering reminded everyone that CDC and Georgia Tech have developed an immunization scheduler which is a downloadable, computerized program that is free of charge. In this system, adults can store their vaccine records and their records can be forwarded to their physicians. If this system becomes widely used, it will help everyone remember what vaccines they have received and when. There is a link to this program on CDC's website.

Dr. Temte reported that in his state, he has the luxury of a very good statewide registry that is tied into his electronic medical record and is something that he uses on a daily basis. All of his adult patients are routinely assessed for Tdap. This infrastructure is needed in all states, and vendors need to make EMR fully compatible with registries.

Dr. Gall (ACOG) strongly recommended that the committee revisit the recommendation to give this vaccine to moms during pregnancy in order to get antibodies into babies. They have been doing this at his place for the last 5 years. It is well-tolerated and they have unpublished data on significantly elevated cord levels to the antigens. The cocoon strategy has never really been tried in the field, and it really does not work. It was "rammed in" at the last minute after a year and a half of discussion on the pregnancy statement. He also suggested reading the previous week's lead editorial in the *New England Journal of Medicine* (*NEJM*) written by a few members from the FDA stating that pregnant women should be included in the studies.

Dr. Baker replied that the FDA needed to change some of their current regulations. She requested that someone address the comment that the cocoon strategy had not been proven to work, and whether anybody had tested this strategy for efficacy.

Dr. Messonnier responded that there were two parts regarding what is considered to be efficacy. The individuals can be vaccinated effectively, and several studies assess feasibility. In small populations, moms have been vaccinated. However, vaccinating the rest of the family members has been difficult. These are small, focused studies that are not scalable. The second piece is that are some early data on the effectiveness of cocooning in preventing disease among infants. There is a pilot study in California and some work in Texas. Thus, there may be some data available within the next 6 months on the effectiveness of the cocooning strategy.

Dr. Turner (ACHA) urged everyone to consider how to convince emergency departments and urgent care centers to administer Tdap. This is a missed opportunity.

Dr. Baker agreed. For adult immunization, this is a very difficult transition. If someone has tetanus prone wound, most practitioners are very comfortable giving a tetanus immunization at a 5-year. Administering Tdap as part of that protocol would be quite appropriate based on emerging data. While trials of the vaccine died due to lack of interest, they are using an interval for their tetanus protein conjugate in intervals as short as a year. The increased reactogenicity from the tetanus-containing component is approximately the same amount of tetanus antigen as is in Tdap.

13-Valent Pneumococcal Conjugate Vaccine (PCV13)

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

Dr. Rodewald reported that on February 24, 2010, 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar13®) was licensed by FDA. That morning, ACIP recommended the vaccine and included it in the VFC program. Part of the recommendation for the PCV13 vaccine was a new eligibility group: children 6 through 18 years of age with sickle cell disease, HIV infection, or other immunocompromising conditions. On March 12, 2010, the work group and CDC published the final recommendation for the vaccine. That was refined to include four other groups of children in the highest risk group for invasive pneumococcal disease (e.g., children with anatomic or functional asplenia, recipients of cochlear implant, and children with cerebrospinal fluid leak) in the 6 through 18 year old age range. This created a situation in which the ACIP recommendation was out of synch with the ACIP resolution for the VFC program. Parenthetically, the AAP recently published a recommendation that aligns with the new ACIP / CDC recommendation for these four additional groups. The purpose of this resolution is to update the eligible groups of children ages 6 through 18 years of age to be consistent with the ACIP recommendation for PCV13. The proposed language to rectify the difference in the current resolution was as follows, with the updated groups underlined:

Eligible Groups

Children 6 through 18 years of age who are at increased risk of invasive pneumococcal disease because of anatomic or functional asplenia, including sickle cell disease, HIV infection, or other immunocompromising condition, cochlear implant, or cerebrospinal fluid leak.

Schedule and Dosage Intervals

Children 6 through 18 years of age: A single dose of PCV13 may be administered for children 6 through 18 years of age who are at increased risk for invasive pneumococcal disease because of anatomic or functional asplenia, including sickle cell disease, HIV-infection or other immunocompromising condition, cochlear implant, or cerebrospinal fluid leak, regardless of whether they have previously received PCV7 or PPSV23.®

Motion: VFC Vote

Dr. Keitel made a motion to accept the rewording of the recommendation for the VFC as proposed. Dr. Marcy seconded the motion. The motion carried unanimously with 15 affirmative votes, 0 abstentions, and 0 negative votes.

Vaccine Supply

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

During this session, Dr. Rodewald reported on the following:

Adult Hepatitis B Vaccine

Merck is not currently distributing its adult / dialysis hepatitis B vaccines. Dialysis formulation is anticipated to return in the 3rd Quarter of 2010. The adult formulation will not be available for the rest of 2010. GSK has monovalent and combination product available. GSK expects to have at least one presentation of monovalent product continuously available to be able to meet national demand during the remainder of 2010. The combination product, Hep A-Hep B vaccine, is available as an alternative.

Adult Hepatitis A Vaccine

Merck will not be distributing adult hepatitis vaccine for the rest of 2010. GSK is currently out of stock on both presentations of its adult hepatitis A vaccine (Adult Havrix®), but anticipates that sufficient supply of at least one presentation will be available to meet demand for routine adult usage of this product by the end of June 2010. GSK's adult hepatitis A / hepatitis B combination vaccine (Twinrix®) is available as an alternative product.

MMR-V Vaccine

Merck began taking orders for MMRV (ProQuad®) on May 10, 2010. A limited number of doses are available for distribution. Merck has adequate supply of both their MMR and varicella vaccines to meet current demand. Dr. David Bach reported that Merck has about 1 million doses of ProQuad® remaining in their inventory that are available for distribution.

Zoster Vaccine

Merck continues to accept new orders for ZOSTAVAX®; however, the product is currently backordered. Orders placed through mid-May are expected to be filled by the end of July. Orders received after mid-May are expected to be filled in November / December of 2010. Backorders may continue into 2011.

Hib / Hep B Vaccine

Merck anticipates availability of its combination Hib / Hepatitis B vaccine, COMVAX®, in the 3rd Quarter of 2010.

Supply Constraints Related to Specific Presentations

GSK anticipates intermittent supply constraints for individual presentations during the second half of 2010 for Kinrix vials, Kinrix syringes, Havrix ®Pediatric syringes, Engerix® B Adult syringes. Alternative products, presentations, and brands are available.

CDC's Vaccine Supply / Shortage Webpage

This and further information is available at: http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm

Day 1: Public Comments

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

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat reported that CDC is actively involved in upgrading its information technology system, the Vaccine Tracking System (VTrckS), that manages and distributes vaccines and helps the states with their vaccine ordering and allocations. This system is in a very active phase this summer, and Dr. Schuchat plans to offer updates during future ACIP meetings.

To address the challenges that providers are having with vaccine hesitancy, CDC has been working with AAP and other partners to develop research-based materials that will aid in the physician / patient conversation. As this suite of materials is developed, they are being posted on a new site: http://www.cdc.gov/vaccines/spec-grps/hcp/conversations.htm. There are tools for providers and updated materials that can be given to patients, which is particularly beneficial in the case of hesitant patients. There is a new healthcare worker portal on the website that includes items such as the adult vaccine scheduler.

Related to Dr. Temte's comments, the American Recovery and Reinvestment Act (ARRA) also referred to as the "stimulus funding" recently permitted CDC to announce a funding opportunity for which over 30 states are eligible. The purpose of these funds is to facilitate the improvement of the interoperability of immunization information systems and electronic health records. Approximately $25 million dollars are available for this one-time funding to make these connections more sustainable and effective.

On Friday, WHO launched a new strategic plan for the next two years for the Global Polio Eradication Initiative. It is a very important and both promising and difficult time currently, with major progress in Nigeria and India and for the new outbreak in Tajikistan. The purpose of this strategic plan is to address the difficult last 1% of disease.

Centers for Medicare and Medicaid Services (CMS)

Linda Murphy indicated that in October 2010 when the permissive VFC resolution was voted on to make HPV permissive for boys, potential problems were anticipated by CMS. CMS and CDC have developed and submitted a response to one of the states with which a problem was encountered. As a result of that joint agency letter, once the state has acknowledged that the vaccine is permissive with respect to whether the provider and parent opt to utilize the vaccine versus it being permissive for the state to cover it or not, the content of letter will be posted on CMS's website and will be distributed to ACIP members.

Ms. Murphy also reported that administration rates are currently in final clearance. The goal is to make the administration rates readily updatable based upon when Medicare updates their rates so that an extensive clearance process will no longer be necessary.

Food & Drug Administration (FDA)

Dr. Sun reported that FDA is working very closely with many of its colleagues and other regulatory agencies and manufacturers with respect to some of the issues being discussed during this ACIP meeting (e.g., influenza and rotavirus). Since the last ACIP meeting, there have been approvals on some concomitant administrations of vaccines.

Department of Defense (DoD)

No report.

Department of Veterans Affairs (DVA)

Dr. Kinsinger reported that an update was published in May 2010 in the *Annals of Internal Medicine* by the VA research group who conducted the Shingles Prevention Study pertaining to the longer term safety of Zoster vaccine showing that it continues to be safe and effective.

The VA is very interested in the safety and effectiveness of pertussis vaccine in those 65 years of age and older. The issue was raised a few months ago, and the VA determined that a number of veterans have received that vaccine who are ≥ 65 and older. VA is interested in knowing how effective pertussis vaccine is in this population.

Also of interest to the VA is guidance for high dose influenza vaccine for those 65 years of age and older, and whether the vaccine information statement will offer information regarding how to decide which vaccine to administer.

Heath Resources and Services Administration (HRSA)

Rosemary Johann-Liang, filling in for Geoff Evans from the National Vaccine Injury Compensation Program (VICP), reminded everyone that 5,600 claims alleging vaccine-related autism were filed with the program, with peak numbers in the thousands in 2003 and 2004. Claims are currently much less, with only 12 autism claims filed thus far in fiscal year 2010 versus over 100 in fiscal year 2009. Regarding the Omnibus Autism Trials, 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 Hazlehurst family may next seek review by the Supreme Court. The second test case, Cedillo, has been appealed to the Federal Circuit and a decision is expected later in 2010. The last test case was not appealed.

In March 2010, the Special Masters ruled in favor of HHS on the general causation of the three test cases for Theory 2. None of these three test cases was appealed by the petitioners. The petitioners are also no longer pursuing the third theory that Measles, Mumps, Rubella (MMR) alone causes autism or autism spectrum disorder.

In terms of non-autism claims, the program is on pace for its largest number of submitted claims filed since 1999. Approximately half of these claims alleged injury from influenza vaccines, and nearly 60% of the filings were on behalf of adults. The total compensation as of June 2010 was $1.987 billion from the program. The trust fund currently totals $3.3 billion.

Indian Health Services (IHS)

Jim Cheek indicated that IHS's collaboration with FDA to monitor potential adverse events following the H1N1 influenza vaccine continued to go well, and IHS is utilizing their electronic health record to look for possible signals. They plan to expand this work to cover additional vaccines over the next few months.

National Institutes of Health (NIH)

Dr. Gorman indicated that he was the newly appointed NIH liaison for ACIP, and that Francis Collins is NIH's new director. Dr. Collins has recommitted to translational research, so NIH will continue to focus on engaging in work that has an immediate impact on the health of Americans. NIH hopes to provide some of the information that ACIP would like in order to move to evidenced-based recommendations.

National Vaccine Advisory Committee (NVAC)

Dr. Birkhead reported that during NVAC's June 2010 meeting, Assistant Secretary for Health, Howard Koh, charged NVAC with three new priority requests to address. Regarding Healthy People 2020 goals, which should be announced formally in Fall 2010, Dr. Koh asked NVAC to help identify implementation barriers and challenges to establishing and reaching the Healthy People 2010 goals and to give him an annual report on the status toward reaching those goals. Second, Dr. Koh requested an evaluation of the racial and ethnic disparities in influenza and pneumococcal vaccination. This activity will be moved to the Adult Immunizations Work Group. Third, Dr. Koh asked NVAC to be involved in the Viral Hepatitis Interagency Workgroup that has been formed at HHS. John Ward from CDC attended the meeting. NVAC's role will be to review documents prepared by the Interagency Working Group as they relate to hepatitis vaccination.

During the NVAC meeting in early June, presentations were delivered regarding healthcare reform, and NVAC passed a resolution that was forwarded to the Assistant Secretary recommending that prior NVAC resolutions, particularly the extensive set of vaccine finance recommendations that were published in 2008, be used by HHS as a guide in developing and implementing healthcare reform, particularly in terms of reimbursement activities. Presentations were also offered about the development and finalization of the National Vaccine Plan (NVP) since 1994. The current timetable for that is to have a final plan ready for public comment by

Fall 2010, which will be completed shortly thereafter. The HHS and the National Vaccine Program will develop an implementation plan for the NVP, which is expected in early 2011. It is hoped that the NVP will be the blueprint for on-going coordination of federal agency activities regarding all vaccination issues (e.g., development, implementation, and evaluation). NVAC has two very active working groups: Vaccine Safety and Adult Immunization Working Groups. The Vaccine Safety Working Group is moving toward recommendations pertaining to the broad federal vaccine safety system by NVAC's February 2011 meeting. The Adult Immunization Working Group is focusing on the many sets of recommendations for adult immunization, trying to hone in on barriers to implementation of a comprehensive adult vaccination program in the US and commitment at the federal level to support such an effort. They hope to have final recommendations from that group by the June 2011 meeting.

The H1N1 Influenza Vaccine Safety Risk Assessment Working Group was part of the unprecedented effort by HHS and NVAC to provide oversight to the coordinated efforts pertaining to H1N1 vaccine safety. Dr. Marie McCormick, an NVAC member, chaired the group. This working group was comprised of members from all of the federal vaccine committees. They met bi-weekly to oversee all vaccine safety efforts related to H1N1. The basic findings to date are that the data have been adequate to detect a signal. There have been weak signals detected for three conditions: Guillain Barré Syndrome (GBS), Bell's Palsy, and thrombocytopenia / idiopathic thrombocytopenicpurpura. On-going studies are needed to determine whether there is an actual causal relationship. Vaccine monitoring should continue as more data are accumulated.

The H1N1 Influenza Vaccine Safety Risk Assessment Working Group is an on-going working group. Two additional reports to NVAC are planned. Since last summer, two off-schedule NVAC meetings were convened by teleconference to assess the vaccine safety of H1N1. Two additional meetings were scheduled for July 27, 2010 and August 25, 2010. These are public teleconferences. By that time, NCAC hopes to have an end of season analysis regarding the safety of the H1N1 vaccine and a final report to address the issue of the weak signals.

National Vaccine Program Office (NVPO)

Dr. Gellin noted that everything Dr. Birkhead mentioned for NVAC represented a large part of the work stream and themes of NVPO. In addition, Dr. Gellin highlighted three efforts. He expressed his hope that the NVP would be completed by the time of the next ACIP meeting in October 2010, and that this could be further discussed at that time.

Regarding coming attractions from Washington, there was a review by the President's Council on Science and Technology, which was their second review related to influenza. The second review was inspired by how late the vaccine was this year. A report from this review will soon be disseminated, the focus of which will regard what can be done in terms of technology and the regulatory stream to shorten timeframes.

Related to that, a medical countermeasures review was conducted by the Office of the Assistant Secretary for Preparedness and Response, which has some of the same themes. A report will soon be distributed on that review as well, which will focus on emerging threats and bioterrorism issues, and nimble technology.

Influenza

Introduction

Kathy Neuzil, MD, MPH
Chair, Influenza Vaccine Workgroup

Dr. Neuzil began by acknowledging some history. In addition to being the year that ACIP made the historic universal influenza vaccine recommendation, 2010 also marks the 50th anniversary of the first influenza vaccine recommendation. A publication from 1960 in *Public Health Reports* by the Surgeon General, Dr. Burney, illustrates the beginning of influenza recommendations for high risk groups [Burney LE. Public Health Rep. 1960 Oct;75(10):944]. The three high risk groups contributing most to the excess deaths and who the Public Health Service then believed should be routinely immunized each year included: 1) Persons of all ages who suffer from chronic debilitating disease (e.g., rheumatic heart disease, other cardiovascular diseases, chronic bronchopulmonary disease, diabetes, and Addison's disease); 2) Pregnant women; and 3) All persons 65 years or older.

Noting that those first Surgeon General recommendations predated the ACIP, the second piece of history Dr. Neuzil shared was the agenda, provided by Dr. Jean Smith, of the first meeting of the ACIP convened on May 25-26, 1964. A description of the committee's purpose and function and the initial charter topped the agenda. In 1964 as in 2010, influenza took up more than its fair share of the agenda.

Also important to acknowledge is the history of the past year. It was a busy and unusual year with many surprises, and a tremendous amount of work was done by the people in the room. It was certainly historical that it was the first year in which two influenza vaccine recommendations were made within a month of each other.

Dr. Neuzil acknowledged that this would be her last ACIP meeting, stressing that the Influenza Vaccine Work Group would be in excellent hands with Dr. Wendy Keitel taking over as the chairperson. Dr. Keitel is an internationally recognized influenza expert. Her positive impact on this committee was immediate. She has made significant contributions already and everyone is very pleased that she agreed to chair this committee beginning July 1, 2010.

In addition, Dr. Neuzil acknowledged that this would be Dr. Tony Fiore's last ACIP meeting as the CDC lead for the Influenza Vaccine Work Group. Dr. Fiore will be the Associate Director for Science in the Division of Parasitic Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases (NCZVED) at CDC. On behalf of the group, Dr. Neuzil thanked him and wished him all the best.

To begin the session, Dr. Neuzil stressed that public policy is always difficult, but is particularly difficult with regard to influenza. To quote Drs. Neustadt and Fineberg, "Policy decisions regarding influenza rest on judgments about the behavior of the virus, the impact of the disease and our ability to interdict its course. But the virus is capricious, the disease elusive, and our remedies imperfect" [Neustadt R, Fineberg H. The Swine Flu Affair: Decision-making on a

slippery slope. http://www.iom.edu/?id=65926]. She thought the past year very nicely demonstrated the sentiments of this quotation.

Influenza Season Update and Summary

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

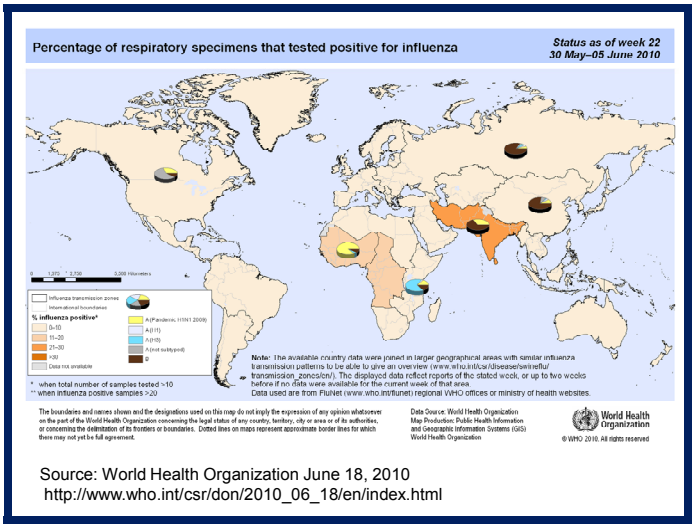
Dr. Fiore acknowledged again that they were losing two key Influenza Vaccine Work Group members who were rotating off of ACIP. The first was Dr. Susan Lett, who had been the voice of immunization programmatic reason, informing the work group about what programs could, could not, and perhaps would not do. That has been an important reality check on some of the ideas the work group has had over the past several years. Dr. Kathy Neuzil has been absolutely the right person, in the right place, at the right time during all of the turmoil over the last three years. On behalf of all members and CDC, Dr. Fiore extended a heartfelt thanks to Dr. Neuzil for all of her hard work and leadership.

With that, Dr. Fiore turned to the epidemiology of influenza over the past few months. The Influenza-like Illness (ILI) Surveillance Network (ILINet) shows that over the past few months, there has been very little influenza-like illness observed in providers' offices. ILI has been well below baseline over the past several months in contrast to the very sharp peak last fall with the pandemic [Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, October 1, 2006 – June 12, 2010].

Regarding notifiable deaths among children, a reporting system has been in place since 2004. These reports tend to lag somewhat, so they reflect higher numbers than in February. The key points are that during the 2007-08 influenza season, 88 deaths were reported. In the fairly mild season of April 2008-2009 season, 68 deaths were reported. During the pandemic, 341 deaths were reported. Of course, that far exceeds anything that has been observed in this system thus far. These are laboratory-confirmed reported deaths. This does not account for children whose deaths were not reported. The estimate of the real number could be expected to be higher [Number of Influenza-Associated Pediatric Deaths by Week of Death: 2007-08 season to 29 May 2010].

The viral surveillance system, through the WHO / NREVSS labs, also shows very few viruses reported since February 2010. The viruses that are reported are either influenza A and not subtypes, or 2009 H1N1. In the US, very few other viruses are being isolated. Over 99% of viruses have been 2009 H1N1. When these are sub-typed, there does not appear to be a substantial antigenic drift in the US or elsewhere in the world at this point. Over 99% of these viruses are susceptible to oseltamivir and all are susceptible to zanamivir. Over 99% are resistant to adamantine drugs [Influenza Positive Tests Reported to CDC from U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2009-10].

This world map depicts the type and subtype distribution of viruses isolated from around the world in recent weeks. The Southern hemisphere season is beginning, although there has been relatively little activity in most countries thus far. On this map, 2009 H1N1 viruses are the yellow slice, H3N2 viruses are the blue slice, and influenza B viruses (mostly B Victoria) are the maroon slice. In Africa, there have been a number of H3N2 viruses. There are a variety of viruses types, with Asia in particular reporting B viruses. There is still 2009 H1N1 in every region:



Source: World Health Organization June 18, 2010
http://www.who.int/csr/don/2010_06_18/en/index.html

The manufacturers are usually asked in June about supply projections, and they always caution CDC that this is going to be subject to change based upon issues such as regulatory approvals, production yields, demand for the product, et cetera. Therefore, these are merely projections. Together, it appears that manufacturers plan to provide approximately 170 million doses, and all manufacturers report likely availability of at least half of the projected supply by the end of September:

Manufacturer	Projected Production
CSL	12.5-12.7 M doses (reduced by 1.5 M from prior estimates due to unavailability of 0.25mL product)
GSK	~36 M doses
MedImmune	~16 M doses
Novartis	35-40 M doses
Sanofi	~70 M doses
TOTAL	169.5-174.7 M doses

Effectiveness of U.S. influenza A(H1N1) 2009 Monovalent Vaccines in Preventing Health Care Visits Associated with RT-PCR-Confirmed 2009 H1N1 Infections

David Shay MD, MPH
Prevention and Modeling Team
Epidemiology and Prevention Branch
Influenza Division, NCIRD, CDC

Dr. Shay reported preliminary estimates of pandemic vaccine effectiveness. The outcome that this group studied was prevention of RT-PCR confirmed medically attended 2009 H1N1 influenza. The setting was 4 communities located near the Marshfield Clinic in Southeast Michigan; University of Michigan and Henry Ford Health Systems; Rochester, New York; and Nashville, Tennessee. This was a case-control study conducted from October 2009 through January 2010. The enrollees were patients evaluated for acute respiratory symptoms in outpatient or inpatient settings who were prospectively enrolled and tested for influenza viruses by real time RT-PCR methods. Cases were those who tested positive for 2009 H1N1, and controls were those who tested negative for influenza.

Vaccination status was based on data collected by self-report and confirmed by record review. Immunization was defined by receipt of at least one dose of 2009 H1N1 vaccine greater than 7 or greater than 14 days before the onset of respiratory symptoms. The analysis was conducted in the usual way with VE=(1-adjusted OR)x100, estimated with logistic regression models and assessment for potential confounding by age, date of symptom onset, days between symptom onset and enrolling in testing, insurance status, and the presence of high risk medical conditions. The most important confounder was date of symptom onset.

The descriptive data are reflected in the following two tables:

Results – Descriptive data

Characteristic	Pandemic nfluenza cases N 897	% of total	Influenza-negative controls N=3,259	% of tota
Sex				
Female	476	53.1%	1,831	56.2%
Age groups				
6 mo-9 years	338	37.7%	989	30.3%
10-18 years	200	22.3%	303	9.3%
19-29 years	149	16.6%	346	10.6%
30-39 years	58	6.5%	327	10.0%
40-49 years	66	7.4%	329	10.1%
50-64 years	71	7.9%	529	16.2%
65+ years	15	1.7%	436	13.4%
H gh-risk cond t on				
No	617	68.8%	1,805	55.4%
Yes	280	31.2%	1,454	44.6%
Insurance status				
Not insured	74	8.2%	167	5.1%
Pr vate insurance	590	65.8%	1,914	58.7%
Pub ic nsurance	233	26.0%	1,178	36.1%
Enrollment s te				
Outpatient	740	82.5%	1,932	59.3%
Emergency dept	87	9.7%	446	13.7%
Inpatient	70	7.8%	881	27.0%

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Results – Immunization status*

Character st c	Enrollees No.	Seasona vacc ne No.	%	H1N1 vaccine No.	%	Both vaccines No.	%
To a	4,156	1,371	33.0%	408	9.8%	315	7.6%
Study community							
Marshf e d, WI	1,932	643	33.3%	251	13.0%	189	9.8%
Rochester, NY	282	75	26.6%	15	5.3%	11	3.9%
Southeast, MI	760	208	27.4%	29	3.8%	23	3.0%
Nashv lle, TN	1,182	445	37.6%	113	9.6%	92	7.8%
Age groups							
6 months 9 years							
1 dose on y	1,327	106	8.0%	157	11.8%	118	8.9%
2 doses	1,327	361	27.2%	55	4.1%	39	2.9%
10 18 years	503	117	23.3%	28	5.6%	19	3.8%
19 49 years	1,275	312	24.5%	93	7.3%	73	5.7%
50 64 years	600	240	40.0%	53	8.8%	49	8.2%
65+ years	451	235	52.1%	22	4.9%	17	3.8%
H gh-risk cond t on							
No	2,422	680	28.1%	241	10.0%	175	7.2%
Yes	1,734	691	39.9%	167	9.6%	140	8.1%
Case status							
Controls	3,259	1,183	36.3%	400	12.3%	308	9.5%
Cases	897	188	21.0%	8	0.9%	7	0.8%

* mmun zat on defined by receipt of at leas 1 dose of vacc ne >14 days before symp om onset

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Note that the cases were more likely to be age 6 months through 9 years or 10 to 18 years, with more than half of the cases and relatively few of the controls being in that age group. The attack rate for this particular virus in older individuals was low. For example, 1.9% of the cases versus 13% of the controls were age 65 and greater. Similar proportions of people had high risk conditions. Most of the cases and controls were enrolled in outpatient settings, with a larger proportion of cases than controls enrolled as outpatients.

Regarding immunization status, 33% of the enrollees in the time period studied had received the seasonal vaccine, 9.8% had received H1N1 vaccine, and 7.6% had received both. There were some differences by the study community, particularly when contrasting receipt of seasonal vaccine with H1N1 vaccine. The greatest difference was among the younger group in which 27% received two doses of seasonal vaccine versus 8% who received only one dose. For H1N1, only 12% of youth received one dose of vaccine and only 4% received 2 doses. Therefore, the investigators were unable to make an assessment of the effect of two doses versus one dose vaccine in this age group. Based on the crude data, 12.3% of controls versus only 0.9% of cases received H1N1 vaccine, but the time component must be taken into account. During the peak of disease, there were relatively few vaccinated cases or controls. The availability of vaccine varied from available before the peak of disease or only available after the peak of disease in some of the sites.

In all ages, there were 897 cases and 3259 controls. After adjusting for site, age, and onset date, vaccine effectiveness was 62% (95% CI, 30% to 79%) if vaccination occurred greater than 7 days prior to symptom onset, and 62% (95% CI, -4% to 86%) if vaccination occurred 8 to 14 days prior to symptom onset. The investigators were unable to stratify vaccine effectiveness estimates by vaccine type, high-risk status, or by 1 or 2 doses among children aged <10 years because of small sample sizes. There was no effect of seasonal vaccine against pandemic outcomes, as might be expected.

In conclusion, receipt of US monovalent, non-adjuvanted pandemic vaccine was associated with substantial protection against medically attended 2009 H1N1 illness. This is the highest estimate for vaccine effectiveness that has been observed in this system in several years of operation. Vaccine estimates were similar if vaccine was received greater than 7 or greater than 14 days prior to symptom onset. These estimates of vaccine effectiveness are similar to those obtained by studies in Europe, where a variety of vaccines were used, but where adjuvanted vaccines were predominantly used. No effect was observed of the seasonal 2009-10 vaccine on 2009 H1N1 illness.

ACIP Influenza Vaccine Workgroup Discussions and Recommendations

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

Dr. Fiore reminded everyone that Wendy Keitel would become the Chair Apparent of the Influenza Vaccine Work Group beginning July 1, 2010. Tim Uyeki will be taking Dr. Fiore's place as Acting CDC Liaison to Influenza Vaccine Work Group. Dr. Uyeki has a 10-year history in the Influenza Division, so this transition should be relatively smooth.

Dr. Fiore reminded everyone that the Influenza Vaccine Work Group convenes teleconferences every two weeks, engages in on-going email and telephone discussions, and scans the horizon for upcoming influenza issues and brings them to the attention of the full ACIP during public meetings, including proposals for votes on new recommendations for use of vaccines and antivirals. Major topics discussed by the group from February 2010 to June 2010 have included, but have not been limited to, the following: 1) antiviral recommendations; 2) vaccination recommendations for children <9 years old who did not receive any doses of 2009 H1N1 monovalent vaccine; and 3) vaccine safety monitoring, including data from the H1N1 2009 monovalent vaccine program, plans for the 2010-11 season, and fever and febrile seizures among young Australian children who received an inactivated 2010 southern hemisphere trivalent seasonal vaccine.

In February 2009 before the pandemic, the major concern for the Influenza Vaccine Work Group was the development of antiviral resistance among the seasonal H1N1s. For that reason, the vote for the antiviral recommendations was tabled during the February 2009 meeting and the antiviral recommendations were separated from the vaccine recommendations.

Antiviral recommendations were discussed during the June 2009 ACIP meeting. The antiviral recommendations were changed very little from the usual recommendations that had appeared in 2006, 2007, and 2008. The important changes to the recommendations included greater emphasis on empiric treatment pending diagnostic testing results when influenza is suspected for hospitalized or severely ill patients; outpatients with medical conditions that confer higher risk of influenza complications (e.g., chronic illness, pregnancy, immunosuppression); persons ages 65 or older; and young children. This was driven by the relatively low sensitivity of rapid influenza diagnostic testing and the concern that clinicians were waiting until they received definitive results or were placing too much faith in negative results. There was also an emphasis on using local epidemiology and viral surveillance when available in choice of antiviral (e.g., when circulating viruses are >99% 2009 H1N1, use oseltamivir or zanamivir but not adamantanes). Emphasis was also placed on judicious use of chemoprophylaxis in selected circumstances based on epidemiologic setting, patient risk, and clinical judgment. During that public meeting, ACIP encouraged consultation with local public health authorities and seeking guidance from the CDC website to learn about the latest antiviral recommendations versus codifying a blanket set of recommendations for chemoprophylaxis.

Based upon these variations, the antiviral recommendations text was finalized and updated through September 2009. However, submission for publication in the *MMWR* was delayed because this was the peak of the pandemic. Treatment and chemoprophylaxis recommendations are consistent with CDC (Last updated December 7, 2009), IDSA (April 2009; updated FAQs October 2009), AAP (Update planned summer 2010), and WHO (May 2010).

The Influenza Vaccine Work Group resumed work on the antiviral recommendations over the past few months to determine whether they were still useful. The group concluded that the current epidemiologic situation is unchanged in that >99% of viruses are sensitive to oseltamivir, and the majority are 2009 H1N1. Groups at higher risk who are recommended for empiric treatment remain unchanged from the 2009 H1N1 pandemic period. There are continued concerns about inappropriate use of chemoprophylaxis with respect to the potential for increasing risk of antiviral resistance and adverse events. Watchful waiting, with early treatment when indicated, is often a better approach. The work group's recommendations were approved during the June 2009 ACIP meeting. It was agreed that the recommendations should be submitted for *MMWR* publication as the 2010 antiviral recommendation after updating the references.

The second topic discussed by the work group was the 2010-2011 influenza vaccine recommendations for the number of vaccine doses for children ages 6 months through 8 years. The current recommendations are as follows:

- Previous immunogenicity and vaccine effectiveness studies indicate that children ages 6 months through 8 years old should receive 2 doses in current season:
  - → If they have never received trivalent vaccine before
  - → If they only received 1 dose last season and it was the first time they had ever been vaccinated

- Children ages 6 months through 8 years old who have been vaccinated in a year before last season (i.e., 2008-09 or before) are currently recommended to receive 1 seasonal influenza vaccine dose annually

- Need for two doses in children who have not previously been vaccinated is believed to be due to need for a priming dose followed by a booster
    - → Many children ages 6 months through 8 years old lack previous immunologic experience with influenza or influenza vaccine

Data from the Immunization Information System Sentinel Sites, 2007-08 and 2008-09 influenza seasons, suggests that full vaccination (e.g., 2 doses) in children aged 6 through 23 months and 2 through 4 years is hovering around 20% to 30%. Vaccination coverage is low among children <9. Most young children are due to be given 2 doses of seasonal vaccine each season according to current recommendations [Source: CDC MMWR 2009].

Data presented by Jim Singleton at the National Immunization Conference a few months ago show that slightly over 50% of children received at least one influenza vaccine of some sort by March 2010. There has not been much vaccination since then. H1N1 coverage was approximately 40%. Some children received one or the other or both types of vaccine [J Singleton, National H1N1 Flu Survey. National Immunization Conference April 2010].

Key Influenza Vaccine Work Group considerations have been that <10% of children <9 years old had antibodies to the 2009 H1N1 virus before the pandemic. The presence of antibodies before the pandemic is not associated with previous seasonal influenza vaccination. The dosing schedule recommended for 2009 H1N1 monovalent vaccine was that children ages 6 months through 9 years should receive 2 doses, and that older children and adults should receive 1 dose. Pandemic 2009 influenza A(H1N1)-like viruses are expected to circulate during the 2010-2011 season. Epidemiologic evidence indicates that unvaccinated young children had little or no protection against the antigenically distinct pandemic 2009 influenza A(H1N1) viruses.

Children entering the 2010-2011 season have a variety of immunologic profiles:

- Susceptible: Those who were not infected, were not vaccinated, or did not respond to vaccine.

- Naturally Immune: Those who are immune following natural infection. Seroprevalance data just coming out more or less agrees across studies conducted throughout the world that there is a fairly high prevalence of antibody to the H1N1 antigen among young children, especially school aged children. For example, the Miller et al studies conducted in the London area published in *Lancet* in early 2010 showed approximately 21.3% seropositvity among children less than 5 years of age and 42% among school aged children after the fall pandemic wave, compared to studies that showed <5% seropositivity in this age group before the pandemic. Ross et al published a study conducted in the Pittsburgh area (PLoS Currents 2010) that showed 28% seropositivity among 0 to 9 year olds, including some children who had relatively little or perhaps no symptoms.

- Immune after receiving 2 doses of monovalent vaccine: Those who are immune after 2 doses of the monovalent vaccine.

- Monovalent Immune / 1 Dose: Those who are immune after 1 dose of the monovalent vaccine. However, the proportion of young children who develop immunity after 1 dose is much less certain.

The following tables summarize a number of study arms that assessed immunogenicity data in older children and adults:

2009 influenza A(H1N1) monovalent vaccine immunogenicity summary: Older children or adults, day 21 post dose 1 (15 mcg)

Manufacturer (Dose)	% Baseline anti-HA≥ 1:40 (95% CI)	% Post dose 1 anti-HA≥ 1:40 (95% CI)	Seroconversion % (95% CI)	GMT (95% CI)	GMT fold increase (95% CI)
Novartis (9y-17y) [1]	29 (21-37)	96 (88-98)	NR	883	NR
CSL (18y-64y) [2]	33 (26-42)	97 (92-99)	71 (63-78)	217 (177-266)	11
Sanofi (10y-17y)[3]	11 (6-19)	93 (86-97)	90 (82-95)	390 (289-528)	49 (35-69)
Sanofi (18y-64y)[4]	26 (19-34)	98 (94-100)	96 (91-99)	1405 (1120-1763)	64 (51-82)
Sanofi (65y+)[4]	25 (17-35)	93 (86-97)	89 (81-94)	390 (283-537)	21 (16-29)

[1]Arguedas et al NEJM 2010
[2]Greenberg et al N Engl J Med 2009
[3]NIH/VTEU investigators, unpublished
[4]Plennevaux et al Lancet 2009

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The second data column shows the percentage of persons who are 10 years of age or older who responded with an anti-HA titer ≥ 1:40, which is believed to be the protective level. This ranges from 93% to 98% after just one dose, which is a very high rate of seropositivity after just a single dose for these older children and adults.

In younger children, this is somewhat different. The following table includes data from the published studies and also data provided by the National Institute of Health / Vaccine Treatment Evaluation Unit (NIH/VTEU) investigators that is not yet published:

2009 influenza A(H1N1) monovalent vaccine immunogenicity summary: Children ages 3y to 8-9y, day 21 post dose 1 (15 mcg)

Manufacturer (Dose)	% Baseline anti-HA≥ 1:40 (95% CI)	% Post dose 1 anti-HA≥ 1:40 (95% CI)	Seroconversion % (95% CI)	GMT (95% CI)	GMT fold increase (95% CI)
Novartis (15 mcg)[1]	26 (17-37)	72 (60-82)	NR	147 (90-200)	12
CSL2 (15 mcg)[2]	28 (20-37)	93 (86-97)	86 (77-91)	201 (156-260)	13 (11-16)
Sanofi (15 mcg)[3]	4 (1-9)	75 (66-83)	75 (66-83)	111 (84-147)	10 (8-14)
Sanofi (15 mcg)[4]	6 (2-13)	48 (35-60)	48 (35-60)	35 (22-58)	5 (3-9)
Sanofi (15 mcg)[4]	10 (3-21)	44 (30-59)	40 (26-55)	28 (16-49)	4 (3-6)

[1]Arguedas et al NEJM 2010
[2]Nolan et al N Engl J Med 2009
[3]Plennevaux et al Lancet 2009
[4]NIH/VTEU investigators, unpublished (NIH trial 09-0054 and DMID 09-0047)

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The above data are for children 3 years to roughly 8 to 9 years, depending upon the study arm. These data show that approximately 44% to 93% of these children responded to with an anti-HA titer ≥ 1:40 to a single dose of 15 micrograms (µg) by 21 days after the dosing. The last two columns show the antibody levels that were reached. The GMTs ranged from nearly 400 to over 1000 in the older children and adults in the first table. In the younger children, GMTs range from 28 to about 200.

The following table includes children ages 6 months through 36 months:

2009 influenza A(H1N1) monovalent vaccine immunogenicity summary: Children ages 6 months--36 months, day 21 post dose 1 (7.5-15 mcg)

Manufacturer (Dose)	% Baseline anti-HA≥ 1:40 (95% CI)	% Post dose 1 anti-HA≥ 1:40 (95% CI)	Seroconversion % (95% CI)	GMT (95% CI)	GMT fold increase (95% CI)
CSL (15 mcg)[1]	9 (5-18)	92 (84-96)	88 (79-94)	113 (87-147)	14 (11-17)
Sanofi (7.5 mcg)[2]	5 (2-11)	45 (35-55)	44 (34-54)	31 (23-43)	3 (2-4)
Sanofi (15 mcg)[3]	4 (1-10)	21 (12-32)	21 (12-32)	12 (8-19)	2 (1.5-2.8)
Sanofi (15 mcg)[3]	0 (0-12)	19 (7-39)	19 (7-39)	13 (8-22)	2.7 (2-4)

[1]Nolan JAMA 2010
[2]Plennevaux et al Lancet 2009
[3]NIH/VTEU investigators, unpublished (NIH trial 09-0054 and DMID 09-0047)

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Some of these children received the 7.5 µg dose that is currently recommended. Some of them also received a 15 µg dose, or double what they would receive in the seasonal vaccine. Again, looking at that second column, from 19% to 92% of children in this age group responded to one dose. That is even lower than for the somewhat older children, the 3 to 9 year olds. Again, the GMTs are a lot lower than they were for older children and adults and somewhat lower that they are for 3 to 9 year olds.

One of the NIH studies compared the response after one dose and after two doses. Approximately 20% of the 6 to 35 month olds responded to one dose. Close to 80% responded to two doses. Approximately 50% to 80% of 3 through 9 year olds and 90% of 10 to 17 year olds responded to just one dose. This is a fairly marked difference by age in response to the first dose. The good news is that two doses brings a large majority of children to an antibody level that is thought to be protective [Source: NIH VTEUs, preliminary data].

The work group's conclusions regarding immunogenicity of influenza A(H1N1) 2009 monovalent vaccines were as follows:

- After 1 dose of 2009 pandemic H1N1 monovalent vaccine, hemagglutinin inhibition (HI) titers considered to be protective (≥40) develop in:
  - → 81% of adults 65 years and older
  - → 90%-97% of older children and adults
  - → 44%-93% of children 3 years through 9 years
  - → 19%-92% of children ages 6 months through 35 months
- Responses after 1 dose of children < 9 years old vary across studies:
  - → Some children who are currently recommended to receive 1 seasonal 2010-11 dose, and who received no monovalent vaccine doses, might benefit from 2 doses of 2009 H1N1 antigen
  - → After 2 doses, 73% to 100% of infants and young children develop HI titers considered to be protective
  - → There appears to be no increase in reactogenicity with the second dose

- Previous studies of seasonal influenza vaccine demonstrate that 2 doses separated in time (Spring-Fall) are immunologically equivalent to 2 Fall doses when vaccine virus antigen does not change [Walter et al. Pediatrics 2006]

The final piece of information that may arise in the discussions regards what is known about separating the doses. In other words, the child who received one monovalent dose in the spring and receives a single dose of trivalent inactivated vaccine (TIV) in the fall, receives the two total 2009 H1N1 antigen doses. What are the implications for that for achievable protection? The work group considered two options with regard to this issue:

Option 1: Continue current recommendations for determining which children ages 6 months through 8 years should receive 2 doses of seasonal vaccine based on previous receipt of seasonal influenza vaccine:

- All children ages 6 months through 8 years who receive a seasonal influenza vaccine for the first time should be given 2 doses.

- Children who receive only one dose of a seasonal influenza vaccine in the first influenza season they receive vaccine should receive two doses, rather than one, in the following influenza season.

Option 1 is consistent with the current recommendations, so no new communication message would be required. This option is consistent with actions when B lineage changes or drifted H3N2 appears (no recommendation for 2 doses). Most children ages 6 months through 8 years old will still be recommended for 2 doses because they have never been fully vaccinated with seasonal vaccine before. However, some children who did not receive any monovalent vaccine doses would receive only 1 dose of the 2009 H1N1 antigen (with the 2010-11 seasonal dose), and some young children who receive only 1 dose might not develop an immune response considered to be protective.

Option 2: Change the recommendation for determining which children ages 6 months through 8 years should receive 2 doses of seasonal vaccine, taking both seasonal and 2009 H1N1 monovalent doses received into account:

- All children ages 6 months through 8 years who receive a seasonal influenza vaccine for the first time should be given 2 doses.

- Children who receive only one dose of a seasonal influenza vaccine in the first influenza season they receive vaccine should receive two doses, rather than one, in the following influenza season.

- In addition, for the 2010-11 influenza season, children ages 6 months through 8 years who did not receive at least 1 dose of an influenza A(H1N1) 2009 monovalent vaccine should receive 2 doses of a 2010-11 seasonal influenza vaccine, regardless of previous seasonal influenza vaccination history.

Considerations for Option 2 are that it is consistent with the monovalent vaccine recommendations to give 2 doses of 2009 H1N1 vaccine antigen to all children ages 6 months through 9 years old. As expected, most young children receiving a vaccine to protect against a virus with a major antigenic change require 2 doses. This option is likely to increase the number of children who develop an immune response. However, this differs from previous seasonal

influenza vaccine recommendations. Some children who would normally receive one seasonal vaccine dose will be recommended for two doses. More total vaccine doses will be required for this age group. The added public health benefit of two dose recommendation might be small, given that many children's immunity is based on natural infection, relatively low coverage might persist, and many will be recommended for 2 doses anyway based upon lack of previous seasonal vaccine.

Discussion Points

Dr. Temte inquired as to what the best guess would be (if summing what is known about natural seropositivity from exposure to the virus, the amount of vaccine distributed, and number of people immunized) of current immunity for the US population and what modeling suggests about the likelihood that H1N1 will ever recur.

Dr. Fiore replied that he did not think he could answer this unless they continued to see virus around the world. In previous pandemics, with many susceptibles presumably, there is not as much pressure for the virus to change. There could be considerable overlap between children who are naturally infected, especially among those who were asymptomatic and those who were vaccinated. One cannot simply add together the seropositivity data with the vaccination data because there are serologic studies, many of which were conducted before the vaccination campaigns were finished. Accounting for that overlap, there might be in the neighborhood of 50% of children who are seropositive in the school aged group, and it is probably lower for children less than 5 years of age. That is at least what the seropositivity data would suggest. CDC's interpretation of that is that there is still plenty of fuel for continued transmission for that particular virus. There are plenty of susceptible children, even with that degree of seropositivity, among whom continued community outbreaks could occur with this particular virus.

Dr. Marcy asked whether Dr. Fiore could account for the difference in immunogenicity in children 6 months to 8 to 9 years between the CSL Biotherapies vaccine and the Sanofi Pasteur vaccine. There seemed to be striking differences in the immunogenicity data presented. He also wondered whether there were any data showing that use of oseltamivir, or patterns of oseltamivir or zanamivir use in communities or in countries, has in any way affected the resistance patterns of the H1N1 to those antivirals.

Dr. Fiore responded that to answer the question about differences across the studies in response to the vaccines was that they were conducted at somewhat different times in the epidemiology of the country in which the study was conducted. The CSL study was conducted in Australia in the midst of their winter pandemic wave, which was different from the other studies. The implication of that is that many more children were seropositive going into that study than in some of the other studies. For the younger age group, this was in the neighborhood of 10% to 15%. Over 20% of the 3 through 9 year olds were seropositive at the time they were enrolled. The vaccine for those children might have acted more as a booster than as a priming dose if they had already been infected. The testing itself also varied across studies. The test is not fully standardized across labs and identical specimens might test differently in different laboratories. In addition, there may be more immunogenicity differences amongst the vaccines that is not fully understand even though they are made in essentially the same way. With regard to whether use of oseltamivir drives resistance, there has been relatively little resistance in the 2009 H1N1 viruses. Resistance has typically been observed in one of two circumstances: immunocompromised persons who are being treated for a long time because they are having trouble clearing the virus; and in situations where a lot of people receive chemoprophylaxis (e.g., camp situation). Community wide transmission of resistant

viruses according to how much oseltamivir is used in that community has not been observed. During the 2007-08 season, Norway was the first country to see widespread resistance. They had almost no oseltamivir use.

Ms. Ehresmann asked what the sample size was for the immunogenicity studies, and requested clarification with respect to whether they were going to include 9 year olds in the new recommendations.

Dr. Fiore replied that for most of these studies, the sample sizes were on the order of several hundred children per arm. Though fairly small, the sizes were enough that statistical significance was achieved in terms of showing immunogenicity. In terms of the new recommendations, he said it was difficult to draw and exact line between the point at which one needs 1 or 2 doses. Clearly, the need appears to be more acute in the younger side of the age range. At 8 to 9 years of age, the rate of being seropositive to the viruses increases. There is some arbitrariness to the cutoff in terms of whether it is 9 or 10, but the work group thought it was reasonable to go back to the standard age cutoff for two doses, i.e., 2 doses for children < 9 years old.

Ms. Ehresmann noted that there had been no comments regarding the length of time between having received an H1N1 vaccine and receiving a seasonal vaccine that contains H1N1. Minnesota providers who have been administering vaccines very late into the season are wondering if there needs to be any time delay.

Dr. Fiore responded that they should follow the interval currently being used for the two doses of seasonal vaccine of at least 28 days apart; however, he did not believe the time interval of two or three months would pose a problem.

Dr. Sumaya noted that while enhanced immunogenicity is the goal, coverage is glaringly poor. He wondered whether there were any new strategies to increase immunogenicity procedurally versus increasing the coverage of children in particular.

Dr. Fiore responded that for children approaching school age, there has been an increased emphasis on the use of school-based vaccination. This is probably a very nice way to increase coverage in that age group. This was a sign of great success in several states during the pandemic in which the achieved coverage rates in school-aged children reached 60% to 70%. CDC supports developing these programs, evaluating how well they work, and assessing best practices. For the younger age group, most children are vaccinated in the medical home. As pediatricians and family practitioners become more accustomed to gearing up for influenza season by vaccinating everyone in their practices, the hope is that they will get better at it.

Dr. Sawyer expressed concern about the added complexity of Option 2 and the ability of physicians to determine whether children received vaccine in the past year, particularly with regard to school-located clinics in which communication back to the medical home may not have been ideal. In trying to understand what percentage of young children this extra dose will ultimately apply to, he wondered whether there was any information about children who did not receive H1N1 in the past season, but who had previously received two doses of seasonal vaccine or received one dose in years past.

Dr. Fiore responded that there are no longitudinal data in the coverage surveys that indicate a child's immunization history going back more than one year, because it just became too difficult to ask the question. It remains unknown how many children this affects. The bottom line is that that most children, regardless of whether Option 1 or 2 is selected, are probably going to be recommended for two doses of seasonal vaccine this year because they have never been vaccinated before.

With regard to the 9 year old group, Dr. Neuzil reassured everyone that the work group asked for data breakdowns from NIH by age. While the numbers were small, there was a clear relationship with increasing seroprotection after one dose with increasing age. The work group felt comfortable looking at the cumulative evidence that children 9 and over would be protected with one dose.

Returning to the coverage issue and the pertussis discussion, Ms. Rosenbaum said she thought they were in a "chicken / egg" problem. They are ramping up the practice, and ramping up alternative practice sites as associated with ramping up the financial basis for ramping up the practice. She wondered whether there had been any discussion between CDC and the public and private insurers about rethinking the structure of coverage agreements so that contingencies are built into the agreements to allow for an adjustment of the coverage in the event of an epidemic where suddenly there is a change in practice standard and a second dose and second administration have to be administered. This is not an insurmountable problem, and it would create some certainly on the part of everybody in the system that if suddenly the professional standard changes, the payment system essentially will rise to the standard of care. Trying to get a pivot going in the practice system means financing that pivot to occur. She strongly recommended that they try to develop for further discussion within the ACIP this constant problem, which is going to be a problem for any condition for which a change in practice standard is needed. They really cannot afford lag times of one to two years while old contracts expire and new contracts have to be developed when, in fact, a professional body is saying they need to ramp up immediately because it would be safer.

Dr. Englund commented that as a pediatrician, one of the major reasons for the low pediatric coverage was the delay in receipt of vaccine. No fault intended, but it was a fact that there was no vaccine available. For the pediatric practices and health clinics to have vaccine available earlier, which is going to occur this year, is expected to make a big difference in availability of the children having the potential to receive vaccine. Granted, there is still the problem of time. There are ample data on reactogenicity showing that multiple doses of inactivated influenza vaccine or live attenuated vaccine are safe and non-reactogenic in this patient population. She thought ACIP, as a committee, needed to acknowledge that there are data both in concomitant and simultaneous administration of old TIV, the new H1N1, and in the past years. It should be safe and is an important cornerstone of what the work group recommended. There are also ample data about spreading the time between vaccines as much as one year. She voiced her support for Option 2, which is slightly complicated, but addresses the need for two doses of pandemic H1N1 vaccine in younger children under the age of 9.

Dr. Baker added that the vaccine was not only late, but also it was allocated state-by-state and distribution evenness and equity were issues in some states.

Regarding coverage issues moving forward, Dr. Schuchat pointed out that the next season would be of unprecedented complexity. In terms of comments about the vaccine being late last

year, the disease was early. It is not clear what is going to happen this fall with regard to whether the disease will be early and when the vaccine will arrive. Parents, providers, and adults have many questions because there were two different vaccines last year. CDC's communication team has been working with partners and conducting a lot of formative research to understand what the issues are and to create communication strategies that will address some of the barriers. They are trying to anticipate some of the challenges, but are learning from last year that they must be very careful with expectations, realize that there is a lot of complexity, and that they must work incrementally. She does not think that influenza pediatric coverage is principally a financing issue. The VFC program and good insurance have been covering influenza vaccine for children for a long time. It is more likely practitioner and parent attitudes that are driving this. During the pandemic, there were emergency circumstances such that vaccine was free but the administration was covered in unusual circumstances. The lag that Ms. Rosenbaum mentioned is really important for routine vaccines, but the low coverage of influenza vaccine is different from other pediatric vaccines and is something they have to work on seriously over time.

Ms. Rosenbaum clarified that it is the administration fee not simply the dosage. It is ramping up of the contractual obligation to pay the second administration fee, which should be unequivocal. In her area, the administration fee was nearly $50 and became a tremendous problem for privately insured children who were not from high income families. This is a problem that can and should be addressed. It is simply a minor blip in otherwise complex contracts that can be clarified.

Dr. Baker agreed that disease was early and it certainly was not CDC's fault. The vaccine was late, given the promise date that was spread throughout the media.

Dr. Meissner added that even though the vaccine was late, it was manufactured and distributed in a record amount of time nevertheless. Although the disease was very early, the system worked very well to a certain extent. At this point, he thought he favored Option 2. He wondered whether Dr. Fiore had any sense of the number of people who would be able to remember accurately whether they received the 2009 H1N1 vaccine last year.

Dr. Fiore did not have any sense of this, but agreed that it would be a challenge.

Dr. Keitel thought it was very unfortunate that they had to devise a very complicated strategy. One simple way to think about it is that children are unprimed to the three antigens in the vaccine and it may require that they receive two doses to cover each of the antigens in the vaccine. That is consistent with ACIP's prior thinking about influenza vaccination. The number of doses being suggested is to optimize the immunogenicity to provide protection. Some of these studies were actually conducted with simultaneous administration and some were conducted with the three week interval, which shorter than usually preferred. At least with a three week interval, there should be absolutely no concern about matching these types of results. The questions about distribution, uptake, and availability of vaccine simply need work. The on-going need for two doses of vaccine in a single season for young children and the difficultly in achieving or accomplishing that goal really lays out a research agenda in terms of develop ways to immunize infants and young children successfully with a single dose of vaccine, particularly since they are recommending this on an annual basis. Until they have the marvelous universal vaccines that will protect everyone for years on end, she thought there were existing vaccines that needed to be explored for their ability to confer protection after a single dose. There are limited data suggesting that live attenuated vaccines can do this in contrast to the limited data showing that inactivated vaccines cannot.

Dr. Cieslak said he had always understood the need for two doses of vaccine in younger children as being a result of their not having been exposed to previous seasonal influenza strains. Over age 10, it is not that the immune system matures, but rather that this age group has probably been exposed to influenza previously and will respond to one dose of vaccine even though the strain may differ. For example, a child who had two doses of influenza vaccine and seasonal influenza vaccine two years ago, did not receive monovalent H1N1 vaccine in the past season, in the coming season receives a seasonal vaccine, and responds to one dose of monovalent H1N1 may be precisely the child who has been exposed to influenza before or vaccinated with previous influenza strains. With that in mind, he wondered whether the additional recommendation was needed. That is, are there data that suggest that children who have received seasonal vaccine before do not respond to even one dose of monovalent H1N1?

Dr. Fiore responded that the immunogenicity studies did not characterize very well the previous receipt of seasonal vaccine. Data are usually collected on the current season or the previous season, but they do not go backwards to determine whether a child might have received a couple of seasonal doses two or three years ago and whether that increased the response rate.

Dr. Marcy did not think they were giving enough credence to what Dr. Meissner said. He thought the confusion would be significant. He suggested an Option 3: Give two doses to all children 6 months to 9 years of age.

Dr. Baker agreed with Dr. Schuchat that for parents, there would be a great deal of confusion and many questions. Therefore, communicating to them is very important. She also thought the message for practitioners must be straightforward, and should provide them with the ability to answer all of the complex questions patients and parents would have.

Dr. Judson asked what the overall attack rate was in the US population for H1N1 last year.

Dr. Fiore replied that this is unknown in terms of immunologic data. The estimate from modeling data is over 60 million persons are thought to have been cases some of whom did not develop symptoms. That would be over 20% and would be much higher in younger age groups. Those over 65 years of age are largely unaffected, which represents a large part of the population.

Regarding the spacing of doses, Dr. Judson said he had tracked this for quite a while. There are often three doses vaccines such as hepatitis. There is probably significant leeway with the third dose in that a booster dose is being used. He wondered whether any studies had been conducted to give the booster dose at 2, 3, 4, 5, 6, 7, 8, 9 months to clarify whether (if using the same influenza antigen, the same vaccine) there really is a major recall difference with a booster given at 2 months versus a year later. Is the immunologic memory thought to be completely lost in an 8 year old from the first prime?

Dr. Keitel pointed out that when middle aged, 30 to 60 year old people, were vaccinated repeatedly year after year, there is not a huge immunologic booster. She thought some of the data shown were pretty clear that in people who were primed, those people over age 10 years, the GMTs were much higher. Similar observations were made in adults who were given pandemic vaccines in past pandemics. They would respond after two doses of vaccine and would have low GMTs; whereas, older people who had been primed would have much higher GMTs of antibody.

Dr. Chilton thought in the previous season there had been a higher than ever immunization rate among school aged children at about 40% across the country. Part of that was a result of school-located clinics and part of it was spill over of anxiety on the part of parents that came about because of the H1N1 scare. However, this was misplaced to the seasonal vaccine which did not have much effect this year. With respect to Dr. Rosenbaum's question, it has been demonstrated in a couple of projects that have been carried out with CDC support in Rochester, Denver, and Arizona that health plans have responded quite well to billing for administration fees for influenza vaccine. New Mexico is hoping for this as well. With regard to Dr. Marcy's comment, he thought that given the choice between the complexities of Option 3 and the need to immunize every child under the age of 9 with two doses, he would choose Option 2.

Following up on Dr. Marcy's comment, Dr. Pickering wondered whether there would be a statement in the recommendations, regardless of which option was voted for, that it would be crystal clear that if a practitioner is not certain which vaccine or the number of vaccines a child has received, children ages 6 months through 8 years should receive two doses of seasonal immunization. He thought this was a great Category 1, Grade B comment.

Dr. Campos-Outcalt (AAFP) advocated in favor of simplicity. They must keep in mind that this decision is not the only one that would probably be made during that visit. The vaccine schedule is getting more complicated, so this will be one of a multitude of decisions that are going to be made. For a single decision, which is one or two doses, if there are more than one or two decision points, this will be done incorrectly a high proportion of the time.

Dr. Joe Bocchini (AAP) thanked Drs. Fiore and Neuzil for allowing the Committee on Infectious Diseases (COID) to participate in the work group, and stated that COID favors Option 2. This has been discussed in detail, and although a number of people were in favor of Option 1 because of its simplicity, the majority of the COID members were in favor of Option 2 because of the epidemiologic and serologic data. He thought Option 1 would cover more children effectively than Option 2. It actually adds just one additional decision and, in fact, the practitioner does have to go through for the first two parts of Option 2 with the same review of immunization history to determine if the child has received two doses of seasonal, et cetera. Although it will add some complexity and it may be more difficult for this year, it is appropriate to deal with that difficulty.

Dr. Stan Grogg (AOA) said that as a pediatrician who liked to keep it simple, he liked Option 2.

Dr. Whitley-Williams (NMA) asked whether the group examined any data on children who had proven real time PCR H1N1 and perhaps two doses of seasonal vaccine.

Dr. Fiore said the short answer was that there is not anything known about long-term protection after natural infection with the 2009 H1N1. It presumably would be for at least several years, so in that sense perhaps there are children who had true laboratory confirmed 2009 H1N1 who will not have to worry so much about that particular virus. They might have to worry about a drifted H1N1. It is difficult to determine whether a child received influenza vaccine doses in the previous year, and it will be more difficult to figure out whether they truly had lab confirmed, PCR confirmed, H1N1. The advise would be to err on the side of vaccine according to the dosage received rather than a laboratory test, which is probably not going to be available to most immunizers.

Ms. Stinchfield (NAPNAP) said that as a working group member, she also tried to share the voice of simplicity. Last year, vaccines were given in medical homes, schools, malls, tents, and all sorts of strange places. Given the data, she thought Option 2 seemed the most reasonable. (e.g., if unsure what was received, give 2 doses).

Paul Etkind (NACCHO) would hardily endorse the simpler, the better. In terms of Ms. Rosenbaum's comments, any barriers that can be eliminated in terms of billing would be of extraordinary help.

Dr. Katie Brewer (ANA) favored Option 1 pointing out that if they continued to create complexities in terms of the schedule, they would also continue to alienate people who are trying hard to immunize.

Following up on Ms. Rosenbaum's comments, Dr. Birkhead (NVAC) noted that in 2008, NVAC adopted a comprehensive set of finance recommendations for pediatrics and adolescents that included a recommendation that managed care plans in particular be flexible in the mid-contract cycle to adopt new changes. With H1N1, a number of the large plans did at least send letters indicating that they were going to cover the administration fee for 2 doses. Clearly, that was not universally adopted. Those recommendations were a consensus set of recommendations that included support from AHIP, so he thought the challenge now was to disseminate those recommendations in order to bring them to the attention of the various plans so that they can be implemented across the board. He also inquired as to what the evidence basis was for the current recommendation that children who receive one dose of seasonal vaccine in their first season should receive two doses again in the next season versus a single dose.

Dr. Fiore responded that the recommendation was largely based on a study conducted during the 2003-2004 season and published in the *Journal of Pediatrics*, which used a managed care database to assess differences in the effectiveness of ILI for children who had those two scenarios (e.g., those who received a single dose in their first year and a single dose in their second year, versus those who received two doses in their first year. There was a significant difference in the rates of ILI in those two groups, but it is a fairly limited database.

Dr. Baker reminded the committee members ACIP is a policy committee, not a implementation committee. She then called for a motion.

Dr. Cieslak pointed out that they had not seen any data to suggest that people who met the criterion of having had two doses in a previous season do not respond to one dose of H1N1 vaccine. Where is the burden of proof? He thought the burden of proof was on those who would add complexity to the recommendation, so he supported Option 1.

Dr. Neuzil said they must remember that this is an antigenically distinct virus and it caused a pandemic. Going into a pandemic situation, it was fully expected that the whole population would need two doses. The idea is that this virus is so antigenically distinct that priming for the seasonal viruses would not boost a response. That is substantiated by the tremendous differences in the responses in the younger age groups versus the older age groups who were exposed to H1N1 50 years ago.

Dr. Temte said he had looked at Option 2 a number of times prior to the meeting and he still had difficulty understanding exactly how he would implement this in his practice. He loved Dr. Marcy's suggestion because in the coming year, he is more concerned about the H3 virus than H1N1. Therefore, he would opt for simplicity in relationship to clinicians who have to implement this.

Dr. Cieslak said his response to Dr. Neuzil was that those who did not see H1N1 50 years ago did respond to a single dose of H1N1 vaccine this year.

Dr. Keitel indicated that in at least one of the NIH studies, the history was obtained of prior priming and the children were supposed to have been primed based on a verbal history from the parents. She thought it was very interesting that they fully understood the immunologic reasons for the 10 years of age plus, but her way of thinking about that would be that those people had more opportunity for naturally occurring H1N1 infections as opposed to trying to prime them with an inactivated H1N1 vaccine antigen.

Dr. Englund indicated that some data would soon be available.

Dr. Gorman (NIH) indicated that the studies conducted for the H1N1 vaccine were designed to answer the question regarding how many doses it took to generate an immune response. Data were collected about the previous vaccination status of individuals. This was done by recall, and the numbers of that particular data field did not prove to be very predictive in any way of response. In addition, the numbers were small. While he would love to offer this committee data, the only data he could provided would be data based on recall, which would not be useful and would not contribute in any realistic way to the discussion they were having.

Dr. Englund added that certainly data from that trial indicated that, regardless of receipt of vaccine, children under 3 responded poorly. Based on this it is obvious that the youngest age group, those under 3, absolutely need two doses regardless of previous vaccines.

Dr. Ehresmann requested a reminder of Dr. Marcy's Option 3.

Dr. Meissner agreed that the default should be 2 doses for any child for whom previous doses are unclear. However, some practices will keep very clear records and some families will know that their child received 2009 H1N1 vaccine in the previous year. Therefore, he did not think they needed to recommend it for everybody.

Motion: Influenza Vaccine

Dr. Chilton moved that ACIP adopt Option 2 with the addition that children who have not received one previous dose of H1N1 vaccine have to receive 2 doses in the coming season if they are under the age of 9. Dr. Meissner seconded the motion. The motion carried with 10 affirmative votes, 5 negative votes, and 0 abstentions.

Vaccines for Children (VFC) Program Resolution Update: Influenza Vaccine

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

Dr. Rodewald indicated that with this vote, there became an inconsistency with what ACIP recommended for all children and what was allowable under the VFC program. The purpose of this session was to update the recommendation for the 2 doses of vaccine in children ages 6 months through 8 years based on receipt of the influenza A(H1N1) monovalent vaccine, and to streamline the resolution through the use of links to published documents. In addition, an additional phrase would have to be added to the resolution to state something to the effect that children with uncertain status could be receiving two doses of the vaccine.

Additions are underlined in the following recommended schedule:

Recommended Vaccination Schedule (TIV)

- 6 months through 8 years: 1 or 2* doses
- 9 through 18 years: 1 dose

- *All children ages 6 months through 8 years who receive a seasonal influenza vaccine for the first time should be given 2 doses. Children who receive only one dose <u>of a seasonal influenza vaccine</u> in the first influenza season they receive vaccine should receive two doses, rather than one, in the following influenza season. <u>In addition, for the 2010-11 influenza season, children ages 6 months through 8 years who did not receive at least 1 dose of an influenza A(H1N1) 2009 monovalent vaccine should receive 2 doses of a 2010-11 seasonal influenza vaccine, regardless of previous influenza vaccination history.</u>

Recommended Vaccination Schedule (LAIV)

- 2 years through 8 years of age: 1 or 2* doses
- 9 through 18 years of age: 1 dose

- *All children ages 6 months through <u>8</u> years who receive <u>a seasonal</u> influenza vaccine for the first time should be given 2 doses. Children who receive only one dose <u>of a seasonal influenza vaccine</u> in the first influenza season they receive vaccine should receive two doses, rather than one, in the following influenza season. <u>In addition, for the 2010-11 influenza season, children ages 6 months through 8 years who did not receive at least 1 dose of an influenza A(H1N1) 2009 monovalent vaccine should receive 2 doses of a 2010-11 seasonal influenza vaccine, regardless of previous influenza vaccination history.</u>

Contraindications (LAIV)

- If an ACIP recommendation regarding influenza vaccination is published within 6 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 URL.

- Contraindications and precautions can be found at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5808a1.htm?s_cid=rr5808a1_e

There is a statement in all the resolutions that if an ACIP recommendation regarding influenza vaccination is published within 6 months following a resolution, the role of the language except the eligibility groups, will be replaced by the language in the recommendations and incorporated by a reference to the link, which is shown above.

Discussion Points

Dr. Chilton did not believe the Recommended Vaccination Schedule (TIV) language was entirely consistent on the strange question of whether a child received the first dose in a year prior to the year under consideration. For example, if a child received a single dose in 2007-2008 and it is 2010, then that child would need only one dose in the current year. That was in the recommendation, but not in the VFC recommendation.

Dr. Fiore responded that the intent was that a child who only received a single dose in a previous season that was not the last season would only be getting one dose for the upcoming season. However, with the addition of taking the monovalent vaccine into account, some of those children will fall into the two dose requirement. In other words, they got a dose at 6, 7, and nothing since then, so they would receive two doses of the seasonal this year because they need two doses of the 2009 H1N1 antigen.

Dr. Campos-Outcalt (AAFP) noted that if a child received H1N1 last year, that was not a question. However, if they received no seasonal vaccine last year, and the year before that was their first time and they only got one dose, it would be unclear whether they should received 1 or 2 seasonal shots this year. It still says “in the following year” and that makes in unclear. If they were out two years from that first dose, that terminology (the following year) makes it unclear whether it is two doses this year or one dose this year.

Dr. Fiore replied that this is in harmonization with AAP recommendations a couple of years ago when it was decided that the data supported giving two doses to a child who had only had one dose in their first season, and extended to that following season. He welcomed suggestions about how to make this clearer.

Motion: VFC Resolution for Influenza Vaccine

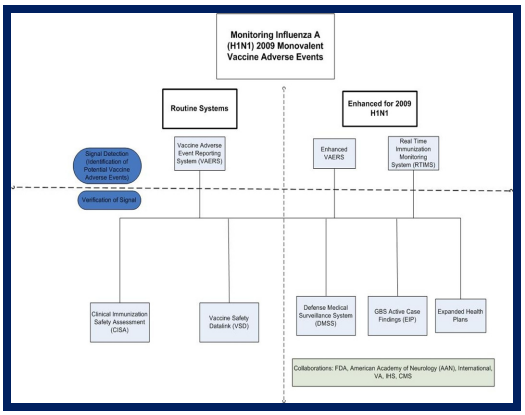
Dr. Neuzil moved that ACIP approve the language as stated with the addition of the “default of two doses” language. Dr. Meissner seconded the motion. The motion carried unanimously with 15 affirmative votes, 0 negative votes, and 0 abstentions.

Monitoring Influenza A (H1N1) 2009 Monovalent Vaccine Safety: Preliminary Findings from Three Systems

Frank DeStefano, MD, MPH
Immunization Safety Office
Division of Healthcare Quality Promotion,
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention (CDC)

Dr. DeStefano presented an update on the safety of H1N1 vaccine from several systems that have been used for monitoring. His presentation covered VAERS, the Real Time Immunization Monitoring System (RTIMS), and the Emerging Infections Program (EIP) GBS Surveillance Project.

The routine systems that have been in place for several years include VAERS, the Vaccine Safety Data Link (VSDL), and the Clinical Immunization Safety Assessment Network (CISA) for case reviews. The following diagram shows the systems used:



The right side of the screen shows either enhancements primarily to VAERS and some of the new systems that were presented during this session. The top half indicates systems that are primarily used to detect signals, while the lower half shows the systems that can be used to follow up signals.

Dr. DeStefano explained that VAERS is a spontaneous reporting system that is used primarily for signal detection. The system is subject to the well-known limitations of spontaneous reporting systems, such as various reporting biases (e.g., underreporting, differential reporting, stimulated reporting; inconsistent data quality and completeness; and lack of an unvaccinated comparison group to conduct causality assessments). Various methods are used to evaluate VAERS reports. One of the first is to look at the safety profile, which is usually done in comparison with vaccines that have an established vaccine safety profile. For the 2009–2010 H1N1 vaccine, the main comparator was seasonal vaccine used either during the current season or in past season. This is felt to be a valid comparator because seasonal influenza vaccines have a well-established safety record. The total reports for H1N1 are considerably more than received from past seasons or even a current season (n=7241). It is believed that

this is due to stimulated reporting. Serious reports include such things as hospitalization or long-term disability. H1N1 has had a similar serious proportion as previous seasonal vaccines. These results are based on an estimated 65 million vaccinated people. This was as of January 31, 2010. The number of reports is similar for live attenuated vaccines, based on an estimated 17 million vaccines (n=2068).

Another method that was used to evaluate VAERS reports was formal data mining. This basically asseses all types of symptoms and conditions that have been reported for a particular vaccine and compares those to other vaccines. This has been done through this season by the FDA. They rely on a method called Empirical Bayes. The analyses exclude non-US reports, there is adjustment for age and gender, and the comparison groups are an appropriate comparative vaccine (e.g., the inactivated vaccine is compared with other inactivated vaccines, and the live attenuated vaccines as compared to other live vaccines). With regard to the data mining results for the inactivated vaccine, there was only one adverse event signal, which was for incorrect dose administration in the age group 0-1. The cutoff is the EB05, which stands for the Empirical Bayes measure that indicates a cutoff of the lower 5th percentile of the confidence interval. The FDA uses a cutoff EB05 of 2 or higher for an indication of possible signal. This particular signal was 2.7 and was in the infants who received an inappropriate dose for their age. The data mining results for the live attenuated vaccine found the expected results from the clinical trials from the vaccine (e.g., cough and oropharyngeal pain, and contraindication to vaccination). This represented a vaccination of a live attenuated vaccine of pregnant women, individuals with asthma, or immunosupressed individuals.

The other main approach to evaluating VAERS reports is to conduct extensive clinical case reviews of the reports and supplementary medical record review by medical officers, supplemented as needed by CISA experts.

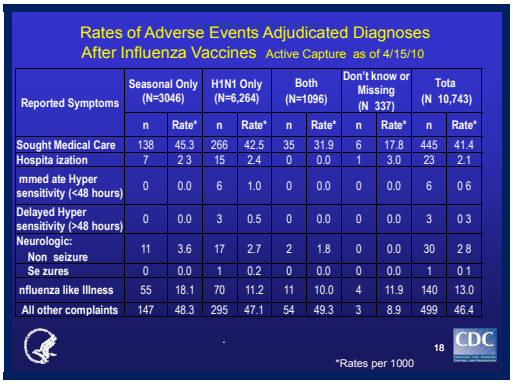
VAERS reports of deaths following inactivated H1N1 vaccine by body system in 42 vaccinees included: 20 cardiac (includes 1 pregnant), 8 infectious (1 with GBS), 5 multiple systems, 4 neurologic (includes 1 with GBS), 1 respiratory, 1 trauma, 1 pregnancy complication, and 2 unknown. The 6 VAERS reports of death following live H1N1 vaccine by body system included: 2 cardiac (myocardial infarction, hypertrophic cardiomyopathy*), 2 infectious (pneumococcal pneumonia* with pandemic influenza, pneumococcal sepsis*), 1 neurologic 1 (sequelae of spina bifida), and 1 respiratory (aspiration from choking on food). * Lung tissue from 3 death reports was tested at CDC for molecular evidence of vaccine strain H1N1 and was found to be negative.

Clinical case reviews were conducted of selected adverse events, including GBS. Reviews of those cases identified 99 confirmed reports of GBS and 117 reports of anaphylaxis. When reporting rates were calculated using estimates of vaccine coverage from immunization surveys, the reporting rates for GBS were 1.1 per million and for anaphylaxis were 1.4 per million. Both of those were right at or less than would be expected from background rates.

In summary of VAERS, the H1N1 reported adverse event pattern was consistent with expectations in that there were no new signals, the most common non-fatal serious reports after inactivated vaccine were neurologic (results not presented), the most common non-fatal serious event after the live attenuated vaccine were respiratory / influenza type conditions. GBS and anaphylaxis reports after H1N1 vaccination were rare, each occurring less than 2 per million doses administered.

Dr. DeStefano explained that the RTIMS was conceived and operated at John's Hopkins University by Dr. Neal Halsey, who is the principal investigator. This is automated web-based active surveillance targeting health care workers, pregnant women, and children. This was a collaboration between CDC and Johns Hopkins School of Public Health. There were two methods of enrollment of participants: 1) active capture (permission to contact at time of vaccination); and 2) passive capture (enter via websites maintained by Johns Hopkins, CDC, states). Individuals were followed up periodically post-vaccination up to 42 days. There were a total of over 14,000 enrollees, of which 10,700 were enrolled through the active capture method.

The following table summarizes the results from this system:



Rates of Adverse Events Adjudicated Diagnoses After Influenza Vaccines Active Capture as of 4/15/10

Reported Symptoms	Seasonal Only (N=3046)		H1N1 Only (N=6,264)		Both (N=1096)		Don't know or Missing (N 337)		Tota (N 10,743)	
	n	Rate*	n	Rate*	n	Rate*	n	Rate*	n	Rate*
Sought Medical Care	138	45.3	266	42.5	35	31.9	6	17.8	445	41.4
Hospita ization	7	2 3	15	2.4	0	0.0	1	3.0	23	2.1
mmed ate Hyper sensitivity (<48 hours)	0	0.0	6	1.0	0	0.0	0	0.0	6	0 6
Delayed Hyper sensitivity (>48 hours)	0	0.0	3	0.5	0	0.0	0	0.0	3	0 3
Neurologic: Non seizure	11	3.6	17	2.7	2	1.8	0	0.0	30	2 8
Se zures	0	0.0	1	0.2	0	0.0	0	0.0	1	0 1
nfluenza like Illness	55	18.1	70	11.2	11	10.0	4	11.9	140	13.0
All other complaints	147	48.3	295	47.1	54	49.3	3	8.9	499	46.4

*Rates per 1000

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These results are from about 10,000 active capture of participants. The main comparison to focus on would be the left most columns that indicate the results for seasonal only and H1N1 only. The results are very similar suggesting that the adverse event patterns for the H1N1 vaccine is quite similar to the seasonal vaccine.

During this session, Dr. DeStefano also described the EIP program for GBS. This was recently published in the *MMWR* [MMWR June 4, 2010 vol 59 (21): 657-661]. This system is a collaboration between CDC, state health departments, and academic centers. The population covered is about 45 million people in 10 catchment areas. Active case finding is conducted by surveillance officers using neurologist networks and hospital discharge diagnoses. Case vaccination status has been determined by telephone interview and physician records. The population vaccinated was determined from telephone surveys (BRFSS). Brighton case definitions were used to define GBS. The timeframe was October 1, 2009-March 31, 2010.

The preliminary results are that 326 cases met the Brighton case definition, of whom 27 received H1N1 vaccination during the 42 days before GBS onset. Of note, antecedent respiratory or gastrointestinal illness had occurred in about 59% of the vaccinated versus 78% of the unvaccinated cases. Calculating the rate of GBS per 100,000 person years, it was 1.92 in the vaccinated versus 1.21 in the unvaccinated. This translated into an age-adjusted rate ratio of 1.77. The confidence interval does not overlap 1, indicating that this was a statistically significant result at P of less than .05. It is estimated that this would account for 0.8 excess cases of GBS per million vaccinated, which is similar to what has been observed for seasonal vaccines in some years.

Planned additional analyses in the EIP project will be a self-controlled case series. This is a fairly established method in vaccine safety research. This method avoids potential biases introduced by survey estimation of vaccinated population and comparing vaccinated to unvaccinated, and uses only vaccinated cases to estimate the relative risk of vaccine (cases serve as their own controls). This method is commonly used in vaccine safety studies, and results correlate well with cohort studies. A final sweep of hospital records is important to ensure that all cases found. The results from these analyses will be available in the early fall.

H1N1 Vaccine Safety Findings from the Vaccine Safety Datalink (VSD) Project and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Network

Tracy Lieu, MD, MPH, and Grace Lee, MD, MPH
Department of Population Medicine
Harvard Pilgrim Health Care Institute and Harvard Medical School

Dr. Lieu reported the findings from the VSD project and the PRISM Network, focusing on findings pertaining to GBS, Bell's palsy, and seizures. VSD and PRISM are two of the largest active surveillance systems that participated in H1N1 safety monitoring this past season. VSD is organized by CDC and includes 9 million people in managed care settings. The PRISM system is a completely new system that has been organized by FDA, NVPO, and CDC. It includes 35 million persons. DoD, CMS, VA, and IHS also have participated in monitoring. The VSD project includes 8 health plans. It is sponsored and coordinated by CDC, and includes data on 9 million persons (3% of the US population) and has an annual birth cohort of 95,000. This system has very good geographic diversity and an amazing set of collaborators.

In the VSD study, vaccination records are linked with hospital and emergency department (ED) diagnosis codes, as well as outpatient visit diagnosis codes. The data are linked by study IDs, they are kept at each site, and the data sets are actually never sent to CDC. This was one of the earliest distributed data networks in the country. Rapid cycle analysis is conducted for influenza vaccine and for most newly introduced vaccines. Data are updated on all vaccines and all outcomes every week, and data are analyzed every week. Pre-specified outcomes are monitored that are selected for each vaccine based on the literature as well as VAERS and other reports. The number of outcomes is evaluated in vaccinated persons, and these numbers are compared to an expected number of outcomes from a comparison group.

In weekly monitoring of H1N1 vaccines, the risk or exposure window is assessed. That is the period after H1N1 vaccination. The length of the risk window depends on the outcome and can be up to 42 days or shorter in the case of certain outcomes like seizures that would biologically not be expected to last that long. Comparisons are made using historical rates after seasonal influenza vaccination and the self-controlled case series comparison, which uses unexposed time periods from the same person. Sequential analytic methods must be used, given that data are being analyzed every week, so they must adjust for the false positives that could result from repeated testing of this accumulating data. For this evaluation, the maximized sequential probability ratio test was used.

For H1N1 vaccine, there are several analytic challenges. The priority groups for H1N1 vaccination differ from the historical comparison groups who received TIV vaccine. Influenza vaccines are given over a relatively short period of time. The data, especially hospital claims

data from health plans, can take about three months to fully settle and be reliable. Finally, there may be confounding by seasonality if the outcomes of interest themselves are seasonal.

With regard to the VSDs results, the total number of H1N1 doses under surveillance in the VSD project totals 1.6 million including 1.3 million doses of inactivated and 267,000 doses of live vaccine. The inactivated vaccine includes 37,000 doses that were given to pregnant women. The overall vaccine coverage rate was 20%, which varied a great deal by age group. The lull is about 10% in the 18-24 year old age group. The high was 54% in the 6-23 month age group. The VSD is monitoring 10 outcomes in all persons plus three additional outcomes that are pregnancy-related. All of the outcomes are monitored using computerized ICD-9 codes. For GBS, in addition to the ICD-9 codes, chart reviews have been done for the cases and a comparison group of all of the historical cases. These are being adjudicated by an expert neurologist.

Regarding the findings for GBS after inactivated H1N1 vaccine, there were 15 cases observed. The expected number of cases based on historical computerized data is 9.2 for a relative risk of 1.6, and this was not significant. Of these 15 cases, 8 were confirmed after chart review. These 8 cases were compared to the historical cases that also had been chart reviewed. Based on that historical chart review data, there would have been 3.4 cases expected for a relative risk of 2.3. This also was not statistically significant, although the test statistic did move in the direction of significance. It is possible that the relative risk of 2.3 is due to an increase case identification in the current year compared with historical years.

All of these cases were adjudicated by a team of expert neurologists, and the level of certainty about these cases was based on the Brighton collaboration criteria. People usually look at Brighton levels 1, 2, and 3 as being probable GBS cases. In terms of the percentage of cases that are in these categories, the pattern for the cases after H1N1 in the current season does not look different from the pattern for historical cases after TIV in past seasons. There is really no support for the hypothesis that this elevated relative risk is simply due to a lower bar for case identification in the current year compared with in the past.

A one-time interim analysis was also conducted, partly because of the finding of relative risk that was reported by the EIP. In this type of analysis, the investigators were able to adjust for more confounders. This model was adjusted for age group, sex, and VSD site. This analysis used Poisson regression, using an exact method to deal with the low numbers of cases, and found a relative risk of 2.44. This relative risk is relative to the TIV vaccinees in historical data. The 95% CI from this analysis was 0.96 to 5.42. This CI includes 1, so it is not statistically significant, but it is close, which is a cause for some concern. GBS is rare, so this relative risk is going to translate into a very small attributable risk.

The team is currently evaluating the attributable or excess risk of GBS that could be associated with inactivated H1N1 vaccine. There are several important issues being considered. The rapid cycle and interim analyses compare H1N1 in the current season to trivalent influenza vaccine in historical years, and the estimate of attributable risk is going to depend on what is chosen as the most appropriate background rate. It is preferable to use a background rate that is most comparable to the analyses in terms of the population and the case definition being used. In other words, they would like a background rate that is based on chart reviewed and adjudicated GBS cases in vaccinated persons. The interim analysis findings are very new, and the team and the Vaccine Safety Risk Assessment Working Group (VSRAWG) need to discuss what the appropriate background rate to use for the attributable risk would be.

An end of season analysis of GBS after H1N1 vaccine is planned. Also planned is a self-controlled case series design. Because of the need for the risk windows to lapse and the comparison windows to lapse, and another three months for the data to settle, it will not be possible to conduct an accurate end of season analyses until August. These analyses are expected to shed more light on whether the increase in risk observed in the interim analysis represents a true association, or whether it is due to other explanations, such as unmeasured confounding or other issues with the analysis.

Turning to the other outcomes of greatest interest, in the rapid cycle analysis, the relative risk of Bell's Palsy in adults 25 years or older was 1.7. This was statistically significant using the self-controlled case series method. Statistical signals do not necessarily represent true associations. When a signal like this is observed, an effort is made to try to confirm or exclude it based on additional analysis and, if needed, additional data collection. The initial signal was a relative risk of 1.7 in the self-controlled case series analysis. An alternative analysis was conducted using a historical TIV group as a comparison, and no signal was found. A temporal scan of these cases was done and no clustering of cases was found. A case-centered analysis was done that adjusted for seasonality, age group, gender, and site that found an odds ratio of 1.2 and 95% CI that was .093 to 1.57, and was not significant.

Several additional analyses are in progress. Most of the team members involved with working up this signal do not believe that this statistical signal represents a true increase in risk. There are several possible explanations for the Bell's Palsy signal. From least to most likely, there could be a true excess risk. The additional analyses being conducted are starting to provide evidence against this being a true excess risk. There could be confounding by indication, meaning that the vaccinees differ from the comparison groups. This seems somewhat unlikely for clinical reasons, and such an effect is not observed for TIV in the historical data. There could be some seasonality effect, which seems like a potential partial explanation given that the seasonal distribution of H1N1 inactivated vaccine was different from the current and prior TIV vaccines. Finally, chance is actually the most likely primary cause of the signal, because even though the statistical methods attempt to adjust for this, surveillance is being conducted for so many outcomes, sometimes age-stratified, and 4 different influenza vaccine types are being assessed (e.g., live and attenuated H1N1 and seasonal influenza vaccines).

There have been concerns raised in Australia that influenza vaccines cause seizures in children. In the initial VSD analysis of seizures after H1N1 vaccine, a relative risk of 1.9 was observed in persons who were less than 24 years old. This was not statistically significant, but because of the Australian data, the team opted to take a closer look. This age group was stratified into those who were less than 4 years old and those who are 5 to 24 years old. A historical comparison approach was used because the numbers became too small for the initial self-controlled case series approach to be reliable. The relative risks on this closer look at the youngest age groups were not significantly elevated.

Other outcomes being monitored include encephalomyelitis, demyelinating disease, ataxia, anaphylaxis, and allergic reactions. The relative risks are all close to 1, and none are statistically significant.

There are some general lessons with respect to the VSD project. The VSD's success has depended on very robust relationships among the collaborators, as well as endless pursuit of data quality. The intense public health interest this past season has led to higher demands and

higher accountability, and the team is quite thankful to have VSRAWG to discuss these findings with. However, even the VSD project has limited power to detect signals for extremely rare outcomes. The VSD operated through much of the H1N1 season with a sense of crisis due to the high levels of public concern, the media coverage, the websites, and the expressed concerns about this H1N1 vaccine. Dr. Lieu reminded everyone that the Chinese word for crisis combines characters from danger and opportunity. The sense of crisis over H1N1 vaccine safety has opened a chance to strengthen the national vaccine safety monitoring infrastructure for the long-term.

The major new effort Dr. Lieu was involved in was the PRISM network, which includes four national health plans and 9 state immunization registries. There were two reasons that PRISM was started. The impetus was to assess larger populations to help monitor GBS and other rare events. Having larger populations should shorten the time to identifying problems. It was also anticipated during H1N1 season that much of the H1N1 vaccine would be distributed through public providers who would not necessarily be captured in traditional health plan claims. The PRISM network was formed to help capture vaccine exposure from these settings. The four health plans that participated were selected on the basis of their ability to rapidly assemble data to update it every one to two weeks. The participants were Aetna, CIGNA, Humana, and HealthCore, which represented Blue Cross Blue Shield plans in four states. From among these health plans, PRISM included a total of 35 million persons. The state immunization registries were selected based on having timely H1N1 vaccine data and having experience in matching these data with health plans on the basis of size. There were 9 participating states including Arizona, Florida, Georgia, Michigan, Minnesota, New York, New York City, Pennsylvania, and Wisconsin. There were a total of 12 million persons in the participating health plans who lived in these 9 states.

PRISM is a very large collaboration that involves HHS, AHIP, Population Medicine at Harvard Medical School and Harvard Pilgrim Health Care, Computer Sciences Corporation which is providing technical support, states, health plans, and the Public Health Informatics Institute. More than 100 people have been involved, and special credit goes to Daniel Salmon, who spearheaded this entire effort and stood by and pushed. To be honest, it was a strenuous scramble to put all of this together in the late summer and the early fall. The participants deserve tons of credit. The leadership team of PRISM also includes Bob Ball of FDA and Jerry Tokars and Eric Weintraub of CDC who participate in the leadership calls.

Comparing VSD and PRISM, VSD is nearly 20 years old and it has the strong advantages of experience, stable data, the ability to launch major new efforts like H1N1 monitoring in a timely way, and rapid access to the charts of the people who may have the ICD-9 coded cases. PRISM has the advantage of a larger size and it includes much more extensive state immunizations registry data. PRISM has also an additional few novel features. There is a full population linkage between the health plans and state registries. The freshest possible claims from the health plans are being used and it is not classified as research. Interestingly, VSD has always been classified as research. In PRISM, part of the reason the team was able to get these systems going within a few months is that they had a letter from the Office for Human Research Protections (OHRP) that it is not research. They did not have to go through IRB oversight, which has really sped some of the HIPAA and other arrangements that the health plans and states needed to make. In PRISM, the current season surveillance takes all of the current health plan members, obtains their H1N1 vaccine exposure data from both the health plan claims and the immunization registries, and then the outcome data on all the vaccinated persons come from health plan claims. Historical data are gathered in the same way, but all of the data are from health plan claims in the historical seasons after seasonal influenza vaccine.

Data confidentiality is maintained by keeping all of the personal level data behind health plan firewalls. Standardized programs are written that aggregate these data into counts of immunizations in outcomes. Then these counts can be sent beyond the health plan firewalls and analyzed by Harvard and at Computer Sciences Corporation.

PRISM monitors a total of 2.7 million vaccine doses. About 112 of these are known to be live vaccine and the rest are either inactivated or of unknown vaccine type. In PRISM, the overall coverage rate is about 15% and the pattern by age group is very similar to VSD's registries. Of the H1N1 vaccine doses being monitored in PRISM, state registry data alone contributed 57% of those doses. Thus, all of the work put into making these matches between the 9 state registries and the 4 health plans strengthened the diversity of data that were captured by this system. For seasonal TIV, the percent that are captured in state registry data alone is actually lower at 26%, so the patterns here are quite different. In terms of the findings from PRISM, for GBS, the analysis of computerized data from PRISM actually did not find an increase in the relative risk of GBS. The relative risk was 0.8, which is quite different from the VSD finding. At this point, an extensive review is being conducted of the PRISM data, and a chart review is being initiated of the GBS cases in the current and historical groups in PRISM. The rest of the findings from PRISM are quite reassuring. For Bell's Palsy and seizures, the relative risk is under 1, and they are not significant. In terms of the rest of the outcomes, the relative risks are not also marketedly elevated and they are not statistically significant.

In summary, 1.6 million doses of H1N1 have been monitored in VSD and 2.7 million doses have been monitored in PRISM. For GBS, there is a relative risk of 2.4 from chart-confirmed data in VSD, with a 95% CI that ranges from 0.96 to 5.4. The attributable risk of GBS is being discussed and is being worked out. There is a weak signal for Bell's palsy after inactivated H1N1 in VSD, but not in PRISM. It seems unlikely that this represents a true increase in risk.

The next steps are to conduct end-of-season analyses after the data settle in August. Comparisons will be done with those post-vaccination windows. Additional outcomes will be evaluated. Overlapping H1N1 and seasonal influenza vaccination will be assessed because that is what the coming vaccine will look like. Analyses of pregnancy-related outcomes will be refined, and Daniel Salmon is leading a plan to combine chart review data from VSD, PRISM, and several other systems for the purpose of gaining more power to do a clean evaluation of GBS.

H1N1 VACCINE SAFETY MONITORING Medicare Population

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Centers for Disease Control and Prevention (CDC)

Dr. DeStefano presented on behalf of Dr. Hector Izurieta. For H1N1 monitoring, FDA coordinated bringing some other large healthcare databases into the monitoring system. In this presentation, Dr. DeStefano covered the primary results from three systems: Medicare, VA, and IHS.

Medicare covers data on 38 million people 65 years or older and an additional 8 million people under 65 with disabilities. This particular system was used to monitor for GBS. The main risk interval used was 0 to 42 days post-vaccination. A couple of different risk intervals were used

for secondary analyses. The expected adverse event rate was obtained from the occurrence after in five prior influenza seasons among seasonal influenza vaccinated individuals. Basically, as with the other systems, they have been conducting sequential testing throughout the vaccination season and have adapted methods to account for multiple testing. Also, they have adjusted delays in claims accrual. So the expected adverse event rate is modified by the delay in adverse events derived from historical distribution of delay times.

Regarding the main result from the Medicare data for GBS monitoring, for the 0 to 42 window among all vaccinees (n=over 3 million vaccines), 14 cases of GBS were observed with an expected 14.67. The relative risk was 0.95, which was not statistically significant. In the other risk windows, the relative risk still remains close to 1 and none were statistically significant.

The VA has an integrated electronic database for which data on vaccination, outpatient visits, and hospitalizations are considered complete and available in real time for rapid cycle analysis. This database includes an approximate total of 2.1 million veterans and over 300,000 H1N1 vaccine doses administered. They also have been able to integrate prescription databases, the National Patient Care Databases, mortality data, and other disease registries. The rapid cycle analysis for the VA is a pilot integrated database and immunization tracking system. It is focused on the inactivated H1N1 vaccine, abbreviated MIV. Two analyses have been conducted with VA data, and the comparison is based on historical background rates from previous seasonal influenza seasons. Regarding the two analyses, the first version uses currently available data whereas the second version allows a full week data delay in the analyses.

Regarding the primary findings from those analyses, the preliminary results for a total of over 350,000 people vaccinated with inactivated H1N1 vaccine showed no signals for any of the pre-specified outcomes, with the exception of thrombocytopenia. Results for the outcome TP II are stratified, and TP I is the broader category of conditions. TP II restricts the thrombocytopenia cases to those coded as 287.31, which is ITP or idiopathic thrombocytopenic purpura. This is a highly specific code that did not signal. Moreover, in this on-going investigation, out of 70 thrombocytopenia cases already reviewed by VA researchers, only 4 (6%) were confirmed as ITP. Although there was no signal for GBS, the number of cases (n=5) was too small to be conclusive. The results for version 2, allowing the 4-week delay, are very similar to the version 1 results. Regarding limitations, prevalent TP diagnoses remain with an adjusted wash-out of 24 versus 6 months. The diagnosis is not always picked up as previous ICD-9 codes in the database because many patients have multiple co-morbidities exceeding the max of 10 diagnoses in the administrative databases. Many veterans are ill and can have up to 15 or more co-morbid conditions.

There is a proposed end-of-season analysis plan to evaluate risk of pre-specified diagnoses following inactivated H1N1 vaccine. Indirect adjustment will be to assess standardized incidence ratios of pre-specified adverse events (GBS, encephalitis / myelitis, optic neuritis, thrombocytopenia, Bell's Palsy, and anaphylaxis) following inactivated H1N1 vaccine using background data as the source of reference rates, adjusting for seasonal influenza vaccine exposure and / or other potential confounding factors among the VA population. Self-controlled case series will assess the associations between inactivated H1N1 vaccine and Bell's Palsy or other outcomes, if the sample size is sufficient, occurring in the VA population.

IHS H1N1 coverage was over 20%. Most (77%) of the vaccine doses administered were inactivated H1N1 vaccines. The analysis to follow all H1N1 vaccines was combined. The standardized incidence ratio provides the summary results from their analyses. It compares

expected number of cases using background rates generated from a previous influenza season, 2007-2008. The observed cases are from the H1N1 surveillance system. There were no GBS cases among the vaccines; therefore, GBS was not included in this table. The overall thrombocytopenia events observed (adding 287.31, 287.4, and 287.5) were significantly higher than expected, but the individual code was less for the specific code of 287.31 for which there were only 4 observed cases. The code 351 for Bell's Palsy also had a statistically significant signal, but for a very low relative risk 1.24.

Some of the limitations were that the expected number of cases from the IHS National Data Repository is limited. 100% of the facilities are included for the current analysis, as for the expected number; whereas, the observed number was obtained from 60% of facilities.

Future steps include case verification for background cases. For signal detection, stratified analysis will include age, gender, and temporal and geographic analyses. Rapid cycle analysis using MaxSPRT methods will be conducted. End-of-season studies include a self-controlled case series study of confirmed cases.

In summary, the findings were not consistent across the system. There were possible signals identified and some data sources for GBS, thrombocytopenia, and Bell's Palsy. The rates for GBS were higher than expected in some analyses, but they did not achieve statistical significance. Further analyses are planned of confirmed cases using self-controlled case series and other methodologies, and these will be implemented at the end of the season. There are enough integrated data for most partners for end-of-season analyses, particularly for the GBS analyses.

Discussion Points

Dr. Marcy was under the impression in the conversation they had with the VSD that there was attributable risk for GBS.

Dr. Lieu replied that it was certainly possible to make estimates of what the attributable risk would be if there was a particular background rate. This can be done, but these are back of the envelope estimates. She suggested that they had to be confident about it and wait until there is some consensus on what background rate ought to be used. If the background risk per million TIV doses is believed to be around 1, the attributable risk per million H1N1 doses would be 1.5. If the background risk is thought to be higher than 1, then the attributable risk of H1N1 would be higher. However, the CI are very wide. They include 0 and they include higher numbers. There needs to be better consensus on what should be used as the background risk. Larger numbers and more systems need to be involved as well so that the confidence intervals are more reliable.

Febrile Seizures in Australia and CDC Monitoring Plan for 2010-2011 Seasonal Influenza Vaccine

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Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases (proposed)

Dr. McNeil presented information to familiarize ACIP with a situation in Australia with febrile seizures, and the CDC seasonal influenza vaccine monitoring plan for 2010–2011.

Febrile seizures are seizures that occur with fever, usually in younger age groups between 6 months and 5 years. The peak age group is 14 to 18 months, and typically affects approximately 2% to 5% of young children in the US. It has an excellent prognosis, although one third of children who have a first febrile seizure will have a recurrence. Importantly, febrile seizures have not been associated with seasonal trivalent influenza vaccines in past seasons. There are three VSD studies. Safety monitoring during the recent H1N1 monovalent vaccination program did not show any signal for febrile seizures in the US [AAP. Pediatrics. 2008; Johnston M. Nelson Textbook of Pediatrics. 2007; Baulac. Lancet Neurology. 2004; Hambidge et al. JAMA 2006; France et al. Arch Pediatr Adolesc Med 2004; and Greene et al. Am J Epidemiol 2010].

Regarding the Australian situation, the recommendation for the entire country prior to April 2010 was that seasonal vaccination was recommended for children with chronic medical conditions ages 6 months to 18 years with unadjuvanted inactivated trivalent vaccine. There was a funded program in the State of Western Australia, and the recommendation was for vaccination of all children ages 6 months through 5 years. This followed some deaths that occurred in 2007 and has been in place for the last two years at least.

For seasonal inactivated trivalent influenza vaccine (TIV) in Australia, trivalent Fluvax® Junior (CSL) dominates market. Vaxigrip® (sanofi pasteur) and Influvac® (Solvay) are also available. The 2010 Southern Hemisphere formulation includes pandemic 2009 H1N1 antigen, and is the same as recommended for 2010-2011 Northern Hemisphere vaccine. Nearly all TIV distributed by late April 2010 was Fluvax® Junior (CSL).

On April 23, 2010, Australia's Chief Medical Officer suspended the 2010 seasonal trivalent vaccinations for all children less than 5 years old. This followed reports of febrile seizures following vaccination. The suspension included all 2010 TIV manufacturers, but not monovalent 2009 pandemic H1N1 vaccine. There was an investigation by authorities in Australia, including the Therapeutic Goods Administration (TGA), which is the Australian equivalent of the FDA. The preliminary investigation revealed that there was a signal suggesting an increase in febrile seizures, primarily in children less than 5 within 24 hours, approximately 7 hours, after vaccination with the 2010 seasonal TIV. There was no increased febrile seizure risk documented with non-CSL TIV products. It was estimated that up to 9 per 1000, compared with an estimate less than 1 per 1000 risk for febrile seizures, was identified. The Chief Medical Officer is quoted as saying that "No biological, clinical, or epidemiological factors have been identified to explain these higher than expected rates of febrile convulsions. Vaccine testing has shown no abnormalities."

The updated recommendations from the Chief Medical Officer were made on June 1, 2010. The update reiterated suspension of use of trivalent vaccines for healthy children less than 5 years of age. Again, the Panvax® (monovalent 2009 H1N1 vaccine) was available for use. For children with chronic medical conditions, there were options. They could use the Panvax® monovalent 2009 H1N1 vaccine or TIV. The recommendation was to prefer the other manufacturers' preparations (Influvac® or Vaxigrip®). Also, Fluvax® Junior manufactured by CSL could be used, but there was a warning label added about the increased risk of fever and febrile convulsions. There was also a statement by the TGA that had considered overall the balance of the benefits and risks of Fluvax® and Fluvax® Junior, manufactured by CSL, continued to be positive and that these were available still for older age children.

The manufacturer, CSL Biotherapies in Australia, also posted on its website that it had noted a significant increase in reports of fever and febrile seizures in children less than 5 years of age after receiving the 2010 CSL preparation compared to the earlier seasons. It also commented that the extensive investigations had not established an explanation. It ceased distribution of its pediatric influenza vaccine and collaborated on investigations with the government authorities. It also updated prescribing information for influenza vaccine and sent a letter to providers informing them; moreover, it commenced a retrieval program for its remaining 2010 pediatric influenza vaccine obtaining back unused supplies from suppliers and medical offices.

Other countries in the Southern Hemisphere are using 2010 seasonal influenza vaccine. CDC has been in contact with WHO and some of these countries. New Zealand also experienced a few cases of febrile seizures following use of CSL pediatric influenza vaccine, and as a precautionary measure, had also suspended its use. South America and South Africa have typically received the same CSL product in the past, and CDC has been in contact with officials in both countries. There are no reports to WHO of febrile seizures associated with the 2010 influenza vaccines.

With regard to the use of CSL vaccines in the US, CSL vaccines have been licensed for use in persons aged 18 years and older since 2007. The CSL influenza vaccine, Afluria®, was licensed for use in persons aged 6 months and older in November 2009. Very few doses were distributed during 2009-2010 influenza season. CSL pandemic H1N1 monovalent vaccine was licensed for use in November 2009 for ages 6 months and older. A review of the current monitoring systems for all manufacturers of trivalent seasonal influenza vaccine for the last season showed that there were 162 seizure reports, none of which followed receipt of CSL TIV, Afluria®. For the 2009 H1N1 monovalent influenza vaccine, there were 211 seizure reports, 4 of which were after receipt of CSL MIV preparation. All of these were in adults aged 18, 30, 32, and 59 years old. There was adequate information on the first two to confirm that these were seizures without fever. It is important to note that a report to VAERS does not indicate the adverse event was caused by the vaccine.

These reports were reviewed in more detail. Of the seasonal influenza vaccine, 39 of the 162 were classified using only metric codes as febrile seizures, and 40 of the 211 following the monovalent were classed as febrile seizures. Again, these are from the automated data. The other method of assessing VAERS data is data mining. This method looks for patterns of disproportionate reporting for adverse events, and has not detected any signal for seizure following either the seasonal trivalent flu vaccines, including the CSL preparation, or the live preparation by MedImmune. VAERS will be in the front line for monitoring for adverse events with the coming influenza season.

The other major system for monitoring safety of the vaccines is the VSD. Its data has also been assessed in terms of febrile seizures. For all ages, a total of 47,824 doses of seasonal vaccine were monitored. Of these doses, 6 seizure cases were detected in Days 0 to 7, and 5 were on Day 0, vaccination day. They were adults. There was one Day 2 case in an adult. There were only 11,175 doses of the monovalent in the VSD. No seizure cases were detected within days 0-7. In the age group 6 months to less than 5, there were 23 doses of TIV and 347 doses of MIV.

Future plans with the VSD are to monitor for seizures in three age groups (6 m/o–4 y/o, 5-24 y/o, and >25 y/o). If signals are detected, charts are reviewed to confirm a seizure and whether it is associated with fever or not. The current seizure definition includes ICD-9 codes 345.0*, 345.9*, 780.3* (generalized non convulsive epilepsy: convulsions). Seizures are looked for in in-patient settings and in the emergency room. The exposure window is days 0 to 7. There is a lot of power in the VSD to detect a relative risk. The estimates of relative risk from Australia have ranged between 5 and 10, so there is greater than 99% power to detect a relative risk of 3 or more, and 76% power to detect a relative risk of 2. This would be looking at seizures day 0 – 1 in the age groups 6 months to less than 5 years, and a background rate calculated from previous seasons of 5 per 100,000 doses. This also assumes that there would be similar vaccine uptake and coverage to what was observed in the 2008-2009 season, the last regular influenza season.

The next steps are to maintain close collaboration with international scientists, partners, and regulatory authorities, including FDA; collaborate on laboratory (animal pyrogenicity) studies using CSL vaccine at CDC; monitor for seizures / febrile seizures following 2010-2011 TIV using existing vaccine safety data systems (VAERS, VSD) currently in place for 2009 H1N1 vaccine; and communicate with ACIP and other stakeholders.

Discussion Points

Dr. Baker observed that the safety monitoring appears to be robust and in place to look for this potential safety issue.

Dr. Pickering thought it was interesting that in the NIH studies they just heard about, the CSL seroconversions or antibody levels were much higher than they were with the other vaccine manufacturers. Although enough patients may not have been enrolled to look for febrile seizures, he wondered if the rates of fever or local reactions were higher in those age groups, and extrapolating that on to what occurred in Australia, whether there was a connection, particularly if these are the same vaccines.

Dr. Englund noted that the data that Dr. Fiore showed about the CSL vaccines was Australian data and not NIH data, so she thought it was really important to realize that the CSL data shown earlier in this session with the very high antibody titers was done in a different population, with disease on-going, in a totally different study, with a different laboratory.

Dr. Neuzil added that as discussed in the work group, no signal was observed for increased seizures after use of the monovalent H1N1 in Australia.

Dr. McNeil replied that there was not, and they have not suspended its use. In fact, it is the major option and they anticipate that H1N1 will be the dominant strain this season in Australia.

Respiratory Syncytial Virus (RSV)

Introduction

Lance Chilton, M.D.
Chair, RSV Immunoprophylaxis Workgroup

Dr. Chilton reported that the RSV Immunoprophylaxis Work Group is moving inexorably and methodically toward developing recommendations for RSV immunoprophylaxis products. The RSV Immunoprophylaxis Work Group was assembled for several reasons. RSV causes a large amount of morbidity, although rather low mortality, every year. Pediatricians know the winter and spring months as bronchiolitis season, even though others think of it as influenza season. Attempts to develop a vaccine against RSV have thus far not been successful, but would change the face of pediatrics perhaps even more than HIB vaccine changed pediatric practice in the past. Aside from oxygen, nasal suction, and fluids, little can be done to help children who are affected by RSV. An effective, but expensive product for passive immunoprophylaxis exists. Current plans for replacement of palivizumab by a newer product, motavizumab, remain on hold given the negative vote on licensing by an FDA advisory board earlier this June. ACIP has ability to bring together individuals from different backgrounds (e.g., infectious disease, pediatrics, epidemiology, economics, pulmonology, neonatology, evidence-based medicine) to develop recommendations for prophylaxis based on disease burden, safety, efficacy, and economics.

Beyond safety and efficacy, the work group believes that special consideration must be given to economics because the cost for a current product, palivizumab, is very high at estimated drug cost of $6,674 per patient per year (4-5 monthly injections; depends on infant weight at 15 mg/kg/dose). A single monthly dose costs more than all of the other vaccines that are given to children in a lifetime. These costs are largely dictated by the cost of the product itself, though the cost of administration can also be high depending upon where it is given. Even though bronchiolitis and pneumonia caused by RSV are common and expensive to care for in hospitals, previous economic evaluations have not shown that providing prophylaxis to be cost-saving, though it may be cost-saving in certain restricted populations. Most cost studies have not found cost savings, and have varying estimates of cost-effectiveness.

Work group economist, Ismael Ortega Sanchez, helped to determine examples of cost estimates. The assumptions for these examples included the following: no wastage, use of 100 mg vials, private sector cost of $2,253 = $22.53/mg, public sector cost of $1,495 = $14.95/mg, weights at the 50th percentile for age for males born at 1.5 kg or 3.5 kg, no administration costs. The following table reflects the results for this example:

Weight at birth	1.5 kg premature infant	3.5 kg infant with CHD
1 mo. weight	1.7 kg	4.5 kg
2 mo. weight	2.4 kg	5.4 kg
3 mo. weight	2.8 kg	6.0 kg
4 month weight	3.3 kg	6.5 kg
5 mo. weight	3.9 kg	7.4 kg
Total cost of palivizumab	$3172- $4759	$6705-$10,058

Current and future RSV workgroup activities are to review the epidemiology of RSV infections, including seasonality and host and environmental risk factors for severe disease; review the safety and efficacy of prophylaxis; assess the costs and benefits of prophylaxis; identify areas in need of further research for informing recommendations; draft recommendations for ACIP consideration and decision making. The work group has begun to examine areas where future research would be beneficial in formulating recommendations in the use of this drug, for example, for children with cystic fibrosis or immune deficiency disorders. The group plans to update the full ACIP membership over the next several meetings, and to have draft recommendations for ACIP approval perhaps as early as June 2011. That means frequent meetings over the next year to review data from a number of standpoints.

One June 2, 2010, the FDA advisory committee voted 14 to 3 not to recommend licensure of motavizumab at this time. FDA action has not yet taken place. With that in mind, the RSV Immunoprophylaxis Work Group has decided to continue to work toward a set of recommendations for use of available products for prophylaxis, including recommendations for motavizumab if and when it is licensed and available.

This informational session included presentations regarding the epidemiology of RSV infections and the history of immunoprophylaxis.

Epidemiology of Respiratory Syncytial Virus (RSV) Infections in Infants and Young Children

Gayle Fischer Langley, MD, MPH
Centers for Disease Control and Prevention
Division of Viral Diseases

Dr. Langley reported on the epidemiology of RSV infections in infants and young children. RSV is an enveloped, single stranded RNA virus. It is part of the paramyxovirus family, which also includes parainfluenza, mumps, and measles viruses. There are two surface proteins that are related protective immunity, the F and G proteins. The F protein promotes fusion of the virus, and host cell membranes. This is the target of the immunoprophylaxis under consideration by the work group. The G protein promotes attachment of the virus to the cell and determines the major genetic groups, of which there are two, A and B.

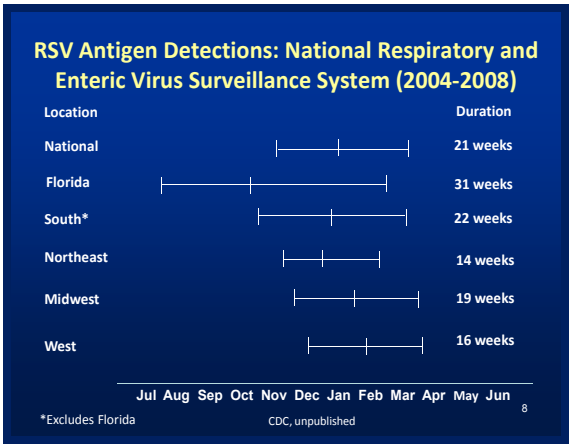
Upon exposure, RSV enters the upper respiratory tract and replicates in the nasopharynx. It then may spread to the lower respiratory tract (LRT) in about 1 to 3 days and causes inflammation of the small airways, leading to obstruction. Persons who are infected are usually symptomatic 2 to 8 days after exposure to the virus. Recovery generally occurs within 1 to 2 weeks, but symptoms may persist for several weeks. Most often, children infected with RSV present with upper respiratory tract infections (e.g., rhinitis, otitis media) and about 20% of young children present with lower respiratory tract infections (LRTI). The majority of these LRTIs are bronchiolitis. Bronchiolitis is inflammation of the small airways or bronchioles. Patients present with the hallmark signs of wheezing on expiration. Pneumonia is also relatively common. Apnea, or the absence of breathing, without other respiratory symptoms, may also occur in young infants.

Severe RSV in early infancy is also associated with recurrent wheezing. However, there are no data establishing a causal link. Recurrent wheezing may be a direct consequence of having RSV infection. Alternatively, children who wheeze with RSV may have an underlying predisposition or susceptibility to reactive airway disease or asthma. Whether RSV infection predisposes children to recurrent wheezing, and whether it can be prevented by immunoprophylaxis, are important considerations when assessing the potential benefits of immunoprophylaxis.

Primary RSV infection occurs early in life. Approximately 70% of children are infected with RSV in the first year of life. Almost all of these infections are symptomatic, with about 20% resulting in LRTI. Primary infection does not confer complete protective immunity and is not long-lasting so re-infection is common. Subsequent infections tend to more mild, but severe infection can occur in any age group. The risk is of severe infection upon re-infection is greatest in persons 65 years and older and in adults with underlying immunodeficiencies or pulmonary or cardiac disease [Glezen, AJDC (1986)].

The symptoms of RSV infections in children and adults are non-specific, so laboratory tests are needed to confirm the diagnosis. Detection of the virus is generally made from respiratory secretions. There are rapid antigen and molecular assays that are used in clinical settings to diagnose RSV. Antigen assays have a sensitivity of 80% to 90% in children and a lower sensitivity in adults. Molecular assays have higher sensitivities, which is particularly important for testing adults who tend to shed less virus. Both assays have high specificities. Results from

cell culture take 3 to 5 days and are used primarily to analyze strains and new mutations. Serology is primarily used for seroprevalence studies [Henrickson, PIDJ (2007)].
The following graph shows the distinct seasonality of RSV infections using antigen detection data from the National Respiratory and Enteric Virus Surveillance System between 2004 and 2008:



The x axis represents the month. The y axis, on the left, represents the geographic location of the detections. The duration of the season is on the right side. The first hash line indicates the season onset, the middle line indicates the season peak, and the end line indicates the season offset. Most laboratory detections of RSV during this time period in the US occurred between early November and the middle of March, with a peak in January. However, there was variation in the timing and the duration of detections by US region or states within regions. In Florida, for instance, season onset occurred in mid-July, peaked in mid-October, and ended in mid-February. Even when Florida is excluded, the Southern states had the earliest onset, peak, and offset, followed in time by the Northeast, Midwest, and West regions. The longest duration occurred in Florida, followed by other states in the Southern region, and then states in the Midwest, West, and Northeast regions.

Within these national and regional patterns, during a given season, outbreaks are generally localized within communities. Evidence for this includes the recognized differences in onset, peak and offset of detections between laboratories located within short distances. Also, molecular studies show that circulating strains may vary between adjacent communities during the same season. Despite outbreaks being localized in communities, approximately 80% of all RSV hospitalizations in the US occur between November and April [Mullins, PIDJ (2003), Panozzo, PIDJ (2007), and Anderson, JID (1991)].

RSV is the most common cause of LRTI in children under 5 years of age in the US. While deaths are rare, it causes a significant number of hospitalizations, ER visits, and outpatient visits. In children under 5 years of age, RSV has been associated with approximately 200 to 500 deaths and between 57,000 and 125,000 hospitalizations per year. The highest annual rates of RSV hospitalizations occur in infancy, with an estimated 16.9 per 1000 infants 0 to 5 months old and 5.1 per 1000 infants 6 to 11 months old hospitalized each year with RSV infection. Additionally, there are over 500,000 ER visits and over 1.5 million outpatient visits for RSV infections each year. In fact, the burden of RSV disease in young infants is more than 2 to 3 times greater than the burden resulting from influenza infections [Shay, JID (2001), Hall, NEJM (2009), Shay, JAMA (1999)].

In terms of absolute numbers, most RSV hospitalizations occur in healthy infants born at full term, but the relative risk is greater in infants and young children with certain underlying medical conditions. These conditions include chronic lung disease (CLD), prematurity, and congenital heart disease (CHD). Other medical conditions, such as neuromuscular disorders and immunodeficiencies, may also place a child at increased risk of RSV hospitalization. Children with CLD, CHD, or prematurity have been the main high risk groups targeted for immunoprophylaxis, which has been shown to reduce the incidence of RSV hospitalizations in these groups.

CLD, which was formerly known as bronchopulmonary dysplasia (BPD), is a condition of immature lung development and lung injury that results from premature birth and medical interventions. As a result, these infants require oxygen and other medical therapies. Even in the absence of CLD, infants born prematurely are more likely to be hospitalized with RSV compared children born at term. This has been attributed to their immature immune system, incomplete transfer of maternal antibodies, and an underdeveloped lung system. Additionally, select infants born with a structural heart defects, referred to as CHD, have an increased risk of RSV hospitalizations. This is particularly true for conditions associated with pulmonary hypertension. The increased risk is due to their inability to increase cardiac output when infected with RSV and their increased exposure to healthcare settings where RSV may circulate during the season. For healthy infants born at full term, the incidence of RSV hospitalization is about 1 to 3 percent per year. For children with CLD, the incidence ranges from 8 to 39% per year. For children with CHD, the incidence ranges from 2 to 15% per year. For children born prematurely, the yearly incidence ranges from 2 to 8%.

Despite the large burden of disease, there are few options for RSV prevention. In healthcare settings, RSV may be prevented by adhering to standard and contact precautions, which includes cohorting of persons with RSV infection. In the community, hand hygiene and avoiding settings where there is a high risk of exposure to RSV, such as crowds and daycare centers, is recommended during the RSV season. For now, immunoprophylaxis remains the main mode of prevention. However, because of costs and other considerations, immunoprophylaxis is generally recommended for select infants and children with CLD, CHD, or prematurity. Because hospitalizations are so common, even in healthy infants and children, providing prophylaxis has limited impact on the overall disease burden. A vaccine is needed to better address this large burden. There are vaccines in early development and testing, but safety and efficacy studies have not yet been done in young infants.

History of RSV Immunoprophylaxis

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Dr. Meissner pointed out that there are three basic approaches to the control of an infectious disease: vaccines, antimicrobial therapy, and passive immunoprophylaxis. Development of a safe and effective RSV vaccine has proven to be a difficult challenge. After 5 decades of research, no RSV vaccine approach has been fully successful at conferring protection among high risk persons. Ribavirin was licensed in 1986 for aerosol treatment of serious RSV infections in hospitalized children, and this drug remains the only FDA licensed drug for treatment of this disease. Ribavirin is seldom used today in non-compromised patients because

of limited efficacy, requirement for a cumbersome delivery system, and high cost. Investigational drugs under development fall into several categories and include fusion inhibitors, antisense drugs, and small interfering RNA. However, none of these are likely to be licensed in the near future. Passive immunization is the third option. Over the past 20 years, progress in the field of immunoprophylaxis for protection of high risk infants and children against RSV infection has achieved considerable success.

RSV causes a primary infection as well as re-infection during infancy and throughout life. Re-infection occurs despite the presence of maternal antibody, and despite the presence of immunity from previous infections. Unlike influenza, re-infection occurs without the need for significant antigenic change. Initially, these observations caused skepticism regarding a protective role for passively administered antibody; however, the observation of a correlation between high maternal antibody levels and less severe RSV infection in the first months of life among certain infants suggested that neutralizing antibody to RSV might afford some measure of protection.

Early studies in cotton rats and owl monkeys by Chanock, Prince, and Hemming suggested that exogenous antibody might indeed be safe and efficacious for preventing RSV lower respiratory tract disease in humans. In the early 1990s, two prophylaxis trials with monthly infusions of standard intravenous immunoglobulin were conducted in high risk infants. These two small trials demonstrated safety, but efficacy was not demonstrated. This was most likely because a sufficient peak seroconcentration of RSV neutralizing antibody was not achieved. In an effort to achieve higher serum antibody concentrations, a hyperimmune globulin was developed at the Massachusetts State Laboratory by George Siber and Jean Leszczynski. This hyperimmune globulin was later called RespiGam® and possessed about 5-fold greater neutralizing activity than standard intravenous immunoglobulin. Three multi-centered randomized control trials were then conducted using monthly infusions of the hyperimmune globulin. Based on results from two of the three trials, the hyperimmune globulin was licensed by FDA in January of 1996 for protection of preterm infants with or without bronchopulmonary dysplasia (BPD), but was contraindicated for children with severe CHD. Because the nasal mucosal represents the portal of entry for RSV, it was reasonable to expect that topically administered immunoglobulin (IgA) might be protective; however, a Phase III trial of once daily intranasal nose drops on monoclonal IgA versus placebo failed to reach the primary endpoint of reduced RSV hospitalization, and no further trials were conducted with this product.

Next, efforts focused on monoclonal antibody development in an effort to avoid several problems associated with the hyperimmune globulins. Two humanized monoclonal antibodies directed against different epitopes on the F protein were developed. F protein appeared to be the most suitable target because this protein mediates a key component of the life cycle of the virus; that is, fusion of the lipid envelope with the plasma membrane of the respiratory epithelial cell. Certain sequences of the F protein are highly conserved. A trial sponsored by SmithKline Beecham with a humanized murine monoclonal antibody failed to demonstrate a statistically significant difference in RSV hospitalization rates between infants who received monthly prophylaxis, every other month prophylaxis, or a control group. Subsequent analysis suggested this particular monoclonal antibody was directed against an epitope on the F glycoprotein, which was less effective at viral neutralization and had less fusion inhibitory activity than monoclonal antibody directed against other epitopes on the F protein.

A trial sponsored by MedImmune evaluated a second murine monoclonal antibody against the F protein in a Phase III trial and this monoclonal antibody demonstrated efficacy. Palivizumab has 50 to 100 times the activity of hyperimmune globulin against RSV in micro neutralization and

fusion inhibition assays and an enabled reduction in dosage from 750 mg per kg per dose of the hyperimmune globulin to 15 mg per kg dose of palivizumab. This enabled administration of a smaller volume by intramuscular root. Results from the IMpact trial of this RSV prophylaxis product demonstrated the efficacy of Palivizumab. This study involved 139 sites in the US, Canada, and the UK and was conducted over one year during the 1996 / 1997 RSV season. A total of 1500 preterm infants with or without chronic lung disease were randomized 2:1 to receive either 5 intramuscular injections of palivizumab or 5 injections of a placebo administered at 30 day intervals. The primary endpoint was efficacy of prophylaxis in reducing the incidence of RSV hospitalization. Overall, monthly prophylaxis with palivizumab was associated with a 55% reduction in hospitalization due to RSV and the primary endpoint was met. In the subgroup analysis, significant reductions were observed in preterm infants without chronic lung disease, as well as those infants with chronic lung disease [Study Group, Pediatr 1998;102:531].

In June 1998, the FDA licensed this monoclonal antibody, establishing palivizumab as the first monoclonal antibody introduced into clinical practice for prevention of an infectious disease. The IMpact RSV trial was the only Phase III data generated at the time of licensure. A second randomized, double-blind, placebo controlled trial with palivizumab was conducted during the 4 years between 1998 and 2002 and involved almost 1300 infants and children with hemodynamically significant CHD. Subjects were randomized 1:1 to receive 5 monthly intramuscular injections of palivizumab or placebo and were stratified at entry by cardiac lesion to a cyanotic or a non-cyanotic group. Palivizumab recipients had a statistically significant 45% decrease in the rate of RSV related hospitalization relative to placebo recipients [Feltes et al. J Pediatr 2003;143:532].

The palivizumab package insert from March 2009 states the following:

> **INDICATIONS AND USAGE:** Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) (see CLINICAL STUDIES).

The number of infants and young children who qualify for prophylaxis using these indications is large. Approximately 8.5% of the 4.1 million births per year in the US are born at or before 35 weeks gestation, which is about 350,000 infants. If all infants in just this one high risk group receive prophylaxis, the annual cost would exceed $2 billion for the drug alone; therefore, in an effort to optimize the benefit cost ratio, the COID generated a series of recommendations starting with the availability of hyperimmune globulin in 1996.

Palivizumab was licensed in 1998, 2.5 years after the licensure of the hyperimmune globulin. Since the first AAP recommendation, these recommendations have been revised and updated several times as new data have become available, principally in regard to the seasonality of RSV disease in different areas of the US and in regard to the new understanding of risk factors for severe RSV disease. During the June 2, 2010 FDA Antiviral Advisory Committee meeting, the Biologic License Application (BLA) was reviewed for motavizumab, a second generation monoclonal antibody which differs from palivizumab by 13 amino acids. The potential advantages of a more potent second generation molecule include fewer breakthrough infections, and because of increased anti-RSV activity in the upper airways, perhaps a role in the treatment of active infection. In cell culture, motavizumab has about 18-fold greater

neutralization activity than palivizumab. At equivalent serum levels in the model, this drug produces 50- to 100-fold greater production in RSV titer over palivizumab in the lungs and a 2 log reduction in nasal RSV titers. However, three weeks ago, the FDA Antiviral Advisory Committee voted 14 to 3 against licensure of motavizumab. Several issues were raised by the advisory committee. One of the overriding concerns was a higher rate of hypersensitivity adverse events in the motavizumab arm relative to the palivizumab arm. Furthermore, because of issues regarding motavizumab's efficacy relative to that of palivizumab, the advisory committee expressed concern that the risk-benefit assessment did not favor licensure of motavizumab.

The results of a head-to-head, non-inferiority comparative trial of palivizumab and motavizumab were published in January 2010. Because palivizumab is the standard of care, no placebo group was included in the design of this trial. Results of this trial demonstrated low rates of RSV hospitalization in both groups. In addition, motavizumab recipients experienced a 26% relative reduction in RSV hospitalization compared with palivizumab recipients. This figure of 26% achieved the predetermined threshold for non-inferiority, but did not reach the superiority threshold. Sub-group analysis by gestational age and chronic lung disease status were consistent with overall non-inferiority. Surprisingly, in comparison with the IMpact trial conducted in 1996, the RSV hospitalization rates were 1.5 to 2.5 times lower among palivizumab recipients for all subgroups in this trial. Possible explanation for this large difference in RSV hospitalization rates among palivizumab recipients in the two trials are first that the trials were conducted in different RSV seasons and it is possible there were different virulence patterns among circulating strains of RSV. Second, the threshold for admission of RSV infected children may have changed between 1996 and 2004 with infected children now more likely to be managed as outpatients. Third, the infants enrolled in the non-inferiority trial had less severe underlying disease than infants in the impact RSV trial. This makes data comparison between the two trials difficult [Pediatrics 2010;125:e35].

Several challenges are encountered when preparing recommendations for RSV prophylaxis with palivizumab. First, only two randomized placebo controlled trials with palivizumab are available. Second, the true RSV hospitalization rate in various groups of infants and children with different risk factors is difficult to establish from the available literature. More than 20 risk factors have been reported, but most of these risk factors have only a modest impact on RSV hospitalization rate. Risk factors to identify those infants most likely to require admission to the ICU or to have a fatal outcome are not easily established. In addition, many of the published studies which attempt to address risk factors for hospitalization were conducted in countries other than the US with different health care systems and different practice patterns, or the studies used historical controls or they were retrospective in nature.

Because of these issues, the goal of establishing evidenced-based recommendations for selection of infants and children in the US has proven to be a difficult task. In an era of limited resources, a responsibility of all advisory groups is the need to optimize the benefit-cost ratio and to exercise responsible stewardship of public funds. The conclusion of the COID is that palivizumab prophylaxis results in a substantial increase in cost, a small increase in quality adjusted life years (QALY) saved as a result of decreased hospitalization, and no measurable reduction in mortality rates in any of the published studies. Finally, it is important that recommendations provide the practitioner with a simplified approach for selection of infants for prophylaxis.

What might the future hold for RSV prevention? The protective immune response to RSV infection is mainly directed against the two major surface viral proteins, G and F. Palivizumab

or antibody to F protein, is not effective in treating active RSV disease and this may be due to lack of control of viral induced host inflammatory response. In contrast, a series of studies suggest that the G protein plays a role in inducing and modulating the inflammatory response during RSV infection. This is in addition to the role of G in attachment of the virus to the cell. In studies largely conducted by Larry Anderson and his group at CDC, a specific segment of the G protein has been shown to modulate the inflammatory response. Treatment with a monoclonal antibody to G inhibits both viral replication and reduces the inflammatory response in experimental models. This suggests that antibody to G could have a role in both prophylaxis and a treatment of RSV infection, and is a promising area of research. However, the greatest promise for overall control of the burden of disease caused by RSV comes from a vaccine administered early in life or perhaps administered during gestation. Presently, passively administered antibody and careful attention to methods which reduce exposure to RSV offer the best options for control of disease among higher risk infants and children.

Discussion Points

As evidenced by the public comments to be delivered at the end of the meeting, Dr. Baker pointed out that this is a controversial area. She requested that Dr. Meissner summarize for the committee members and the audience what the AAP / COID recommendations are. The license is for children with hemodynamically significant CHD and those of less than 35 weeks gestation.

Dr. Meissner replied that the COID engaged in lengthy and difficult discussions to identify the children who are most likely to benefit from prophylaxis, and have identified several categories. Preterm infants represent the largest group. Children who are less than 29 weeks of gestational age are clearly an important group. The groups between 29 and 32 weeks of age represent a second group, and the infants between 32 and 35 weeks of gestational age represent the largest group as mentioned (n=350,000). Risk factors and a maximum of three doses of monthly prophylaxis for children in that category have been suggested. Recommendations have also been made for children with hemodynamically significant CHD from birth through 24 months of age; children with what used to be called bronchopulmonary dysplasia that is now called chronic lung disease of prematurity; and those children who still require medical intervention (e.g., steroids, bronchodilators, diuretics, et cetera), who are eligible up to 24 months of age.

Dr. Whitley-Williams (NMA) indicated that NMA has great concerns regarding the change in the recommendations, particularly given the lack of data with regard to ethnicity in terms of the impact that this might have going forward. There is ethnicity data in the IMpact trial; however, she did not believe there was stratification of the data by ethnicity in the 32 to 35 week age group. She suggested that the unpublished COID data be provided to ACIP to further inform the recommendation development process. The NMA convened a consensus panel meeting in May 2010, and a paper will published following the annual meeting. She has an executive summary of that paper, which she indicated she would make available to the full ACIP membership. The gist of NMA's recommendations is they would like for ACIP to review the change in recommendations, particularly in the 32 to 35 age group, knowing that there is a disparity with regard to prematurity and the potential impact of not protecting those infants. She also requested that any data available for the 0 to 3 month group be provided to ACIP as well.

Dr. Baker said that given the practice changes with regard to admitting patients with RSV to the hospital, she was not surprised that the incidence of hospital admission was lower; however, it would be beneficial for ACIP to review data from that trial.

Responding to Dr. Whitley-Williams, Dr. Chilton thought their approach to this would be zero-based. In other words, they would specifically assess either the 2003 or 2009 recommendations. Instead, they will start at a zero point and move forward from there.

Dr. Pickering requested that Dr. Sun comment on the FDA status of motavizumab.

Dr. Sun replied that he spoke with Dr. Shapiro, who is on the ACIP work group, before he arrived at this ACIP meeting. His division is reviewing the product. At this time, he was not free to comment on the timeline of the review.

Dr. Baker reported that in the interest of full disclosure, Dr. Pickering and she are *ex-officio*, non-voting members of the COID of the AAP.

Dr. Whitley-Williams noted that surveillance in the 0 to 3 month age group varies from state-to-state. Often, deaths that occur at home may fall under sudden infant death syndrome (SIDS) and not be recorded as RSV. She thought improve surveillance of this entity. Published scores are used in evaluating these patients with regard to whether they should be hospitalized. She urged the work group to carefully review this issue, and to support increased surveillance and better diagnostic techniques for this entity to determine which infants should be targeted within the 32 to 35 month age group before making a decision to change the current recommendations.

Dr. Baker added that if they really wanted to do this as a country, we should also look for an all bacterial sepsis agent for deaths in that cause death in that age group.

Health Care Reform and Immunization Policy

Sara Rosenbaum, JD
Hirsh Professor and Chair
GWU / SPHHS
Department of Health Policy

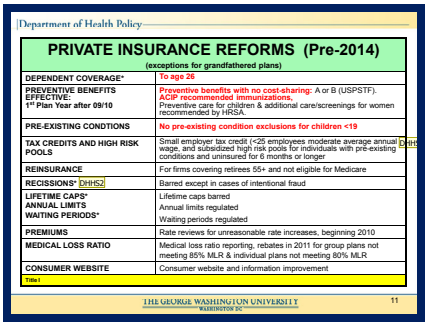
Ms. Rosenbaum reported that the fundamental aim of health care reform was to stabilize the private health insurance market as the principal means by which the health care system is financed, given the national preference for private coverage and the desire to retain the employer system. Moreover, coverage is intended to be accessible, affordable, and include reasonable coverage and investment in preventive services. There is also an emphasis on the introduction over time of cost controls; a fair amount of emphasis on cross-payer quality improvement; and an increase in the national investment in prevention, wellness, primary care, and better management of chronic illness.

With respect to individual responsibility (Title I), by 2014 most individuals will be required to have coverage or pay a fee equal to the greater of $695 per person ($2,085 per family) or 2.5% of household income. This will be phased in from 2014 through 2016. Exceptions include financial hardship; religious objections; American Indians; people who have been uninsured <3 months; persons for whom the lowest cost health plan exceeds 8% of income; and persons with incomes below the tax filing threshold ($9,350 for an individual and $18,700 for a married couple in 2009). Basically, the requirement is universal. There are advance refundable tax

credits and cost sharing assistance for those who have low to moderate income levels. There is Medicaid coverage for the poorest people.

Regarding employer responsibility (Title I), there is no mandate to provide insurance; however, there will be a fee of $2,000 / per employee assessment of employers with 50 or more employees on employers that do not offer coverage and have at least one employee who receives a premium credit through a state exchange. There will be a similar assessment on employers with more than 50 employees that offer coverage but have at least one employee who receives a premium credit through a state exchange. Employers offering coverage must provide a voucher to employees with incomes below 400% FPL, if the employee share of the premium is between 8% to 9.8% of income, to provide their choice of an exchange plan. Large employers (>200 FT employees) offering coverage must automatically enroll employees into the employer's lowest cost premium plan if the employee does not sign up for employer coverage or does not opt out of coverage.

There are numerous private insurance reforms as illustrated in the following tables:



Department of Health Policy

PRIVATE INSURANCE REFORMS (Pre-2014)
(exceptions for grandfathered plans)

DEPENDENT COVERAGE*	To age 26
PREVENTIVE BENEFITS EFFECTIVE: 1st Plan Year after 09/10	Preventive benefits with no cost-sharing: A or B (USPSTF). ACIP recommended immunizations, Preventive care for children & additional care/screenings for women recommended by HRSA.
PRE-EXISTING CONDTIONS	No pre-existing condition exclusions for children <19
TAX CREDITS AND HIGH RISK POOLS	Small employer tax credit (<25 employees moderate average annual wage, and subsidized high risk pools for individuals with pre-existing conditions and uninsured for 6 months or longer
REINSURANCE	For firms covering retirees 55+ and not eligible for Medicare
RECISSIONS* DHHS2	Barred except in cases of intentional fraud
LIFETIME CAPS* ANNUAL LIMITS WAITING PERIODS*	Lifetime caps barred Annual limits regulated Waiting periods regulated
PREMIUMS	Rate reviews for unreasonable rate increases, beginning 2010
MEDICAL LOSS RATIO	Medical loss ratio reporting, rebates in 2011 for group plans not meeting 85% MLR & individual plans not meeting 80% MLR
CONSUMER WEBSITE	Consumer website and information improvement

Title I

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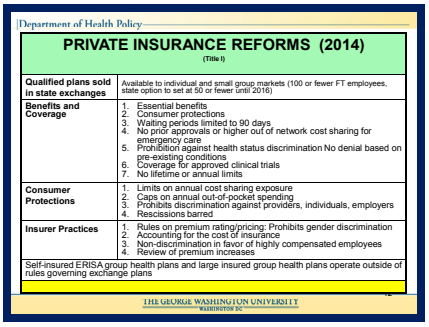

Department of Health Policy

PRIVATE INSURANCE REFORMS (2014)
(Title I)

Qualified plans sold in state exchanges	Available to individual and small group markets (100 or fewer FT employees, state option to set at 50 or fewer until 2016)
Benefits and Coverage	1. Essential benefits 2. Consumer protections 3. Waiting periods limited to 90 days 4. No prior approvals or higher out of network cost sharing for emergency care 5. Prohibition against health status discrimination No denial based on pre-existing conditions 6. Coverage for approved clinical trials 7. No lifetime or annual limits
Consumer Protections	1. Limits on annual cost sharing exposure 2. Caps on annual out-of-pocket spending 3. Prohibits discrimination against providers, individuals, employers 4. Rescissions barred
Insurer Practices	1. Rules on premium rating/pricing: Prohibits gender discrimination 2. Accounting for the cost of insurance 3. Non-discrimination in favor of highly compensated employees 4. Review of premium increases
Self-insured ERISA group health plans and large insured group health plans operate outside of rules governing exchange plans	

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Important items with regard to immunization policies include dependent coverage through age 26; preventive benefits with no cost-sharing; ACIP-required immunization coverage levels; additional preventive services to be designated by the Secretary; changes in limits on coverage for people who are ill; lifetime are barred, annual caps are regulated; waiting periods are regulated; et cetera. Over time the major changes apply, which include access to coverage for everyone, elimination of pre-existing condition requirements for everyone, certain consumer protections, elimination of lifetime and annual limits, limits on cost-sharing and out-of-pocket spending, and a lot of regulation of the business of insurance itself (e.g., setting of premiums, accounting for the cost of insurance, accounting for the medical loss ratio, et cetera).

Other private health insurance markets will remain outside the exchange. The exchanges that will be set up in all states are for the individual and small group markets. States can permit anyone into exchange purchasing, but the assumption is that these are really for individuals and small groups. Ultimately, a small group means under 100 people, which is the vast majority of people who work in the US. Self-insured employer-sponsored group plans and large fully insured employer-sponsored group health plans, meaning 101 people or more, stay out of the exchange and presumable always will. This is important in terms of the benefit design.

Exchange products must meet certain benefit standards, including the following benefit classes:

- ❑ Ambulatory patient services
- ❑ Emergency services
- ❑ Hospitalization
- ❑ Maternity & newborn care
- ❑ Mental health and substance use disorder services including behavioral health treatment
- ❑ Prescription drugs
- ❑ Rehabilitative and habilitative services and devices
- ❑ Laboratory services
- ❑ Prevention and wellness services and chronic disease management
- ❑ Pediatric services including oral and vision care

There may be no discrimination based upon age, disability, or expected length of life. Exchange products must also take into account the health care needs of diverse population segments including women, children, persons with disabilities, and others. There must be emergency access rules.

Coverage of preventive services (Title IV) requires qualified health plans to cover, without cost-sharing, "evidence-based items or services" rated A or B by the USPSTF; ACIP-recommended immunizations; preventive care for infants, children, and adolescents recommended by HRSA; and additional preventive care and screenings for women recommended by HRSA. This will be effective six months following enactment. For all USPSTF A and B recommendations, see the chart at http://www.ahrq.gov/clinic/pocketgd09/gcp09s1.htm. Title IV also provides 1% FMAP increase for states that offer Medicaid coverage of and remove cost-sharing for A and B USPSTF recommended services and ACIP-recommended immunizations effective January 1, 2013. However, newly eligible beneficiaries are covered by benchmark plans, which under Section 1937 SSA must cover "preventive services as designated by the Secretary." Cost-sharing is eliminated for Medicare-covered preventive services USPSTF recommended A or B services. Medicare coverage is authorized for comprehensive health plans and risk assessment and the deductible and coinsurance are waived for personalized prevention planning. The Secretary is authorized to modify Medicare coverage of preventive services based on USPSTF recommendations. Nothing changes about the VFC or the coverage rules for children; however, for the poorest adults, preventive benefits, ironically, may still be an option.

Complex requirements apply to "Grandfathered Plans." Rather than selecting a date by which all products sold in the affected markets are upgraded to the new coverage standards, the law provides for current plans in effect on March 23rd to remain in effect as grandfathered plans and essentially directed the Secretary to set standards for what it means to be a grandfathered plan. Standards were issued the week before this ACIP meeting.

In the case of Medicaid, by 2014, all non-elderly persons with incomes up to 133% FPL, based on "modified adjusted gross income" should be covered. An adult coverage option will be effective July 1, 2010, and additional reforms for women (family planning) and children aging out of foster care are to be included. There are maintenance of effort (MOE) requirements for children under 19 through 2019 and for adults eligible for Medicaid until the Secretary determines that exchanges are fully operational. There is 100% federal funding for the costs of newly eligible persons (2014-2016), dropping to 90% federal funding for 2020 and subsequent years. There is phased in federal funding for states that already have expanded adult eligibility

to 100% of the poverty level. Benchmark coverage for adults includes some level of preventive services as designated by the Secretary. There is an increase Medicaid payments for services of primary care physicians to 100% of Medicare payment rates in 2013 and 2014 with 100% federal financing of increment, and a federal incentive for Medicaid preventive services coverage for all adults (1% FMAP increase).

There are numerous quality improvement requirements (Title III) aimed at insurers, the health care system, and clinical practice. It can be expected, due to the link between quality and efficiency, that there will be numerous efforts to upgrade the quality of practice and to emphasize prevention practice. There is an incentive in the legislation for employee wellness programs, with a broad level of discretion given to employers to design employee wellness programs. Thus, immunization status could be an employee outcome that incentivizes a reduction in premium year cost-sharing.

A considerable amount of funding and attention have gone into access (Title V). There is an investment of $12.5 billion to expand health centers and fund National Health Service Corps ($9.5 billion to expand health center operations, $1.5 billion in health center capital investment, and $1.5 billion for Corps health professionals). A doubling of the program's reach is expected by 2019 once coverage financing also begins. Immunization is a required activity of all health centers. Also included is authorization of school health centers programs (mandatory funding only for construction and development 2010-2013).

In terms of prevention and public health (Title IV), a trust fund has been set up with an appropriation of $15 billion over 10 years ($2 billion a year beginning in FY 2015, $500 million in FY 10, $750 million in FY 11). Some of the funding has already been put into primary care expansion. The remaining funds are expected to be invested in community prevention activities. Moving forward, there is a major emphasis on community prevention activities. Anything that is legal under the Public Health Service Act is a community prevention activity. Therefore, states, localities, and the Secretary could design a lot of interventions aimed at boosting immunization status.

Part of the prevention strategy includes community transformation grants. This is new grant authority (no mandatory appropriation) for community prevention (state, local, and NGOs eligible grantees). There is a requirement for detailed plans for policy, environmental, programmatic and infrastructure changes to promote healthy living and reduce disparities. Immunization status is not specifically identified in the statute as a community health outcome, but could be added by the Secretary. The CDC director is to oversee the program and develop state and local capacity to engage in community transformation activities.

With respect to the immunization program and Medicare immunizations (Title IV), the major news is the use of state authority to utilize the federal contract for adult vaccines. There is a Section 317 demonstration program to improve immunization coverage authorized in concert with the Task Force on Community Preventive Services. Medicare beneficiary access to vaccines is to be studied formally going forward.

In terms of what Ms. Rosenbaum would flag as major issues, she believes that because over time there will be a transformation of what it means to be covered in the US, within the next 10 years the new normal will be full coverage for all ACIP-recommended vaccines across all insurance markets. This places ACIP recommendations into an astounding light. It means that to the extent that ACIP has devoted a lot of its time to children, once the way is cleared to think somewhat more broadly about immunization coverage, the "door will be opened" to a culture

shift in how financial issues are thought of in immunization coverage. She thought they would have to think about this in three ways:

1) Insurer behavior: How do insurers design their benefits? For example, even in states that purport to regulate state-regulated insurance products, there may be public health emergency exceptions. There may be all sorts of limitations and exclusions on vaccine coverage because it does not have to meet the ACIP standard. Moving forward, it will make no difference whether a full or qualified recommendation ACIP recommendation is made. The standard is a recommendation.

2) Provider behavior: Over the next period of time, providers will come to be certain about the financial backdrop for their immunization practices in their offices. The justifications for not being at the ready all of the time and not to have missed opportunities will begin to decrease, and it is assumed will also begin to affect everyone's thinking about what good immunization policy looks like.

3) Family behavior: Family immunization behavior is the product of many things, but one barrier is an uncovered $50 administration fee even if the vaccine itself is free.

In terms of performance and health care quality improvement changes in medical homes, the law provides for a great ramping up of comparative effectiveness research (CER): How much does immunization practice get figured in? How much do ACIP recommendations help inform CER design and execution? How much expansion is there in community health centers? How much do pediatric and adult immunizations become a bedrock for measuring community health center performance?

Discussion Points

Dr. Sumaya inquired as to whether the $12.5 billion represented new dollars or was a component of current funds.

Ms. Rosenbaum responded that the $12.5 billion was on top of the current funds. The assumption on the part of the advocacy world for the program is that they will hold the base as it stands now against inflation following the stimulus, which appropriated additional funds, and that the $12.5 billion ($9.5 billion of which is operating money going forward) is on top of what would be inflation-adjusted. Thus, it is real expansion and the prediction is a doubling in the number of patients served.

Dr. Campos-Outcalt wondered what the implications would be of full coverage for the VFC.

Ms. Rosenbaum replied that there are no changes whatsoever in the VFC, meaning that all children who are entitled to vaccine coverage are in the program, and the purchasing system through Medicaid remains in place. Backing out any children who will not qualify because of legal status in the US, the theory is that some 8 million children are, probably more than any age group, as close to the universal coverage of a population as will be observed. Even if children are covered through the exchange, so not Medicaid, would be entitled to all ACIP-recommended vaccines. The VFC is the delivery mode, but the basic entitlement under Medicaid is to ACIP-recommended vaccines. That has now become the standard for children and adults. In 2014, that will be the standard. The two markets that are outside are large insured employer plans and self-insured employer plans. Basically, the assumption is that over time, even those two markets will fall into place because the companies that sell to the

exchange market and to the larger employer market are going to want to sell a valued product that includes good preventive benefits. That will come to be an expectation on the people's part.

Dr. Pickering requested further information about the grandfather clause in terms of whether it meant that insurance companies would be permitted to function the way they are functioning currently for a prolonged period of time unless they make these significant changes, which would mean that all insurance companies would grandfather in.

Ms. Rosenbaum reminded everyone that the mantra leading up to the passage of the law was, "If you like what you have, you can keep it." The grandfather provision is designed to make good on that. An equally important decisions was made, which is that the grandfather status should not be used as a cover for eroding people's coverage. The House bill veered more toward a data certain to make a shift. The Senate was more lenient. The regulations essentially say that as long as premiums, benefits, coverage, and cost-sharing rules remain stable. There is room to increase these, but the regulations set a threshold amount above which changes result in a loss of grandfathered status. These are cumulative rules, so the assumption is that over the next three years, the federal government estimates that half of all plans will have relinquished their grandfather status. The premium increases that are anticipated may be enough to set off a loss of grandfathering.

Dr. Temte requested information on the change in administrative fees under Medicare, which impacts a great number of children being immunized by private clinicians through the VFC.

Ms. Rosenbaum replied that one of the changes that was made in the law with Medicaid primary care reform was a requirement that Medicaid agencies set their primary care payment rates at the Medicare payment level. That takes effect in 2014. For several years, the federal government will pay the full cost of the increment in payment that would result. The hope is that if Medicaid primary care rates, including administration fees, are brought up to the Medicare level, that will be a decisive increase in compensation rates for immunization, among other things. It is an ironic time to be talking about Medicare as being an improvement, given the pay cut that Medicare-participating physicians are facing. Hopefully, that deadlock will be broken.

Dr. Baker pointed out that currently, Medicare recipients are paying more for their Medicare coverage. She wondered whether this would continue as health care reform moved forward.

Ms. Rosenbaum responded that nothing about health reform would change the premiums. Those with higher incomes, as the law defines higher income, will pay a higher premium.

While Dr. Birkhead (NVAC) thought it was great that vaccines and administration would be covered in the preventive package, the NVAC Finance Working Group identified the question of the adequacy of that reimbursement and whether, in the private sector, vaccine and administration costs were being fully covered by the administration fee. In the public sector, the Medicaid programs for most states do not contribute enough state dollars to draw down the full federal contribution, so some states are paying $2.00 administration fees. He wondered if there was anything in the reform to address the adequacy of the administration fees for the public and private sectors.

Ms. Rosenbaum indicated that there is the change in terms of raising the Medicaid primary care rate, which includes vaccine administration costs to the Medicare level that she just mentioned. That is a full federal contribution for the increment between the state and the Medicare fee.

Dr. Birkhead (NVAC) wondered whether the vaccine administration fee codes would reflect this as well.

Ms. Rosenbaum said she assumed on implementation a major issue for NVPO and NVAC would pertain to how much CMS has internalized exactly what it means to reach Medicare parity levels with respect to vaccine administration. Regarding private coverage, she expected that NVPO and NVAC would want to engage in significant discussions with CMS, the new Center for Health Plans within HHS that is dealing with the exchanges and health plans, the Department of Labor to the extent that they are involved in the small employer market, and the Treasury Department in terms of what it means to cover immunizations recommended by ACIP. The statute states "ACIP-recommended immunization." It does not say "vaccine" or include a list of immunizations. Therefore, the question regarding what it means is left to interpretation.

Rotavirus

Impact of Rotavirus Vaccination Programs

Margaret M. Cortese, MD
on behalf of the
Viral Gastroenteritis Epidemiology Team
Centers for Disease Control and Prevention

Dr. Cortese presented an update on the impact of rotavirus vaccines, and on rotavirus vaccines and circovirus. She reminded everyone that in 2006, the results of the two major safety and efficacy studies were published on the two new rotavirus vaccines, RV5 and RV1. These were among the largest vaccine safety studies ever conducted, with each safety study including >60,000 infants. Safety and high efficacy were demonstrated for both of these vaccines. Efficacy of 85% to 98% was demonstrated against severe rotavirus disease [Vesikari T et al NEJM 2006; Ruiz-Palacios G et al, NEJM 2006].

ACIP recommended RV5 (RotaTeq®) in February 2006 and RV1 (Rotarix®) in June 2008. CDC has monitored the impact of these vaccines in various ways using simple to more sophisticated methods. The National Respiratory and Enteric Virus Surveillance System (NREVSS), a simple but very timely monitoring system, is a network of 67 laboratories throughout the US reporting since 2000. Weekly reporting is done on the number of stool specimens tested for rotavirus by EIA and the number of positive tests. Based on the number of absolute tests performed in these laboratories from 2000 through 2010, since these vaccines were recommended, there has been a dramatic reduction in the number of r of rotavirus-positive tests [Tate J et al Pediatrics 2009; CDC unpublished data].

For the first season following good rotavirus vaccine uptake (for the 2007/08 season, which is when only RV5 was available), comparing proportion of tests that were positive for that year compared to pre-vaccine mean, there was a dramatic reduction overall in the percentage of positive tests and the delay in the timing of the positive tests, suggesting delay in the onset of the season [Rotavirus Test Results at NREVSS Laboratories, 2008 season].

CDC also assesses impact through medical claims data from various data sources. In the Southern US, for example, In the 2007/2008 season, there was almost complete flattening of gastroenteritis admissions across the age groups, compared to previous years. This occurred with only approximately 60% estimated 2008 coverage with ≥1 dose of rotavirus vaccine (RV5) among children aged <1 year.) [Gastroenteritis Hospitalizations and RV5 Coverage; Medical Claims Data, Southern US; Cortese M et al PIDJ 2010].

The estimates of rotavirus burden reduction, can be shown in various ways. In the following table, substantial reductions are shown in all-cause gastroenteritis that occurred during the rotavirus season in ages <1 year and 2 years. This suggests an indirect benefit to older children who were not within the age category who could have received vaccine [Gastroenteritis Hospitalizations and RV5 Coverage; Medical Claims Data; 2008 vs. mean of 3 pre-vaccine years]:

Average 3 US regions (South, Northeast, Midwest)	Reduction in GE Hospitalizations Age <1 Year	Reduction in GE Hospitalizations Age 2 Years
Rotavirus Season • **Excess GE** • **All GE**	**96%** **69%**	**85%** **70%**
Annual • **Rota-coded GE** • **All GE**	**81%** **30%**	**69%** **41%**
Rota vaccine coverage (≥ 1 dose)	**58%**	**<1%**

In a more robust way, Dr. Curns examined complete hospitalization data for gastroenteritis and rotavirus-coded hospitalizations in 18 states for those aged <5 years from 2000-2008. Again in the 2008 season, a marked decline was observed in all gastroenteritis-coded and rotavirus-coded hospitalizations in these 18 states. The estimated reduction in US hospitalizations for children aged<5 years in 2008 was greater than 40,000. [Curns A et al, JID 2010].

The Cadillac method by which CDC monitors the impact of these vaccines is through the National Vaccine Surveillance Network (NVSN) with colleagues the University of Rochester, Cincinnati Children's Hospital Medical Center, and Vanderbilt University where active rotavirus surveillance is performed. This allows for the direct estimates of rotavirus disease burden among children in the counties served by these hospitals. From the baseline of about 50% of children with acute gastroenteritis testing rotavirus positive, in 2008, only 9 children (6%) of children tested positive at these 3 children's hospitals [Payne D et al PAS, 2009 and unpublished data]. Age-specific reductions in rotavirus hospitalization rates demonstrated an 80%-90% reduction, including among children aged 2 who were too old to have received vaccine, indicating what is believed to be herd immunity...

For the 2008-2009 season, the second season post-good uptake of rotavirus vaccine, from NREVSS laboratory system, the percentage of positive tests remained well below the median pre-vaccine percentage. However, the percentage of positive tests was slightly higher than the

2007-2008 season. This season was also not quite as delayed as the first very dramatic season [Rotavirus Test Results at NREVSS Laboratories, 2009 season].

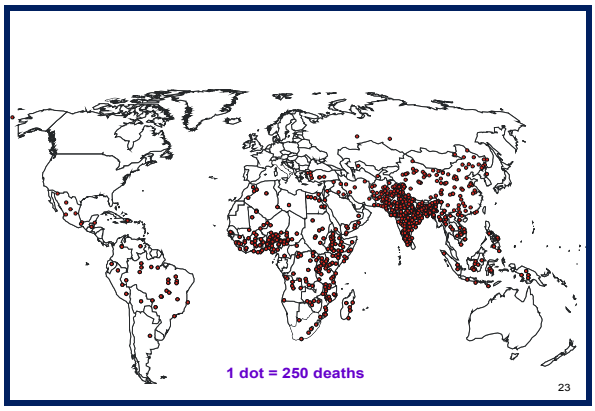
Based on preliminary medical claims data from the 2008/2009 season in the Southern US, in children under the age of 1 there was higher rotavirus vaccine coverage than the previous year and continued blunting of the winter peak in gastroenteritis hospitalizations. In the older children, at least in the South, a resumption in the peak in the winter season was observed. This was still lower than pre-vaccine, but not as flat as in the first year with good coverage post-introduction of vaccine. It is believed that this could a result of disease among children who were neither vaccinated nor previously infected by rotavirus because of the greatly reduced circulation of rotavirus in the previous season [Gastroenteritis Hospitalizations and Rotavirus Vaccine Coverage 2009 Medical Claims Data, Southern US; CDC, unpublished data]. The NVSN data support this. From this active surveillance system, in 2009, there was a modest increase in rotavirus-positive test results among children aged < 3 years, the great majority of whom were, again, in the older, unvaccinated cohort [Total Acute Gastroenteritis and Rotavirus Hospitalizations, age <3 years, NVSN 2006-2009; Payne D et al PAS, 2009 and unpublished data].

Looking at rotavirus test results fort NREVSS laboratories for the 2010 season, it appears that the proportion of positive tests is even further reduced compared with the first very dramatic season. These data are supported by NVSN data that are just coming in, which showed a continued marked reduction in rotavirus circulation in the US.

Fortunately, the US is not the only country that is benefitting from these vaccines. In El Salvador, for example, RV1 was recommended in October 2006. DePalma et al published a paper recently showing a marked reduction in all-cause gastroenteritis hospitalizations and rotavirus-positive hospitalizations in seven hospitals throughout the country where active surveillance is also performed, similar to NVSN. For 2008-2009, there was an estimated reduction in rotavirus hospitalizations following RV1 introduction in El Salvador of 69% to 84% among children aged <5 years [De Palma O et al, BMJ 2010].

A very exciting article was recently published titled “The Effect of Rotavirus Vaccine on Death from Childhood Diarrhea in Mexico.” Using their routine system of collecting data from death certificates in children, they were able to quickly analyze their data and demonstrate a marked decline in childhood diarrhea deaths after RV1 introduction in Mexico. In terms of total diarrhea deaths in Mexico for July 2002 to December 2008, there was a characteristic peak during the fall- winter months that is most prominent among children 0-11 months of age but also occurs among children aged12-23 months. Characteristically, rotavirus is attributed with causing these peaks that occur between December and May. Rotavirus vaccine introduction occurred in May of 2007The peak for the fall-winter months of 2008 that is typically attributed to severe rotavirus cases was blunted for the 0 to 11 month age group, which is the only age group exposed to the rotavirus vaccine [Richardson V et al NEJM 2010]. In winter 2009, there was an estimated 66% reduction in diarrhea-related deaths, strongly suggesting vaccine effect on mortality in Mexico.

The following map illustrates the global distribution of the 527,000 annual rotavirus deaths in young children:



Demonstrating the performance of these vaccines in low-income countries is critical to be able to provide benefit to these children, where mortality is greatest.

Based on an RV1 efficacy trial conducted in Malawi and South Africa, efficacy in both countries was generally lower than typically observed in developed countries, as expected with oral vaccines. Also, as expected, there was some variation by country such that the point estimate for efficacy was 49% in Malawi with 6.7 rotavirus cases prevented per 100 vaccinated, and 77% in South Africa with 4.1 rotavirus cases prevented per 100 vaccinated. Nevertheless, even a vaccine with efficacy of 49% is expected to play an important in such countries, given that the burden of severe disease is extremely high [Madhi S et al NEJM 2010].

Regarding a new finding, rotavirus vaccines and circovirus, Dr. Cortese reported that in March 22, 2010 FDA recommended temporary suspension of Rotarix® while collecting further information on detection of porcine circovirus DNA in Rotarix®. On May 6, 2010, FDA reported detection of porcine circovirus types 1 and 2 DNA in RotaTeq®. On May 7, 2010 an expert Vaccines and Related Biological Products Advisory Committee (VRBPAC) review panel was convened by FDA. On May 14, 2010, FDA lifted the temporary suspension on Rotarix® and recommended continuing to use RotaTeq®. CDC has revised the Rotavirus Vaccine Information Statement.

Update on CBER Activities on Porcine Circovirus in Rotavirus Vaccines

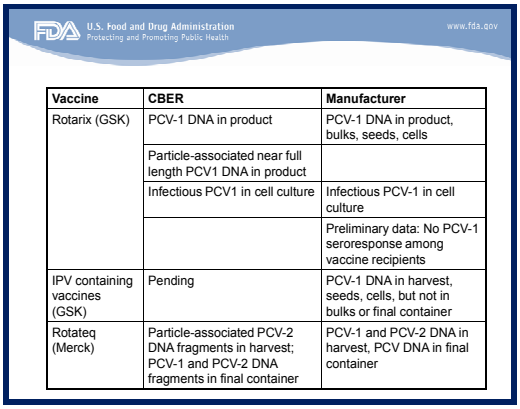
Wellington Sun, MD
FDA / CBER / OVRR

Dr. Sun reported that in February 2010, GSK was informed by a University of California, San Francisco (UCSF) investigator who conducted a study of DNA sequences of live attenuated vaccines, that he had detected PCV-1 in 2 batches of Rotarix® [Victoria et al] GSK initiated experiments to confirm these results and to conduct further investigations. Tests confirmed the presence of PCV-1 DNA in Rotarix® at all stages of the production process. GSK informed FDA of the detection of PCV-1 DNA fragments in Rotarix ® and in harvests, but not in the final product, of inactivated poliovirus (IPV)-containing vaccines that were produced in a related cell bank. The Center for Biologics Evaluation and Research (CBER) testing confirmed the

presence of PCV-1 DNA in Rotarix®. As noted, FDA recommended temporary suspension of use of Rotarix® vaccine on March 22, 2010 as a precautionary measure while CBER gathered additional information. Although testing by Victoria et al did not find PCV1 DNA sequences in Merck's rotavirus vaccine (RotaTeq®), CBER embarked on testing RotaTeq® and recommended that Merck do the same. The FDA was subsequently notified by Merck that preliminary studies identified fragments of DNA from porcine circovirus type 1 and type 2 (PCV1 and PCV2) in RotaTeq® vaccine.

In terms of the CBER lab response to date, CBER has confirmed the presence of PCV-1 DNA in Rotarix®, including complete virus genomes; showed that PCV-1 DNA in Rotarix® is particle-associated, in other words, it is not just DNA; showed that PCV1 virus in Rotarix® can infect swine cells in culture; and confirmed PCV1 and PCV2 DNA fragments in RotaTeq®. To date, there has been no detection of full length PCV genomes and no infectious virus (tested in cell culture) has been found in RotaTeq. These studies are on-going.

PCV-1 and PCV-2 are small DNA viruses containing a single strand of circular DNA. PCV-1 is ubiquitous in pigs and is found in pork products. PCVs are not known to cause disease in humans. There is currently no evidence to suggest that PCV or PCV DNA in US licensed vaccines poses a safety risk. To date, no serious or unexpected safety signals have been observed in pre-licensure studies or post-marketing surveillance of Rotarix® or RotaTeq®. GSK's preliminary serology studies did not show antibody response to PCV-1 among recipients of Rotarix, suggesting that PCV-1 did not infect vaccine recipients. However, those numbers are relatively small. CBER and the manufacturers' results are reflected in the following table:



Vaccine	CBER	Manufacturer
Rotarix (GSK)	PCV-1 DNA in product	PCV-1 DNA in product, bulks, seeds, cells
	Particle-associated near full length PCV1 DNA in product	
	Infectious PCV1 in cell culture	Infectious PCV-1 in cell culture
		Preliminary data: No PCV-1 seroresponse among vaccine recipients
IPV containing vaccines (GSK)	Pending	PCV-1 DNA in harvest, seeds, cells, but not in bulks or final container
Rotateq (Merck)	Particle-associated PCV-2 DNA fragments in harvest; PCV-1 and PCV-2 DNA fragments in final container	PCV-1 and PCV-2 DNA in harvest, PCV DNA in final container

On May 7, 2010, VRBPAC considered the substantial safety record of the vaccines known to contain PCV; considered the benefit of vaccines to outweigh theoretical risks from the presence (or potential presence) of PCV; discussed the importance of transparency and providing information to public; and recommended taking steps to remove PCVs from products. VRBPAC also discussed new genomic techniques that may increase the likelihood of finding additional viruses, virus-like sequences in vaccines. If found, the potential risks from such viruses or sequences may be difficult to assess. Introduction of these techniques in a regulatory setting will require standardization and development of approaches to confirm findings.

Subsequent and on-going FDA actions include a reversal of the recommendation to suspend Rotarix® use; continued testing at CBER; discussions with manufacturers regarding further testing, labeling, and removal of PCV from products; and discussions regarding the implications of new genomic techniques in a regulatory setting.

ROTARIX® (Rotavirus Vaccine, Live Oral): GSK's PCV1 Investigation

Leonard Friedland, MD
Vice President
Clinical and Medical Affairs, Vaccines
GlaxoSmithKline

For context, Dr. Friedland recapped that GSK was notified by independent investigators of an unexpected finding of PCV-1 in Rotarix® (J Virol 2010;84:6033). GSK confirmed the PCV-1 finding in a validated laboratory in mid-March and notified FDA and other regulatory agencies. As noted, on March 22, 2010, FDA recommended temporary suspension of use pending further investigation. On May 6, 2010, FDA notified the public of the presence of PCV1 and PCV2 in RotaTeq®. On May 7, 2010, FDA convened the VRBPAC meeting as noted. Materials and presentations from this meeting are posted on the FDA website at the following url: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm211828.htm. On May 14, 2010, FDA "determined it is appropriate to resume the use of Rotarix® and continue the use of RotaTeq®." All available data support that PCV1 in Rotarix® is a manufacturing quality issue not a safety issue.

Rotarix® is licensed in over 110 countries. More than 69 million doses have been distributed worldwide, and 2.5 million have been distributed in the US. US licensure occurred in 2008. Rotarix® is manufactured in compliance with FDA regulations on adventitious agent testing, and in accordance with guidance in place at the time of licensure.

PCV-1 is a non-pathogenic virus that is common and widespread in pigs. PCV-1 is not known to cause disease in pigs or any other animal, including humans. There is no convincing evidence of human infection by PCV-1. PCV-1 DNA has been detected in US pork products and in human stools in the US. PCV-2 has not been found in Rotarix®. PCV-2 is the causative agent of "postweaning multisystemic wasting syndrome" in pigs. PCV-2 not known to cause disease in humans.

When GSK was notified of the unexpected finding of PCV-1 DNA in Rotarix®, the company set out to determine how PCV-1 originate in Rotarix®. To answer this question, they had to go back in time prior to the initiation of the development of Rotarix®. Vero cells were sourced from the biological resource center, ATCC in 1980. GSK produced the master cell bank in 1983, and further derived the working cell bank in 1993. The working cell bank was used to produce the Rotarix® viral seed in 1999 using an ancestor seed produced on an alternative cell line. Once screening for PCV-1 DNA was performed using quantitative PCR, the vero cell line source from ATCC was found to be negative. The master cell bank and the working cell bank from GSK were found to be positive, while the ancestor of the Rotarix® viral seed was negative. GSK speculates that a likely source of PVC-1 might be the use of the porcine-derived reagent trypsin, which is used to propagate cells in the manufacturing process. Trypsin was not irradiated before 1993. Manufacturing corrective actions to produce a Rotarix® free of PCV1 will be a complex process and will involve generation of a new bank, generation of a new Rotarix® viral seed, and performance of the necessary clinical trial in agreement with regulatory authorities. This will take several years.

GSK has investigated the nature of the PCV-1 signal present in Rotarix®. In this investigation, they followed the same testing algorithm that was used to investigate the presence of Avian Leukosis Virus in a commercial vaccine in the 1990s and sought to answer the following questions:

1. Is this PCV-1 signal associated with presence of viral particles?
2. Is this PCV-1 signal associated with presence of viral particles capable of infecting permissive cells?
3. Is this PCV-1 signal associated with presence of viral particles capable of productive infection in human cells?
4. Is this PCV-1 signal associated with presence of viral particles capable of causing infection in human infants?

For the sake of time, Dr. Friedland did not go into the details of their manufacturing investigations which were reviewed in detail during the May 7, 2010 VRBPAC meeting. In short, the results of the manufacturing investigations showed that the PCV-1 signal is associated with very low amounts of viral particles, that the viral particles are capable of infecting permissive cells (e.g., cells of the natural host such as porcine kidney cells), and that the viral particles are not capable of productive infection in human cells (meaning the ability of the virus to infect cells and produce detectable, intact viral particles). GSK's investigations indicate that there is no evidence that PCV-1 associated with Rotarix® can undergo productive infection in human cell lines. Answering the fourth question (Is PCV-1 capable of causing infection in human infants?) was very important in GSK's investigation.
GSK's clinical investigation had two objectives, which were to: 1) evaluate if infants receiving 2 or 3 doses of Rotarix® or placebo develop an immune response to PCV1 as assessed by the presence of antibodies against PCV-1; and 2) evaluate the presence of PCV1 DNA and pattern of detection in stool samples collected at pre-determined time points after a single dose of Rotarix or placebo.

To do this, GSK performed blinded retrospective laboratory testing, using archived clinical samples collected in completed Rotarix® clinical trials. The studies selected were required to be placebo controlled, to involve the collection of pre- and post-vaccination sera, and to include the collection of stool samples which were obtained in a subset of subjects in the Rotarix® clinical studies at days 3, 7, 10, 15, 22, 30 and 45 after vaccination. Four completed studies were identified. In three of the studies, infants were healthy at study entry and one study evaluated administration of Rotarix® to HIV positive infants. The goal was to test samples from 20 subjects in each of the four studies, for a total of 80 subjects (40 who received Rotarix® and 40 who received placebo). For serum samples, GSK used an immunoperoxydase monolayer assay (IPMA) to detect anti-PCV-1 antibody response. For stool samples, Q-PCR was used to detect PCV DNA. This study was specifically included since it might be speculated that replication of PCV-1, if it were to occur, might be enhanced in an HIV+ population. There were 300 stool samples and 160 serum samples.

The results of these clinical investigations demonstrate lack of PCV-1 infection in infants. None of the infants seroconverted. PCV-1 was detected in the stools of 4 of 40 Rotarix recipients® (2/5 [40%] at day 3, and 2/40 [5%] at day 7. None was detected at later time points (days 10, 15, 22, 30, 45) after vaccination. The adverse event profile in subjects with PCV-1 DNA detected in stools was similar to placebo recipients. Currently available data do not support PCV-1 infection in infants who received Rotarix® in clinical trials. The conclusion of the

currently available data from GSK's clinical investigations is that the PCV-1 present in Rotarix® is not capable of causing infection in infants. These results are consistent with the published literature, which indicates that PCV-1 is not capable of causing infection in humans.

GSK's investigations reveal that PCV-1 has been Rotarix® from the early stages of development, throughout clinical trials and post-marketing to the present. As a vaccine manufacturer, GSK's primary focus is always on patient safety. In parallel with the manufacturing and clinical investigations, when GSK first learned about the presence of PCV-1, they critically reviewed the scientific literature and consulted experts. The unanimous conclusion from all sources is that PCV-1 is not known to be infectious in humans, nor does it cause disease in humans or any other animal. The Rotarix® safety database is large, robust, and extensive. It is continuously monitored over time, and consistently demonstrates the safety of Rotarix®. There is no specific PCV-1 lens by which to query GSK's database because in the absence of disease, there are no symptoms.

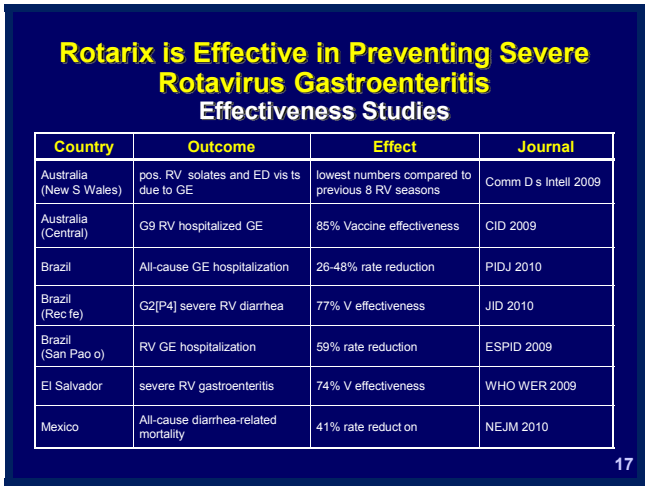
Rotarix® has had one of the largest vaccine development programs. Supporting US licensure in 2008 were 11 studies, with more than 75,000 infants enrolled, 40,000 of whom received Rotarix®. Efficacy was evaluated through 2 years, 2 rotavirus seasons, after vaccination. Therefore, safety was also evaluated for many of the infants up to 2 years after vaccination. The development program included a large safety study in more than 60,000 infants and was specifically powered to assess intussusception (n=63,225).

Recently, Rotarix® was one of multiple products reviewed by the FDA's Pediatric Advisory Committee. This committee conducts routine, periodic safety reviews of pediatric drug and vaccine products. The Pediatric Advisory Committee unanimously agreed with FDA's conclusion that no new safety concerns were identified with Rotarix®, as well as with FDA's recommendations for continued routine monitoring. The Pediatric Advisory Committee did not specifically review the product with the knowledge of PCV-1, because the finding had just become available. However, as has since been learned, the product reviewed contained PCV-1 and has since early development.

In addition to the clinical trial database that supported licensure, a large global post-marketing experience supports Rotarix® safety and effectiveness. Pharmacovigilance activities are in place. GSK has a worldwide network of safety personnel who analyze adverse events and expedite reporting to worldwide regulatory agencies. For spontaneously reported intussusception cases, enhanced pharmacovigilance is used, comparing the number of cases observed to the number expected. Since the worldwide launch in 2006, over 69 million doses of Rotarix® have been distributed, including 2.5 million doses in the US. The company has received approximately 3,000 adverse event reports, approximately 1,200 of which are considered to be serious as defined by regulatory criteria. This represents a reporting rate of 4.3 per 100,000 doses distributed. This rate is consistent with reporting rates expected with new vaccines.

Various Phase 4 clinical trials have been conducted, including safety and immunogenicity trials in HIV positive infants and in premature infants. Rotarix® was found to be immunogenic and well-tolerated in these particularly vulnerable populations. GSK has also conducted a transmission study between twins, demonstrating low rates of transmission with no associated gastroenteritis symptoms, and is also conducting a number of observational studies worldwide to further monitor the safety and effectiveness of Rotarix®. One on-going study in the US will include 55,000 infants receiving Rotarix® to assess the risk of intussusception and other serious adverse events.

GSK has previously presented results from its worldwide randomized placebo-controlled clinical trials to ACIP, which have demonstrated the substantial efficacy of Rotarix®. The published studies shown in the following table demonstrate the considerable impact and effectiveness of Rotarix® in preventing severe rotavirus disease in real-life settings. These data together demonstrate that Rotarix® is a very effective tool for significantly reducing morbidity and mortality due to rotavirus gastroenteritis:



Rotarix is Effective in Preventing Severe Rotavirus Gastroenteritis
Effectiveness Studies

Country	Outcome	Effect	Journal
Australia (New S Wales)	pos. RV solates and ED vis ts due to GE	lowest numbers compared to previous 8 RV seasons	Comm D s Intell 2009
Australia (Central)	G9 RV hospitalized GE	85% Vaccine effectiveness	CID 2009
Brazil	All-cause GE hospitalization	26-48% rate reduction	PIDJ 2010
Brazil (Rec fe)	G2[P4] severe RV diarrhea	77% V effectiveness	JID 2010
Brazil (San Pao o)	RV GE hospitalization	59% rate reduction	ESPID 2009
El Salvador	severe RV gastroenteritis	74% V effectiveness	WHO WER 2009
Mexico	All-cause diarrhea-related mortality	41% rate reduct on	NEJM 2010

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To summarize and conclude, rotavirus infection is the leading cause of severe childhood diarrhea in both developed and developing countries. Prior to the development of vaccines against rotavirus, worldwide one child died from rotavirus every minute. Vaccination is the only effective preventative strategy. Globally, its use has the potential to prevent about 2 million deaths over the next decade. Studies in the US have shown that vaccination has resulted in at least a 60% reduction in rotavirus disease as compared to the pre-vaccine era. Rotarix® confers robust and broad protection against rotavirus gastroenteritis. Rotarix® has been extensively studied before and after approval, and has been found to have an excellent safety record. Material from PCV-1 has been present since the initial stages of the vaccine's development, throughout clinical trials and post-marketing, to the present. Thus, all of the safety data reflect exposure to PCV-1, supporting the safety profile of Rotarix®. Overall, the benefit for Rotarix® remains highly favorable.

It is now known that an adventitious agent, no matter how benign, is present in Rotarix®. GSK is continuing discussions with FDA and other regulatory agencies regarding additional clinical investigations, and is committed to manufacturing Rotarix® using PCV1-free materials. Developing a new manufacturing process is a complex undertaking that will require time to implement. GSK will continue with its comprehensive pharmacovigilance activities already in place worldwide. Use of Rotarix® has been resumed and Rotarix® is available for use by US healthcare providers.

RotaTeq® (Rotavirus Vaccine, Live, Oral, Pentavalent) Update on Porcine Circovirus (PCV)

Kim Dezura
Global Vaccine Technology & Engineering
Merck & Co., Inc.

RotaTeq® was licensed in the US in February 2006. In March 2010, Merck received global WHO pre-qualification. Currently, RotaTeq® is licensed in over 90 countries. Over 37 million doses have been distributed worldwide, of which over 30 million have been distributed in the US. RotaTeq® has an established safety profile based on large, comprehensive pre- and post-licensure studies that have been conducted. Protection against rotavirus gastroenteritis has been demonstrated in developed and developing countries (e.g., North America, Europe, Latin America, Africa, and Asia). A substantial reduction in rotavirus disease burden has been observed across the globe after vaccine introduction, particularly in Australia, France, Nicaragua, and the US.

It is important to note that both PCV-1 and PCV-2 commonly circulate on pig farms. There is frequent detection of PCVs in US pork products and US stool samples. Neither PCV-1 nor PCV-2 is known to cause infection or illness in humans. PCV-2, while linked to wasting syndrome in pigs has not been linked to any illness within humans [Li L et al. *J Virol.* 2010;84:1674–1682; Victoria JG et al. *J Virol.* 2010; 84:6033–6040; Fraile L et al. *Can J Vet Res.* 2009;73:308–312; Food and Drug Administration,fda.gov/BiologicsBloodVaccines/ Vaccines/ApprovedProducts/ucm212140.htm. Accessed May 24, 2010].

Ms. Dezura reported that on March 22, 2010, no PCV was found in RotaTeq® by the US research team at UCSF. On March 23, 2010, FDA recommended that Merck conduct testing for PCV. Initial testing of RotaTeq® by FDA in March and April 2010 was negative for PCV. In the latter part of April 2010, Merck notified regulatory agencies worldwide that very low levels of PCV DNA had been found in RotaTeq® by PCR. On May 6, 2010, FDA preliminary testing revealed low levels of PCV-1 and PCV-2 DNA in RotaTeq® from its own testing. On May 14, 2010, FDA recommended continued use of RotaTeq® and resumption of Rotarix® following the May 7th VRBPAC meeting.

In developing an analytical test plan for the evaluation of RotaTeq® for PCV, Merck focused on the following four key questions:

1. Is PCV DNA present in RotaTeq®?
2. Is PCV DNA detected associated with virus particles?
3. Are PCV virus particles infectious?
4. What is the source of PCV DNA?

QPCR testing of 3 lots of RotaTeq® showed very low levels of PCV DNA. PCR-based assays conducted on 5 rotavirus bulk lots showed very low levels of PCV DNA, with inconclusive results on particle-association. Infectivity assays were initiated on 5 rotavirus bulk lots, with results anticipated July 2010. Initial PCR testing of cell banks, virus seeds, and trypsin lots indicates that PCV DNA in bulk lots is introduced from irradiated trypsin. These data are consistent with finding of no replication of PCV-1 or PCV-2 in RotaTeq®. Although these data suggest that there is no infectious PCV in RotaTeq®, additional studies are ongoing to confirm these results

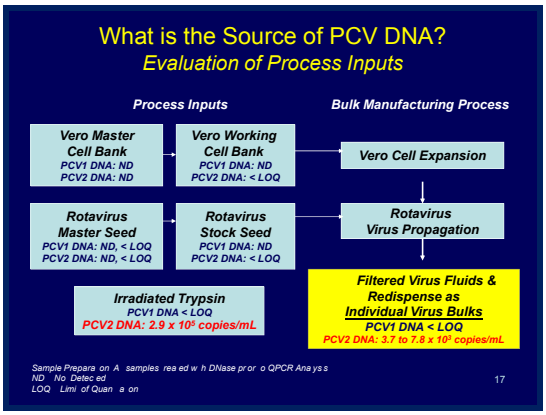
A key challenge in the PCV investigation for RotaTeq® conducted by Merck is that there are very low levels of PCV DNA in RotaTeq® (1.4 to 1.7 $x10^3$ copies / mL of PCV DNA by QPCR). Demonstration of lack of infectious virus in RotaTeq® requires multiple analytical approaches and longer testing periods of up to 28 days in duration. There is a risk of false negatives if assays are not qualified for low levels of PCV DNA. Merck determined that establishing appropriate assay conditions is critical moving forward. In terms of considerations for analytical methods in the PCV investigation for RotaTeq®, Merck employed a 3-fold approach to the assays internal to Merck. First, methods had to be developed to determine DNA particle association. Also important was to overcome the matrix effect (e.g., interference of host DNA in RotaTeq®) within the assays. In addition, they had to generate infectious PCV positive controls to understand the performance of assays. Merck has systematically evaluated all assays to ensure that current and future results are informative and meaningful.

As noted, Merck began testing on 3 final container lots of RotaTeq® and subsequently moved into the bulk inputs into the final containers. In the manufacturing processing, Merck uses 5 bulks, one for each of the 5 reassortants that compose RotaTeq® and blend them with stabilizer as they go into the final container. The advantage of testing bulk inputs is that allows for a more concentrated matrix to be able to look for PCV DNA. What the data have shown from the PCR testing is that there are very low levels of PCV DNA within the Merck product. Specifically within the bulks, f PCV-1 DNA was not detected or was below the limit of quantitation and PCV-2 levels were just higher than the limit of quantitation for the assay. It is also important to note that PCR assays act by detecting DNA fragments, so this does not necessarily indicate a live, intact infectious virus.

In terms of understanding whether the PCV DNA being detected was associated with virus particles, for quantitative PCR Merck used short chain amplicons that look for very small sequences of the DNA. There were non-quanitifiable levels of PCV-1, and a signal was detected for PCV-2 DNA. Longer chain amplicons were investigated through the use of conventional endpoint PCR assays looking at an approximate 400 base pair and 842 base pair. Inconsistent results were observed when moving to the longer chain amplicons. These data indicated that there were fragments of DNA, but that they may not necessarily be associated with an intact virus. This has moved Merck forward into conducting direct infectivity testing using cell culture-based methods.

Merck has leveraged *in vitro* cell culture-based assays to assess the presence of infectious virus particles. Infectivity testing has been initiated on 5 rotavirus bulk lots. Merck is leveraging susceptible cell lines (PK-15 and Vero cells) that they know will replicate PCV readily. Merck focused on the cell culture infectivity conditions to provide a high sensitivity for ensuring that if there is infectious virus, it can be seen. A QPCR detection method is being used to ensure high sensitivity. Infectious PCV positive controls are included, which is essential to ensure confidence in a negative result. Specific culture conditions have been incorporated to ensure viral replication. Duration of testing for a negative result is 21 to 28 days. Initial results were expected to be available in July 2010.

With regard to the source of PCV DNA, the following diagram illustrates the manufacturing process for RotaTeq®:



The approach taken to assess the source of the PCV was to map back the lineage for each of the inputs for the rotavirus process. The presence of PCV was not detected in the Vero master cell bank. For the working cell bank, no detectable levels of PCV-1 and not-quantifiable levels of PCV-2 were observed. Similar results were observed for the master seed and stock seed, again testing the seeds associated with each of the reassortants. , One lot of commercial irradidated trypsin was tested and a positive signal for PCV-2 DNA was observed within that trypsin lot. Thus, Merck focused on the use of irradiated trypsin.

Trypsin is irradiated at 2 stages before use in the manufacturing of RotaTeq. Irradiated trypsin is utilized in the cell bank, virus seed, and bulk manufacturing processes. Each irradiated trypsin lot is tested for a panel of adventitious agents. This trypsin lot was tested by the vendor at time of release and was found negative for infectious PCV-1 and PCV-2. In conclusion, PCV DNA in bulk lots is introduced from irradiated trypsin solutions. The data thus far are consistent with no replication of PCV-1 or PCV-2 virus within RotaTeq®. PCV infectivity testing of bulk lots and trypsin will be performed to confirm these results.

To summarize, the PCV analytical testing for RotaTeq®, QPCR testing of 3 lots of RotaTeq® showed very low levels of PCV DNA. PCR-based assays conducted on 5 rotavirus bulk lots showed very low levels of PCV DNA, with inconclusive results on particle-association. Initial PCR testing of cell banks, virus seeds, and trypsin lots indicates that PCV DNA in bulk lots is introduced from irradiated trypsin. Data support that there is no replication of PCV-1 or PCV-2 in RotaTeq®. Infectivity assays were initiated on 5 rotavirus bulk lots, with results anticipated July 2010. Results will continue to be communicated to global regulatory agencies upon availability.

For the clinical evaluation of RotaTeq® for PCV, Merck has asked three key questions, which are as follows:

1. Is PCV DNA present in clinical bulk lots for RotaTeq®?
2. Is PCV DNA detected in stool samples of vaccine recipients?
3. Are antibody responses to PCV detected in serum samples of vaccine recipients?

Clinical and marketed bulk lots are being evaluated for the presence of PCV-1 and PCV-2 DNA by QPCR. If presence of PCV DNA is confirmed for clinical lots, testing of stools and serum samples will proceed. Merck plans to test serum and / or stool samples from approximately 150 vaccine recipients and 50 placebo recipients, depending upon availability of samples. Stools will be evaluated for PCV-1 and PCV-2 DNA by QPCR. If positive by the PCR-based method, samples will be assessed to determine if the PCV DNA is associated with viral particles. Serum will be evaluated for immune response to PCV-1 and PCV-2 by ELISA.

With respect to the analytical test plan for RotaTeq® to date, analysis of RotaTeq® final containers is complete, assessment of PCV DNA in RotaTeq® and associated bulk lots is complete, and assessment of the source of PCV DNA via PCR is complete (confirmatory data to be completed in June 2010). During July and August 2010, Merck will assess rotavirus bulk lots and trypsin lots via *in vitro* PCV infectivity assays. If presence of PCV DNA is confirmed for clinical lots, testing of stools & serum samples will proceed . Testing of additional clinical bulks will be completed by July 2010. Preliminary QPCR results of clinical stool samples collected during clinical trials will be available in July 2010. In August 2010, preliminary results will be available of clinical serum samples collected during clinical trials, although timing is pending finalization of assay conditions.

Merck is committed to completing PCV analytical and clinical testing of RotaTeq®. The company will continue to share data with regulatory agencies, the scientific community, health care providers, and the public upon availability and is also committed to taking appropriate action as necessary. Approaches will be developed to enhance screening and removal of PCV in RotaTeq®. Merck will partner with scientific experts and regulatory authorities to evaluate current and emerging analytical technologies to enhance product quality assurance.

Discussion Points

Dr. Meissner noted that while there do not appear to be a safety issues, the cell lines mentioned were porcine kidney cells and Vero cells, which are African Green Monkey kidney cells. He wondered whether there had been efforts to infect human line cells with this virus.

Dr. Friedland responded that GSK has tested human cell lines. There is a report in the literature by Hattermann et al who tested 18 human cell lines and found that PCV-1 was not able to produce a productive infection in any of the 18 human cell lines tested. GSK has now tested 5 human cell lines: MRC5 (human diploid cell line), U937 (monocytic human cell line), Hep2 (transformed human cell line), an epithelial colorectal cell line(CaCO) and PBMCs. Again, there is no evidence indicating that PCV-1 associated with Rotarix® can undergo productive infection in human cell lines.

Dr. Cieslak said he was persuaded that perhaps this was an orphan virus. He was more concerned about the pathogenic viruses that they may not even know about. With that in mind, he wondered what could be done to test the cell lines used to grow vaccine viruses. His guess would be that human viruses tend to infect humans, and he would be most concerned about the human cell lines.

Dr. Baker inquired as to whether anyone knew of other human cell line information.

Dr. Sun said he thought that was the question. Assessing adventitious agents is a progressive process that moves as technology moves forward. One of the issues he raised in his summary

pertained to how to use genomic techniques to screen cell substrates for known and unknown viruses. It is imperative to ensure that tests are validated as with any other assay.

Dr. Keitel wondered whether human stools from any of the studies or in other investigations had been assayed for infectious virus on susceptible cell lines.

Ms. Dezura responded that Merck had not yet initiated testing on stool samples, given that they first focused their efforts on the clinical bulk that went into the clinical trials, the results from which will be used to select the patients for which stool testing will be done. The first step is to determine whether PCV DNA is observed within clinical supplies.

Dr. Friedland said it was important to mention that this finding came to light toward the end of March 2010 and GSK was asked to present at an FDA advisory committee 6 weeks later. Thus, a tremendous amount of work needed to be done in an area where PCV had not been studied in humans. There are no humans known to have antibody responses to PCV-1, including people who work in the swine industry. Therefore, GSK had to adapt an assay that was used in pigs for humans in a very short period of time. As noted, discussions continue with respect to collecting additional data.

Ms. Stinchfield (NAPNAP) requested further information about the purpose of the trypsin solution in the manufacturing process.

Ms. Dezura replied that trypsin is an enzyme that is utilized in the cell expansion part of the process to dissociate cells from the disposable cell culture ware. It is also used as part of the virus infection process. It is an incoming raw material to the product.

Day 2: Public Comments

Frankie Millie
Founder / National Director
Meningitis Angels
Mother of Child Who Died from Meningococcemia

Recently, I spent two weeks in Oklahoma with the meningococcal outbreak there. There were nine children in that outbreak over a two-week period: an infant who lost both arms, both legs; a toddler; six second graders, two of whom died, one of whom is still fighting who lost both arms, both legs, and most of his face, including his eyelids and part of his tongue; and a 17-year old. We now see an outbreak in Colorado in young men ages 22 to 29. My concern is that we need to prevent this disease in as many age groups as we possibly can. I encourage and beg this committee, as you move forward in looking at adolescent recommendations, that you leave those in place that are there already, that you add a booster, and that in the future as it comes to pass, that you protect as many infants, children, teens, and young adults from this deadly, debilitating disease as you possibly can. I also encourage manufacturers to work with ACIP to try to create and negotiate reasonable pricing so that more people, more children, more infants, more toddlers, more adults can have access to lifesaving vaccines. Thank you. Dr. Baker clarified that CDC, not ACIP, is responsible for price negotiation.

Keira Sorrells, President
Zoe Rose Memorial Foundation

The Zoe Rose Memorial Foundation is a non-profit that supports families with premature infants. I am here to speak on behalf of the parents across the country who are facing one of the most traumatic life experiences of having and raising a medically fragile child. More importantly, I am a mother. I am a mother of triplets born at 25 weeks, and I am a mother who has had the challenge of protecting and raising a medically fragile infant. I had three of them. I am also a mother who has lost one of my daughters at only 14 months of age because of an infectious disease. I am a mother who spent a week in the hospital with my two survivors watching them fight RSV just six months ago. My family, six months later, is still dealing with the financial hardships of that hospital stay because of lost time at work and medical bills. But we're insured. We have good insurance. We're the lucky ones. But what about the families that aren't so lucky. The cost to these families extends well beyond the hospital stay because of medications, treatments, and therapies that can last a lifetime. As the parent of a medically fragile infant, I was repeatedly informed by our doctors about what we were going to be facing. I knew how fragile they were. I took precautions. I heard time and time again, "Keep your girls healthy. Keep them out of the hospital. Don't let them get RSV." But what about the babies that are born just a few weeks early or even full term? These are babies that you'll read about in our handout. These babies have parents who are told that RSV is just a bad cold, if they are even told about it at all. They are automatically excluded from the possibility of prophylaxis treatment, and yet they contract the virus and in far too many cases have lifelong medical issues or even die. With a virus that is as contagious and vicious as RSV, how can we let these parents think that it's just a bad cold, and how can we exclude these babies from a lifesaving prophylaxis treatment? If you are fortunate enough to have a healthy child, imagine that you are one of these parents like me that stands helplessly by your sick child's bedside knowing that something exists that could have protected your child from the disease, and yet you couldn't get it for them. When you look at the numbers and the statistics and the economics, realize that each of those numbers has a child behind it—a living, breathing child who has a right to a healthy life. The value of a child's life should never be measured in dollars and cents. When you talk about statistical significance, you are talking about my children. You're talking about your children or your grandchildren. This is not just a bad cold, and we should never think that losing even one child to this virus is acceptable. You are the experts. You know what RSV is, and only you hold the power and the influence in your hands to protect our children. Thank you.

Dr. Mitchell Goldstein
President, National Perinatal Association (NPA)
Medical Director, Citrus Valley Medical Center NICU
Associate Professor Pediatrics, Loma Linda University Children's Hospital

We at the NPA have published our own guidelines because of what we perceive to be a need for a truly objective evidence-based guideline for RSV prophylaxis, especially with regard to neonates at 32 to 35 weeks post-conceptual age. The COID, as we feel, is rationing health care. The NPA sees the 2009 COID guidelines as creating potential confusion through encouraging the use of a non-FDA approved dosing regimen. There is lack of medical evidence for the change. Endpoints other than hospitalization are not considered. A large number of babies born at 32 to 35 weeks post-conceptual age are placed at risk. Moreover, by marginalizing risk factors, the 2009 COID guidelines place the most socioeconomically disadvantaged at significant risk. Most importantly, this is not a vaccine. Our guidelines have

the endorsement of over 1500 neonatologists around the country, including representatives of several prominent children's hospitals as well as Alan Spitzer, Senior Vice President and Director of the Center for Research and Education at the Pediatrix Medical Group. Most importantly, we have the support of our parent membership in the NPA whose babies are most at risk and who have, as we have heard, the most to lose. It seems contradictory that while the current data support an emphasis on an understanding of the increased risk for the pre-term or late pre-term infant, the COID redefines them as near-term in the management of their RSV risk. Thank you very much for your consideration.

Dr. Lance Wyble
Florida Healthy Start Coalition

Today I am speaking on behalf of Healthy Start of Florida regarding their concern that ACIP will decide to simply approve the 2009 Redbook guidelines on RSV. Since 1992 in Florida, Healthy Start, a state funded program, has been successful in lowering infant mortality rates by offering wrap around services to at risk pregnant women, mothers, and babies. While the babies covered by Healthy Start don't all qualify for monthly palivizumab injections, they are, we believe, disproportionately affected by the decisions that resulted in changes in the 2009 Redbook. Unfortunately, this group has only a weak voice to verbalize concern. Likewise, the lifestyle, living conditions, and usually fractured relationships with health care providers and the health care system for Healthy Start families creates a formidable barrier for receiving even somewhat reduced and definitely more complicated to follow recommendations of the 2009 Redbook. I hope the committee will recognize that impact when they come forward with their recommendation. When many of the clinicians in Florida understood the significant changes recommended by the 2009 Redbook, over 500 of them spoke out through a petition stating in essence that they did not believe these changes were prudent, whether they were more cost-effective or not. Furthermore, these practitioners and the constituents of Healthy Start see the 2009 changes as minimizing the concern about RSV in Florida. I would like to emphasize to the committee that the most important part of committee work on this is the human side—not the dollar side. As many practitioners nationally point to the aspects of the 2009 changes that Dr. Meissner himself referred to as "difficult to characterize as strong evidence" Healthy Start is concerned that a similar interpretation of the data by this committee, if that is what comes out in the final recommendations of ACIP, will unfortunately disproportionately affect those from a lower socioeconomic background. Thank you.

Lyn Redwood
Safe Minds

As stated by Dr. Friedland and others, the Food and Drug Administration recently convened a panel of experts to review the findings that rotavirus vaccine given to infants in the US, RotaTeq® produced by Merck and Rotarix® produced by GSK) are contaminated with pig viruses. Rotarix® has been shown to contain nucleic acids from both PCV-1 and PCV-2. I want to point out that PCV-2 is a pathogen in pigs that is associated with wasting and immunodeficiency. While acknowledging that the entire short- and long-term risks from porcine circoviruses are yet unknown, the FDA advisory panel decided that "the benefits of the vaccine trumped its risks." Safe Minds disagrees with this conclusion, and calls on the Advisory Committee for Immunization Practices to rescind their recommendations regarding the routine administration of rotavirus vaccine until adequate safety studies have been conducted. While the technology to detect genetic contaminants in vaccines was not available until just recently, the dangers of generating new viruses and bacteria that can cause disease were foreseen by the pioneers of genetic engineering. Horizontal gene transfer (HGT) refers to the direct uptake

and incorporation of genetic material, DNA fragments, into species. In this instance it is from viral contaminants and live viral vaccines into the human host or host-related bacteria. Unlike chemical pollutants which breakdown and become diluted out, nucleic acids are infectious. They can invade cells and genomes. They multiply, mutate, and can recombine indefinitely. Potential hazards of HGT and free nucleic acids include the generation of new viruses and bacteria that can cause disease; spread of drug- and antibiotic-resistant genes among viral and bacterial pathogens, making infections untreatable; random insertion into genomes of cells resulting in harmful effects, including cancer; and the reactivation of dormant viruses present in all cells and genomes, which may also cause disease. These issues have not been adequately investigated. Absence of evidence is not the same as absence of harm. Research demonstrates that the pathogenic potential of PCV-2 to cause AIDS-like disease in pigs is unleashed when there is a simultaneous immune system activation, for example, a current vaccination in the animals. Thus, the concurrent ingestion of rotavirus vaccine contaminated with PCV-2 DNA sequence along with DTaP, HIB, PCV, IPV, and hepatitis B, which is currently recommended by ACIP provides a high risk scenario for disease in humans.

Safe Minds requests that ACIP call on the Immunization Safety Office (ISO) to immediately research adventitious agents in vaccines, especially live viral vaccines. PCV-2 is a lymphotropic virus that affects primarily lymphoid tissue. Its detection in lymphoid tissue of exposed vaccinated children should be the focus of urgent investigations. Such tissue is available in the form of intestinal biopsies from children with a variety of conditions. In addition, lymphatic tissue is also available from Rhesus Macaque monkeys that were exposed to the vaccine schedule as part of on-going safety studies. These tissues should be screened using the same metagenomic and panmicrobial array technology used by Victoria. Such analyses should be conducted by independent scientists and done immediately. If this contamination had been discovered prior to licensure of the rotavirus vaccine, I doubt FDA would have licensed the vaccine. Why should it be any different now? The charter of this committee allows for the alteration or withdrawal of previous recommendations regarding a particular vaccine as new information becomes available on the risk or the disease changes. Ideally, this vaccine should be suspended until such safety studies are completed. Once completed, a new risk / benefit analysis should be conducted based on these new findings, taking into consideration that rotavirus disease carries a low mortality rate in the US. In absence of this necessary research, the precautionary principle should dictate policy. At a minimum, accurate and transparent information regarding PCV contamination in the rotavirus vaccine should be included on the vaccine information sheet given to parents prior to vaccination highlighting the lack of research on health effects. That is not there right now. It’s impossible for parents to give free and informed consent for a vaccine containing pig viruses when the risks are unknown. To continue to administer these vaccines given the impossibility of informed consent is unethical. Thank you.

Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the June 23-24, 2010 ACIP Meeting are accurate and complete.

Date

Dr. Carol J. Baker, Chair
Advisory Committee on
Immunization Practices (ACIP)

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